CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208684Orig1s000
208685Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approve

NDA 208684
Review # 1

Drug Name/Dosage Form	Emflaza (deflazacort) tablets
Strength	6 mg, 18 mg, 30 mg, and 36 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Marathon Pharmaceuticals
US agent, if applicable	N/A

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/BRANCH
Drug Substance	Ray Frankewich	ONDP/DNDP I/Branch I
Drug Product	Andrei Ponta	ONDP/DNDP I/Branch I
Process	Mark Johnson	OPF/DPA/Branch I
Microbiology	Mark Johnson	OPF/DPA/Branch I
Facility	Michael Shanks	OPF/DIA/Branch I
Biopharmaceutics	Yang Zhao	ONDP/DB/Branch I
Regulatory Business Process Manager	Dahlia A. Woody	OPRO/DPRBPM/Branch I
Application Technical Lead	Martha Heimann	ONDP/DNDP I/Branch I
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Analysis (EA)	N/A	

SUBMISSIONS REVIEWED (SD #)	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SD#: 0000	Received: 9-Jun-2016	All
SD#: 0001	Received: 24-Jun-2016	Drug Product
SD#: 0006	Received: 26-Jul-2016	Drug Substance, Facility
SD#: 0007	Received: 27-Jul-2016	Drug Substance
SD#: 0010	Received: 25-Aug-2016	Drug Product
SD#: 0012	Received: 6-Sep-2016	Drug Product
SD#: 0014	Received: 11-Nov-2016	Drug Product
SD#: 0020	Received: 17-Jan-2016	Drug Substance, Facilities
SD#: 0021	Received: 17-Jan-2017	Biopharmaceutics
SD#: 0023 (correction to SD#: 0022)	Received: 23-Jan-2017	Drug Substance, Drug Product
SD: 0024	Received: 23-Jan-2017	Biopharmaceutics

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II		(b) (4)	Adequate	12/1/2016	Reviewed by M. Cooper
	II			Adequate		Reviewed by R. Frankewich for NDA but supplier withdrawn by applicant.
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	

[1] Adequate information in application or no changes to information since previous reviews.

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	(b) (4)	
IND	119258	BA/BE studies to support the current NDAs 208684 and 208585 for Deflazacort tablets and oral suspension, respectively
NDA	208685	Application for Deflazacort 208684 tablet formulation

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The Office of Product Quality (OPQ) review team recommends that the Agency **Approve** NDA 208684 for Emflaza® (deflazacort) tablets. From a quality perspective, the application, as amended, provides adequate information to ensure that the applicant can consistently manufacture a product that is suitable for use by the intended patients.

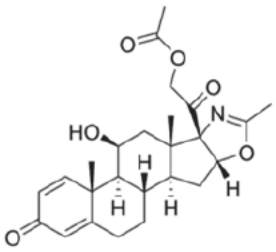
II. Summary of Quality Assessments

A. Product Overview

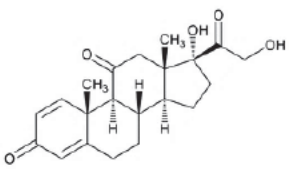
Duchenne muscular dystrophy (DMD) is a rare recessive X-linked disorder that results in progressive muscle weakness and loss of muscle mass, loss of movement, and ultimately death. The disease is caused by mutations in *DMD*, the gene encoding dystrophin, a sarcolemma protein critical to the structural stability of myofibers in skeletal and cardiac muscle. Dystrophin mutations induce a shift in the open reading frame of the dystrophin transcript, leading to the absence of functional dystrophin protein.

One drug, eteplirsen, was approved via the accelerated approval pathway for treatment of DMD in September 2016. Use of eteplirsen, an antisense oligonucleotide that targets specific *DMD* mutations, is limited to a small subset of patients and there is limited clinical evidence of effectiveness. Otherwise, treatment is limited to off-label use of corticosteroids such as prednisone to delay loss of muscle strength and supportive measures.

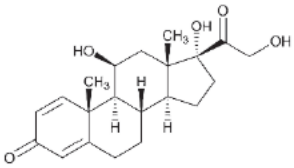
The applicant proposes use of deflazacort, a synthetic glucocorticosteroid structurally similar to prednisone and prednisolone, for treatment of patients with Duchenne muscular dystrophy. Deflazacort is an acetate ester prodrug; the active moiety is the 21-hydroxy metabolite.



Deflazacort



Prednisone



Prednisolone

Deflazacort was first marketed outside the US, under the trade name Calcort, in 1982. It is currently available in several countries as tablets or oral suspension for treatment of a variety of indications responsive to glucocorticoids. (b) (4) Although physicians frequently use deflazacort as an alternative to prednisone to treat patients with DMD, it is not approved for this indication in any country.

Marathon Pharmaceuticals has developed an immediate release tablet that is qualitatively similar to the Calcort tablets marketed by Sanofi-aventis. Under NDA 208684, the applicant proposes marketing of tablets containing 6 mg, 18 mg, 30 mg or 36 mg deflazacort for treatment of DMD.

Proposed Indication(s) including Intended Patient Population	Treatment of patients with Duchenne muscular dystrophy. The patient population is expected to be males ranging in age from children to young adults.
Duration of Treatment	Chronic
Maximum Daily Dose	The recommended dose (b) (4)
Alternative Methods of Administration	Deflazacort tablets may be crushed and mixed with applesauce. The mixture should be consumed immediately after preparation. The applicant proposes an oral suspension under NDA 208685. There are no other alternative routes of administration.

B. Quality Assessment Overview

Drug Substance

Deflazacort is a white (b) (4) powder that is poorly soluble in water and has a relatively high melting point between 254°C and 256°C. It is stable in the solid state (b) (4)

(b) (4)

The bulk active ingredient (API) used to manufacture commercial product will be supplied by (b) (4). Due to its poor solubility, the API is (b) (4). Information regarding the characterization, manufacture, and control of the API is incorporated by cross-reference to (b) (4) drug master file (DMF) (b) (4) The DMF has been reviewed and deemed adequate to support approval of the NDA. [Refer to M. Cooper review dated 12/1/2016.] The NDA itself includes a summary of general properties of deflazacort and the drug product manufacturer's acceptance specification, with associated analytical procedures and method validation. The information provided in the NDA is adequate.

The original NDA submission provided for a second supplier, (b) (4) as the primary source of API for Deflazacort tablets. (b) (4) provided API used for clinical studies under IND 119258 and manufacture of some stability batches. (b) (4) DMF (b) (4) was reviewed and deemed acceptable. [Refer to R. Frankewich review dated 12/6/2016.] The information provided in the NDA is adequate and the applicant has provided data to support equivalence of API (b) (4). However, due to concerns about a (b) (4) contract manufacturer, the applicant has withdrawn (b) (4) as a supplier for commercial manufacture. The review team has determined that the contract manufacturer in question did not produce any materials used to support development of Deflazacort tablets. Thus, there is no material impact on the validity of investigational studies conducted using (b) (4) sourced API.

Drug Product

The proposed products are immediate-release tablets that contain 6 mg, 18 mg, 30 mg, or 36 mg deflazacort per tablet. The tablets contain conventional pharmaceutical excipients, i.e., colloidal silicon dioxide, lactose monohydrate, magnesium stearate, and pre-gelatinized corn starch, all of which comply with compendial standards.

Deflazacort tablets are manufactured from (b) (4)

The data provided support the

lack of any significant effect on content uniformity or dissolution behavior over the ranges studied.

The proposed regulatory specification for Deflazacort tablets includes test parameters that are typical for an immediate-release tablet. In general, the analytical procedures are straightforward and supported by adequate method validation studies. One issue, which does not affect the overall recommendation, was identified during the review. The proposed dissolution medium for Deflazacort tablets contains 0.3% sodium lauryl sulfate (SLS). (b) (4)

Deflazacort tablets are packaged in (b) (4) HDPE bottles with (b) (4) closures. The 6 mg Deflazacort tablets are packaged in 100-count bottles; the remaining strengths are packaged in 30-count bottles. Based on stability data provided in the application, a 36-month shelf life is granted for product stored at controlled room temperature.

Methods Verification

The HPLC methods for determination of assay and related substances in the bulk API and Deflazacort tablets were submitted to the Division of Pharmaceutical Analysis (DPA) for verification. DPA has determined that the methods are suitable for regulatory use with minor modifications. As the methods verification process is ongoing, standard language regarding cooperation with methods verification should be included in the action letter.

Facilities

All facilities that will be involved in commercial manufacture and testing of Deflazacort and Emflaza® (deflazacort) tablets are currently acceptable.

C. Special Product Quality Labeling Recommendations

There are no special labeling recommendations.

D. Final Risk Assessment for Deflazacort Tablets

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, Stability	Impurities due to: excipient reactions, oxidation, hydrolysis	L	Excipients were chosen based on their previous use in Calcort tablets marketed outside the US and compatibility verified during formulation development.	Acceptable	
Content uniformity	Low dose, particle size/shape, segregation, flow property	M	The tablet manufacturer uses (b) (4)	Acceptable	
Physical (solid state) stability	Formulation, process parameters, moisture	L	Deflazacort exists (b) (4) form. Tablet manufacture involves (b) (4)	Acceptable	
Microbial limits	Formulation, raw materials, process parameters, moisture	L	Routine controls for high risk raw materials (b) (4) Testing per USP <61> and <62> at release and on stability.	Acceptable	
Dissolution	Particle size, moisture, hardness, size, shape, film coat, formulation, process parameters	M	Drug substance is (b) (4)	Acceptable	

Martha
Heimann

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(b) (4)

Reviewer's Assessment: Adequate

The applicant's claim for categorical exclusion is acceptable and adequate for approval of the application.

Labeling

Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EMFLAZA™ safely and effectively. See full prescribing information for EMFLAZA.

EMFLAZA™ (deflazacort) tablets, for oral use
EMFLAZA™ (deflazacort) oral suspension
Initial U.S. Approval: 2017

----------INDICATIONS AND USAGE----------
EMFLAZA is a corticosteroid indicated in the treatment of (b) (4) Duchenne muscular dystrophy. (1)

----------DOSAGE AND ADMINISTRATION----------
(b) (4)

----------DOSAGE FORMS AND STRENGTHS----------
- Tablets: 6 mg, 18 mg, 30 mg, and 36 mg (3)
- Oral Suspension: 22.75 mg/mL (b) (4) (3)

----------CONTRAINDICATIONS----------
- Hypersensitivity to deflazacort or any of the inactive ingredients in EMFLAZA (4)

----------WARNINGS AND PRECAUTIONS----------
(b) (4)

(b) (4)

- Behavioral and mood disturbances: May include euphoria, insomnia, mood swings, personality changes, severe depression, and psychosis. (b) (4) (5.5)

(b) (4)

- Ophthalmic effects: May include cataracts, infections, and glaucoma. Monitor intraocular pressure if (b) (4) is continued for more than 6 weeks (5.7)

(b) (4)

----------ADVERSE REACTIONS----------
- Most common adverse reactions (b) (4) 10% for EMFLAZA) are Cushingoid, (b) (4) weight increased, central obesity, (b) (4) and increased appetite. (6.1)

----------DRUG INTERACTIONS----------
(b) (4)

To report SUSPECTED ADVERSE REACTIONS, contact Marathon Pharmaceuticals, LLC at 1-866-562-4620 or DrugSafety@propharmagroup.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

(b) (4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 8/2016

Reviewer's Assessment: *Adequate*

The package insert contains the proprietary and established name. The dosage form and strength is also present on the label. This is acceptable.

(b) "Full Prescribing Information" Section

3 DOSAGE FORMS AND STRENGTHS

Tablets

- 6 mg: White and round with "6" debossed on one side
- 18 mg: White and round with "18" debossed on one side
- 30 mg: White and oval with "30" debossed on one side
- 36 mg: White and oval with "36" debossed on one side

Oral Suspension

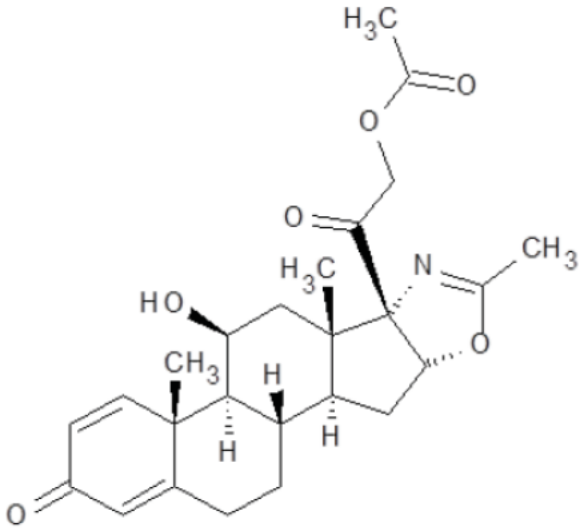
- 22.75 mg/mL: (b) (4) whitish suspension (b) (4)

Reviewer's Assessment: ***Adequate***

The dosage form and strength section contains the dosage form, strength, and identifying characteristics of the dosage form. However, the label contains excipient information which is not appropriate for this section.

11 DESCRIPTION

The active ingredient in EMFLAZA is deflazacort (a corticosteroid). Corticosteroids are adrenocortical steroids, both naturally occurring and synthetic. The molecular formula for deflazacort is $C_{25}H_{31}NO_6$. The chemical name for deflazacort is (11β,16β)-21-(acetyloxy)-11-hydroxy-2'-methyl-5'H-pregna-1,4-dieno[17,16-d]oxazole-3,20-dione, and the structural formula is:



Deflazacort is a white to off white, odorless fine powder and has a molecular weight of 441.517. Deflazacort is freely soluble in acetic acid and dichloromethane and soluble in methanol and acetone.

EMFLAZA is an immediate-release tablet in strengths of 6, 18, 30 and 36 mg and an immediate-release oral suspension in a strength of 22.75 mg/mL. Each tablet contains deflazacort and the following inactive ingredients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, and pre-gelatinized corn starch. The oral suspension contains deflazacort and the following inactive ingredients: acetic acid, aluminum magnesium silicate, benzyl alcohol, carboxymethylcellulose sodium, polysorbate 80, purified water, and sorbitol.

Reviewer's Assessment: ***Adequate***

The description section contains the proprietary and established name, the dosage form, drug product excipients, route of administration, active moiety expression of strength, therapeutic class, chemical name, structural formula, molecular weight.

The statement of strength may need to be reworded.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

EMFLAZA Tablets

- 6 mg are white, round with "6" debossed on one side. They are supplied as follows:

NDC 42998-501-01 Bottle of 100 tablets

- 18 mg are white, round with "18" debossed on one side. They are supplied as follows:
  NDC 42998-502-03 Bottle of 30 tablets

- 30 mg are white, oval with "30" debossed on one side. They are supplied as follows:
  NDC 42998-503-03 Bottle of 30 tablets

- 36 mg are white, oval with "36" debossed on one side. They are supplied as follows:
  NDC 42998-504-03 Bottle of 30 tablets

EMFLAZA Oral Suspension

- 22.75 mg/mL is a whitish colored suspension. Supplied as 13 mL in a 20 mL bottle packaged with two 1 mL oral dispensers.
  NDC 42998-505-21

Reviewer's Assessment: ***Adequate***

The how supplied section contains the following information: dosage form, strength, available units, and the identification of dosage form. This is acceptable.

16.2 Storage and Handling

Store at 20 to 25°C (68 to 77°F). See USP controlled room temperature.

Reviewer's Assessment: ***Adequate***

The storage and handling information is included; however, the excursion temperatures are not included.

Manufactured for:
Marathon Pharmaceuticals, LLC
Northbrook, IL 60062 USA

EMFLAZA Oral Suspension made in Spain

PC####X Month Year

(b) (4)

MARATHON
PHARMACEUTICALS, LLC

EMFLAZA™ (b) (4) rademarks of Marathon Pharmaceuticals, LLC.

Reviewer's Assessment: ***Adequate***

This section contains the (b) (4) name. However, it contains the phrase, (b) (4)

Immediate Container Label

(b) (4)

Reviewer's Assessment: ***Adequate***

The label complies with regulatory requirements from a CMC perspective. It bears the "Rx only" statement, the NDC number, name of manufacturer, lot number, expiration date, net contents, strength, bar code, and the name (proprietary and established). Each strength is differentiated based on color: 6 mg is (b) (4) 18 mg is (b) (4) 30 mg is (b) (4) and 36 mg is (b) (4)

The label contains the phrase (b) (4) which may not be required.

Carton Labeling

(b) (4)

Reviewer's Assessment: ***Adequate***

The label complies with regulatory requirements from a CMC perspective. It bears the "Rx only" statement, the NDC number, name of manufacturer, lot number, expiration date, net contents, bar code, strength, and the name (proprietary and established). Each strength is differentiated based on color: 6 mg is (b) (4) 18 mg is (b) (4), 30 mg is (b) (4), and 36 mg is (b) (4).

Methods Verification Package - None

Reviewer's Assessment: Not Applicable

Comparability Protocols - None

Reviewer's Assessment: Not Applicable

Post-Approval Commitments

Reviewer's Assessment: Not Applicable

Lifecycle Management Considerations

Reviewer's Assessment: Not Applicable

List of Deficiencies - None

Primary Drug Product Reviewer Name and Date: Andrei Ponta, Ph.D.

Secondary Reviewer Name and Date:

Wendy Wilson- Lee

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Andrei Ponta

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BIOPHARMACEUTICS

NDA: 208684-ORIG-1

Drug Product Name/Strength: EMFLAZA™ (deflazacort) Tablets/6 mg, 18 mg, 30 mg, 36 mg

Route of Administration: Oral

Applicant Name: Marathon Pharmaceuticals LLC.

Product Background:

EMFLAZA™ is a corticosteroid indicated in the treatment of patients with Duchenne muscular dystrophy (DMD). The recommended dose of EMFLAZA is 0.9 mg/kg/day administered orally as a single daily dose. EMFLAZA tablets can be taken with or without food. The drug product can be administered whole or crushed and taken immediately after being mixed in applesauce.

Different Drug Product Formulations and Manufacturers:

(b) (4) are former and current manufacturing sites for different deflazacort tablet formulations. In 2014, the manufacturing process and analytical test methods for the deflazacort 6 mg tablets were transferred from (b) (4) which is designated as the commercial manufacturer of deflazacort tablets.

(b) (4) have the same formulations and manufacturing process. (b) (4)

REVIEW SUMMARY:

Submission: *Marathon Pharmaceuticals LLC., submitted this NDA for EMFLAZA™ (deflazacort) Tablets 6 mg, 18 mg, 30 mg, 36 mg under section 505 (b)(1) of the Federal Food, Drug, and Cosmetic Act.*

Reviewer's Assessment:

Dissolution Test: *The following dissolution method and acceptance criterion are acceptable:*

Apparatus:	*USP Type II (Paddle)*
Speed:	*50 rpm*
Medium:	*50 mM NaH_2PO_4 buffer + 0.3% SLS, pH 6.8*
Volume:	*500 mL*
Temperature:	*37 °C*
Dissolution acceptance criterion:	*Q= (b) (4) % in 15 minutes*

(b) (4)

Biowaiver Request: *Based on the provided data, the biowaiver request for the proposed drug product 6 mg, 18 mg, and 30 mg tablet strengths is granted.*

Recommendation: *From the Biopharmaceutics perspective, NDA 208684 for EMFLAZA™ (deflazacort) Tablets 6 mg, 18 mg, 30 mg, 36 mg is recommended for* ***APPROVAL****.*

List Submissions being reviewed:

- Original NDA 208684 submitted on Jun 09, 2016.
- Applicant's Response dated Jan 17, 2017 to the Information Request dated Jan 10, 2017.
- Applicant's Quality Information Amendment dated Jan 19, 2017.

Highlight Key Outstanding Issues from Last Cycle: None. This is the first review cycle.

Concise Description of Outstanding Issues: None.

BCS Designation

The Applicant did not request a BCS designation for either deflazacort drug substance or tablets.

Solubility: Deflazacort API is practically insoluble in water (0.1 mg/mL at 37 °C). It is soluble in DMSO (88 mg/mL at 25 °C) and ethanol (12 mg/mL at 25 °C). It is slightly soluble in methanol and acetone. It is freely soluble in acetic acid and dichloromethane.

Table 1. Solubility of deflazacort in different solutions (Page 97, Module 2.7.1).

	Solubility results - 37°C - magnetical stirring 1H and 24H Filtration on glass fiber filter 1µm				
		Deionized water	USP buffer pH 1.2	USP buffer pH 4.5	USP buffer pH 6.8
[c] mg/mL	1 Hour	0.119	0.521	0.116	0.100
	24 Hour	0.141	0.522	0.137	0.139

Permeability: No permeability data of deflazacort are provided in this NDA.

Dissolution Method and Acceptance Criterion

Dissolution method:

The proposed dissolution method for deflazacort tablets 6 mg, 18 mg, 30 mg, 36 mg is as follows (Page 5, Module 3.2.P.5.2.2):

Apparatus:	USP apparatus II (Paddle)
Paddle Speed:	50 rpm
Medium:	50 mM NaH_2PO_4 buffer + 0.3% SLS, pH 6.8
Volume:	500 mL
Temperature:	37 ºC

Rationale of dissolution medium pH: With respect to the selection of the dissolution medium, 0.01 N HCl (500 mL) was initially tested for the deflazacort 6 mg tablets by (b) (4) (Page 69, Module 2.7.1). (b) (4)

Therefore, the use of sodium phosphate buffer at pH 6.8 is acceptable.

Rationale for using the surfactant, SLS, in the dissolution medium: With respect to the use of surfactant in the dissolution medium, it is reported by the Applicant that sodium lauryl sulfate (SLS) concentrations of 0.3% (b) (4) ensure adequate and comparable solubility of deflazacort.

Given the rapid dissolution (more than (b) (4)% dissolved in 15 minutes) of the proposed deflazacort tablets 6 mg, 18 mg, 30 mg, 36 mg manufactured at (b) (4) (Table 3) tested with and without surfactant, the Applicant was asked in an Information Request dated Jan 10, 2017 to provide the rationale for the proposed SLS concentration (b) (4)

In the Applicant's Response dated Jan 17, 2017 to this Information Request, the Applicant stated that (b) (4)

Since the dissolution of all strengths of [redacted] tablets is fast and not affected by SLS concentration, the use of 50 mM NaH_2PO_4 buffer, pH 6.8 without SLS as the dissolution medium [redacted] for the quality control and stability testing of Deflazacort Tablets.

Therefore, on Jan 19, 2017, a teleconference was held between the FDA and Marathon to discuss the need of including SLS in the dissolution medium, based on the observation of very rapid dissolution (more than [redacted]% dissolved in 15 minutes) of the proposed deflazacort tablets manufactured at [redacted] (Table 3) tested without surfactant. [redacted]

Reviewer's Assessment: The proposed dissolution method (USP apparatus II (Paddle)/50 rpm/500 mL of 50 mM NaH_2PO_4 buffer + 0.3% SLS, pH 6.8) is acceptable.

Although the dissolution medium of 50 mM sodium phosphate buffer at pH 6.8 without SLS is more adequate for this drug product, the use of the dissolution medium with SLS was accepted by this Reviewer [redacted]

Effect of critical quality attributes on the drug release profiles:

Hardness: The Applicant reports that the proposed dissolution method [redacted] owever, based on Figure 1, more than [redacted]% is dissolved in 15 minutes (Page 81, Module 2.7.1).

Figure 1. Influence of tablet hardness on the dissolution profile of deflazacort tablets, 18 mg (Page 81, Module 2.7.1).

Particle Size: The Applicant reports that the dissolution method (b) (4) igure 2 supports the discriminating ability of the dissolution method with respect to API particle size.

Figure 2. Influence of API particle size on the dissolution profile of deflazacort tablets, 6 mg (Page 82, Module 2.7.1).

Formulation Changes: The Applicant states that the proposed dissolution method is not discriminating for the relative amount of (b) (4) (Page 83, Module 2.7.1).

Reviewer's Assessment: The Applicant reports that the proposed dissolution method is discriminating for tablet hardness and API's particle size. However, the proposed dissolution method is not discriminating for tablet hardness and the evaluated formulation changes; but the method is discriminating for the changes in deflazacort particle size distribution. Overall, this Reviewer considers that the proposed dissolution method is adequate for quality control purposes.

Dissolution acceptance criterion:

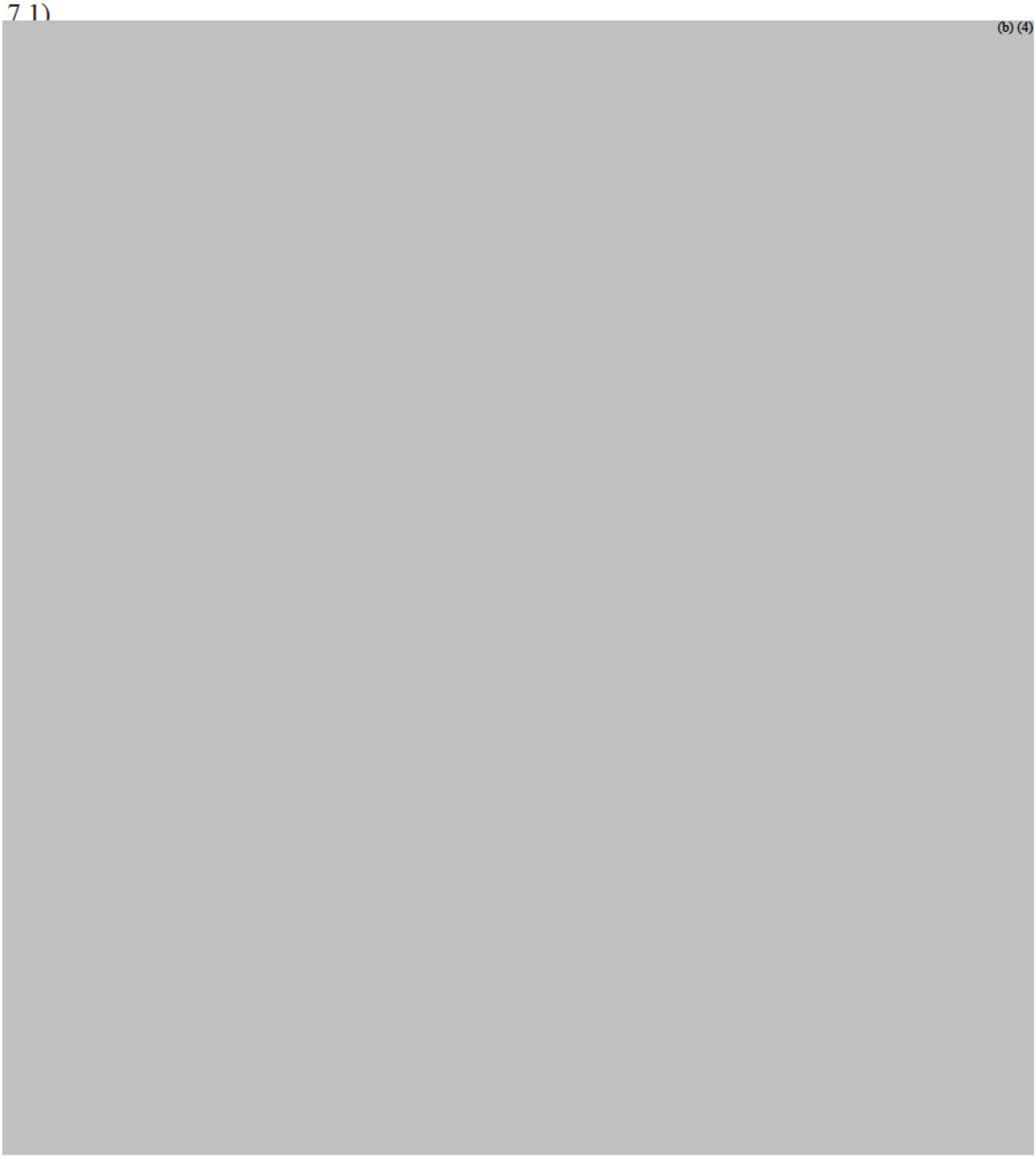
The Applicant's proposed dissolution acceptance criterion for deflazacort tablets 6 mg, 18 mg, 30 mg, and 36 mg is:
NLT (b) (4)% of the labeled amount of deflazacort dissolved in 15 minutes.

Table 2. Different deflazacort formulations used for clinical studies mainly manufactured at (b) (4) (Page 9, Module 2.7.1 and Page 8, Module 3.2.P.5.4). (b) (4) is the commercial manufacturer of deflazacort tablets.

(b) (4)

Table 3. Dissolution profiles of the proposed Deflazacort Tablets manufactured at (b) (4), 6 mg (biobatch no.: B150180), 18 mg (biobatch no.: B150186), 30 mg (biobatch no.: B150188), and 36 mg (biobatch no.: B150182) (Pages 13–16, Module 2.7.1)

(b) (4)



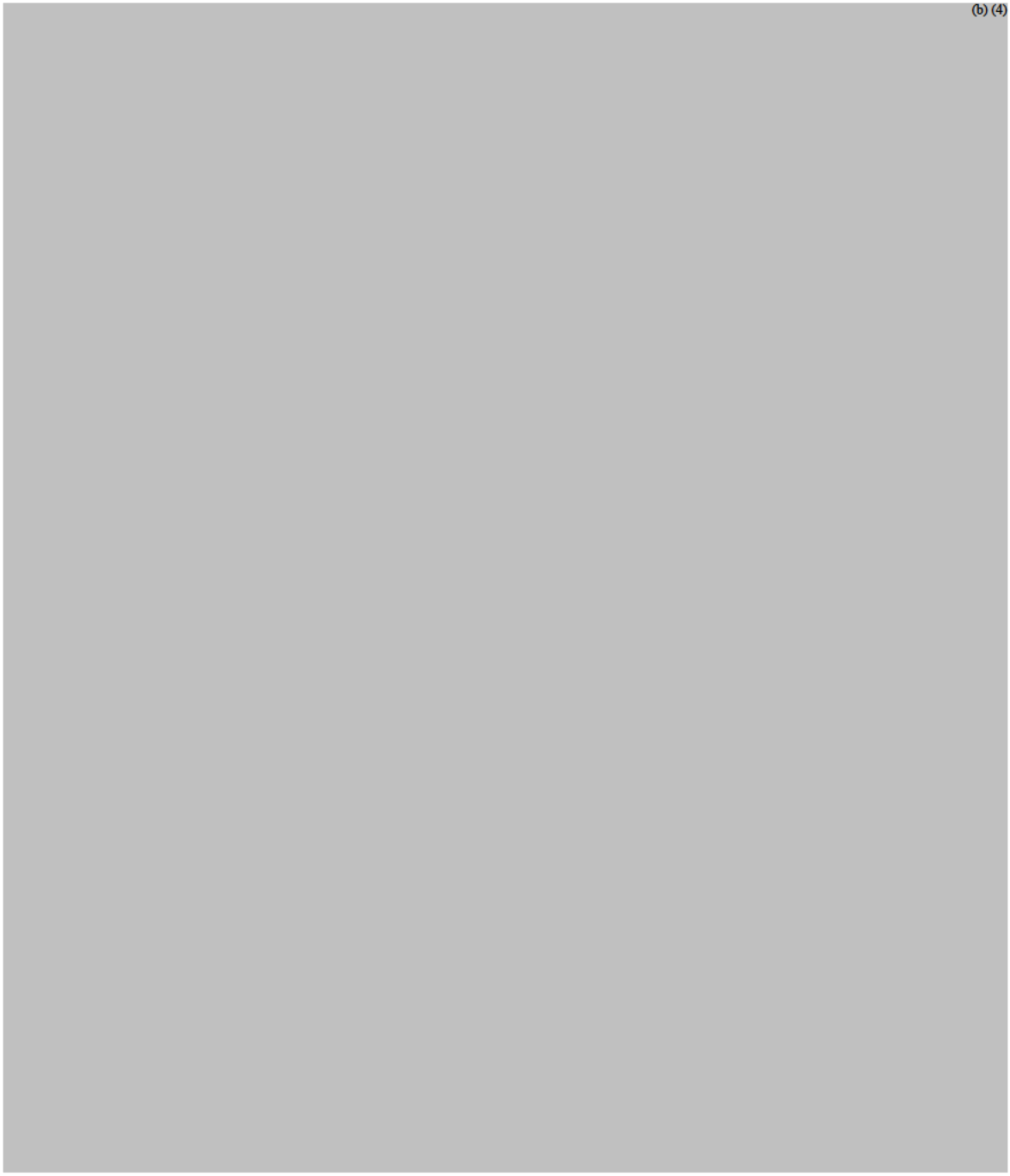

(b) (4)

Figure 3. Dissolution profile similarity for Deflazacort Tablets 6 mg, 18 mg, and 30 mg, 36 mg manufactured a (b) (4) using the proposed dissolution method (Page 85, Module 2.7.1).

The dissolution profiles of different strengths of deflazacort Tablets manufactured at (b) (4) are similar using the proposed dissolution method (Figure 3) and the rapid dissolution profiles for (b) (4) tablets (about (b) (4)% dissolved in 15 minutes) were not affected by the SLS concentrations of (b) (4) 0.3% (Table 3).

Reviewer's Assessment: Based on the provided dissolution data, the proposed dissolution acceptance criterion (Q= (b) (4)% in 15 minutes) is acceptable.

Dissolution stability data:

The Applicant provided dissolution data at 15 (b) (4) minutes of stability samples using the proposed dissolution method in the presence of surfactant SLS (Module 3.2.P.8). There are no apparent changes in the Applicant's provided dissolution data of the stability samples in various storage conditions.

Bridging of Products

Reviewer's Assessment: Different deflazacort formulations manufactured at different sites have been used in clinical studies (Figure 4, DP=drug product).

Figure 4. Different deflazacort tablet formulations used in clinical studies (Page 9, Module 2.7.1 and Page 8, Module 3.2.P.5.4).

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Biowaiver Request

Reviewer's Assessment: The Applicant requested a waiver for the requirement to provide data from in vivo characterization of the 6 mg, 18 mg, and 30 mg tablet strengths of the proposed drug product (In vivo Characterization Waiver Request, Module 1.12.5). The different strengths of deflazacort tablets (b) (4) (Table 4). The dissolution profiles of the 6 mg, 18 mg and 30 mg tablet strengths are comparable (b) (4) to the 36 mg tablet strength (b) (4) In addition, more than (b) (4)% of the drug is dissolved within the first 15 minutes for all tablet strengths, demonstrating similarity

between different strengths (Page 2, In vivo Characterization, Module 1.12.5). Based on the provided data, the biowaiver request for the proposed drug product 6 mg, 18 mg, and 30 mg tablet strengths is granted.

Table 4. Quantitative and qualitative composition of deflazacort tablets 6, 18, 30 and 36 mg.

Component	Quantity in mg per Tablet/Dosage Strength				Quantity (%)	Function	Quality Standard
	6 mg	18 mg	30 mg	36 mg			
Deflazacort, (b) (4)	(b) (4)				(b) (4)	Active ingredient	In-house
Lactose Monohydrate						(b) (4)	NF
Pre-gelatinized Corn Starch							NF
Colloidal Silicon Dioxide							NF
Magnesium Stearate							NF
Total					100.0		

(b) (4)

Figure 11. Comparative dissolution profiles of the proposed Deflazacort Tablets 6 mg, 18 mg, 30 mg, and 36 mg using the proposed dissolution method.

REVIEWER'S OVERALL ASSESSMENT

Dissolution Test:

Method: *The proposed dissolution method using USP apparatus II (Paddle)/50 rpm/500 mL 50 mM NaH_2PO_4 buffer + 0.3% SLS, pH 6.8* ***is acceptable*** *for the quality control of the proposed immediate release drug product, EMFLAZA™ Tablets 6 mg, 18 mg, 30 mg, 36 mg as part of the batch release and stability testing.* (b) (4)

(b) (4)

Acceptance Criterion: *The proposed dissolution acceptance criterion of NLT (b) (4)% (Q) of the labeled amount of deflazacort dissolved in 15 minutes for the proposed EMFLAZA™ Tablets is* ***acceptable****.*

Biowaiver Request:

The provided pharmacokinetic data, formulation (b) (4) *similar multimedia dissolution profile data support the biowaiver request for the proposed drug product 6 mg, 18 mg, and 30 mg tablet strengths and therefore the biowaiver is granted.*

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 208684 for EMFLAZA™ (deflazacort) Tablets 6 mg, 18 mg, 30 mg, 36 mg is recommended for ***APPROVAL****.*

Primary Biopharmaceutics Reviewer Name and Date:

Yang Zhao, Ph.D. *01/23/2016*
Biopharmaceutics Primary Reviewer
Division of Biopharmaceutics
Office of New Drug Products, OPQ

Secondary Reviewer Name and Date:
I concur with Dr. Yang Zhao's assessment and recommendation.

Okpo Eradiri, Ph.D. *01/24/2017*
Biopharmaceutics Lead (Acting)
Division of Biopharmaceutics
Office of New Drug Products, OPQ

Tertiary Reviewer Name and Date:
I concur with Dr. Yang Zhao's assessment and recommendation.

Angelica Dorantes, Ph.D. *01/27/2017*
Biopharmaceutics Branch Chief (Acting)
Division of Biopharmaceutics
Office of New Drug Products, OPQ

Okponanabofa Eradiri

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Yang Zhao

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 24, 2017

FROM: Raymond P. Frankewich, Ph.D., Review Chemist, OPQ/ONDP/DNDAPI/Branch I

THROUGH: Kasturi Srinivasachar, Ph.D., Branch Chief, OPQ/ONDP/DNDAPI/Branch I

SUBJECT: Evaluation of Method Verification Results and Conclusions for NDA 208684 & 208685

TO: NDA 208684 and NDA 208685

Reviews for NDA 208684 and 208685 for Drug Product were finalized on December 8, 2016, and for Drug Substance on December 9, 2016. No deficiencies were established for Emflaza® (Deflazacort) Tablets (NDA 208684) and Emflaza® (Deflazacort) oral suspension (NDA 208685) in those reviews.

A Methods Verification Request was submitted for NDA 208684 & 208685 on July 7, 2016. Verification was requested for the following analytical procedures:

- HPLC Assay, Related Substance and Identification Test Method for deflazacort, (b) (4)
- HPLC Assay, Related Substance and Identification Test Method for deflazacort, (b) (4)
- Deflazacort Assay and Impurities, Identification by HPLC and Identification by UV for Deflazacort Tablets

Method Verification Report, dated October 31, 2016, was submitted the same day. The report was authored by staff from CDER/OPO/OTR/DPA (DPA). The conclusions of the report were as follows:

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

- *HPLC assay, related substances and identification test method for deflazacort* (b) (4)
- *HPLC assay, related substances and identification test method for deflazacort* (b) (4)

The following methods were evaluated and are acceptable with modifications for quality control and regulatory purposes:

- *Deflazacort assay and impurities, identification by HPLC and identification by UV for deflazacort tablets*

It the report it is noted that for the method used for the tablets, an unidentified impurity peak is observed at (b) (4) minutes (RRT (b) (4)) when one of the standard preparations is chromatographed. The level of the impurity was (b) (4)%, which exceeds the acceptance criterion for Individual

Unidentified substances in the Related Substances section of the specification for drug product release (which is ≤ (b)(4)%). The report indicates that this unidentified impurity peak does appear in chromatograms in the validation report provided by the applicant. The following description of the unidentified impurity peak is excerpted from the report.

The firm does not identify this peak in Figure 2, page 12. However, it is present as an unknown impurity throughout the validation report. Sample solution stability studies on pg. 49-50 of the validation report show an increase over time at ambient conditions. By (b)(4) hours, the sample is twice the specification limit. DPA analyzed the sample within 12 hours of preparation at ambient conditions. The method does not include a statement about stability at room temperature while the analyst is preparing the sample. The only note states " ... sample solutions were shown to be stable (b)(4) hours when stored in refrigerator, protected by light."

The problem appears to be that the unidentified impurity increases significantly following standard preparation, indicating the standard preparation is less stable than ideal. It appears that this might be addressed by the applicant including a statement in the analytical procedure description to use the standard and sample preparations within a particular period of time. It is noted in the experimental results that the peak at RRT (b)(4) appeared in the chromatogram of the standard preparation. However, in the chromatograms provided in the analytical procedure description provided in sec. 3.2.P.5.2 of the NDA (and the validation report provided in sec. P.5.3) this peak appears in the chromatograms of both the standard and sample preparations.

In addition to this, it is noted that when the method for assay, related substances and identification by HPLC for deflazacort (b)(4) was performed, deflazacort did not dissolve in diluent (b)(4) as required in the method. By contrast, the method for assay, related substances and identification by HPLC for deflazacort (b)(4) specifies dissolving deflazacort (b)(4) before adding diluent. It was indicated that with the (b)(4) method, deflazacort did dissolve (b)(4). To resolve this issue, DPA recommended that instructions be included to dissolve deflazacort (b)(4) before adding diluent.

Consistent with the recommendations in the report, the following items were sent to the NDA applicant (Marathon Pharmaceuticals LLC) in an electronic communication dated January 10, 2017.

It is requested that the following issues regarding the analytical procedures used for control of deflazacort drug substance and Emflaza® (deflazacort) Tablets be addressed. These analytical procedures were submitted in NDA 208684 for Emflaza® (deflazacort) Tablets.

Regarding the analytical procedure for Deflazacort Assay and Impurities, Identification by HPLC and Identification by UV for Deflazacort Tablets:

1. *Identify the unknown peak which appears at RRT (b)(4) (approximately (b)(4) minutes) in both standard and sample preparations.*

2. *Since the unknown peak at RRT (b) (4) appears to increase after standard / sample solution preparation, amend the analytical procedure description with more specific information regarding solution stability. Specifically, include a statement in the analytical procedure description to use the standard and sample preparations within a particular period of time. A method verification study by FDA indicated that the peak at RRT (b) (4) was (b) (4)% (greater than the acceptance criterion for Individual Unidentified substances in the Related Substances section of the specification for drug product release ((b) (4)%)) when the standard solution was chromatographed within 12 hours of preparation.*

Regarding the analytical procedure for HPLC Assay, Related Substance and Identification Test Method for deflazacort, (b) (4):

3. *Include in the descriptions of preparations of sample and standard solutions instructions to dissolve deflazacort (b) (4) before adding diluent. FDA method verification study indicated that deflazacort did not dissolve in diluent (b) (4) as instructed in the procedure description.*

Response was received in an Amendment to NDA 208684 dated January 17, 2017. Response to each item, followed by a brief evaluation of each response, is provided below.

Item #1. Identify the unknown peak which appears at RRT (b) (4) (approximately (b) (4) minutes) in both standard and sample preparations.

Response. The unknown peak which appears at RRT (b) (4) (approximately (b) (4) minutes) in both sample and standard preparations is discussed in Module 3.2.P.5.5 Characterization of impurities. Efforts are still ongoing to definitively identify this impurity. We are attempting to isolate the unknown compound from sample preparations. This work is not complete and efforts to isolate this unknown will continue. (See Module 3.2.P.5.5 Characterization of impurities, Attachment 1).

Evaluation. In sec. P.5.5 information collected regarding the unknown impurity at RRT (b) (4) is summarized. Some of the information is provided below.

Molecular Weight: (b) (4)

Possible Structures:

(b) (4)

Text from sec. P.5.5:
This impurity was detected in aged sample solutions and also during the forced degradation study in 1N HCl. Small amounts are detected in deflazacort tablet samples. Efforts are still ongoing to definitively identify this impurity. The mass spectrum of the HPLC peak, which was detected at retention time (b) (4) relative to the main component in the method used to control degradation products, included a protonated molecule signal at (b) (4) greater than that of deflazacort. This suggests that the unknown peak results from the addition of a (b) (4) group to the deflazacort structure. It is thought that the most likely structure is (b) (4) deflazacort shown above, but other possible structures, also shown above can't be ruled out based on the MS data. However, efforts to synthesize this compound have failed to produce samples that are stable enough to confirm identity.

It is not expected that any of the proposed structures would exhibit unusual toxicity, since the molecules contain no structural alerts. It is noted that this impurity has been evaluated as part of the drug product, and its levels are expected to be below the acceptance criterion for Individual Unidentified impurities ((b) (4)%). The response is acceptable and no further action is taken at this time.

Item #2. Since the unknown peak at RRT (b) (4) appears to increase after standard / sample solution preparation, amend the analytical procedure description with more specific information regarding solution stability. Specifically, include a statement in the analytical procedure description to use the standard and sample preparations within a particular period of time. A method verification study by FDA indicated that the peak at RRT (b) (4) was (b) (4)% (greater than the acceptance criterion for Individual Unidentified substances in the Related Substances section of the specification for drug product release ((b) (4))) when the standard solution was chromatographed within 12 hours of preparation.

Response. Storage conditions and times are for both the standard and the sample solutions are present both in the test method at the manufacturing site and the registration document, Module 32P52 Assay, impurities and identification by HPLC in the notes for the standard and sample solution preparation, sections 5 and 6. The notes for the standard and sample solution stipulate that the sample and standard solutions are protected from light and that a refrigerated auto-sampler is used to ensure the stability of the standard and sample solutions during analysis.

Evaluation. Standard solution preparation instructions (section 5) include the following notation:

NOTE 3: The standard solution was shown to be stable for 22 days when stored in the refrigerator, protected from light.

Sample preparation instuctions (section 6) include the following notation:

NOTE 2: The 6 mg, 18 mg and 30 mg and 36 mg sample solutions were shown to be stable for (b) (4) hours when stored in the refrigerator, protected from light.

The notations above clarify that the standard and sample solutions should be refrigerated and protected from light when stored. Response is acceptable. No further action is warranted at this time.

Item #3. Regarding the analytical procedure for HPLC Assay, Related Substance and Identification Test Method for deflazacort, (b) (4):
Include in the descriptions of preparations of sample and standard solutions instructions to dissolve deflazacort (b) (4) before adding diluent. FDA method verification study indicated that deflazacort did not dissolve in diluent (b) (4) as instructed in the procedure description.

Response. We will need to evaluate the change in the affected laboratories. Any change will need to be validated and submitted to the NDA prior to implementation.

Evaluation. The applicant has committed to evaluate the proposed change before amending the analytical procedure description. The applicant has committed to perform validation of the revised analytical procedure of necessary. Response is acceptable.

Kasturi Srinivasachar

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Raymond Frankewich

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Martha
Heimann

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Recommendation: Approve

NDA 208685
Review # 1

Drug Name/Dosage Form	Emflaza (Deflazacort) Oral Suspension
Strength	22.75 mg/mL
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Marathon Pharmaceuticals
US agent, if applicable	N/A

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/BRANCH
Drug Substance	Ray Frankewich	ONDP/DNDP I/Branch I
Drug Product	Andrei Ponta	ONDP/DNDP I/Branch I
Process	Mark Johnson	OPF/DPA/Branch I
Microbiology	Yuansha Chen	OPF/DMA/Branch I
Facility	Michael Shanks	OPF/DIA/Branch I
Biopharmaceutics	Yang Zhao	ONDP/DB/Branch I
Regulatory Business Process Manager	Dahlia A. Woody	OPRO/DPRBPM/Branch I
Application Technical Lead	Martha Heimann	ONDP/DNDP I/Branch I
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Analysis (EA)	N/A	

NDA 208685

SUBMISSIONS REVIEWED (SD #)	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SD#: 0000 (original NDA)	Received: 6/9/2016	All
SD#: 0002	Received: 7/1/2016	Drug Product
SD#: 0009	Received: 9/9//2016	Process
SD#: 0010	Received: 9/23/2016	Biopharmaceutics
SD#: 0011	Received: 9/30/2016	Drug Product, Process
SD#: 0012	Received: 10/5/2016	Drug Product
SD#: 0016	Received: 10/26/2016	Drug Substance, Process
SD#: 0018	Received: 12/05/2016	Drug Product
SD#: 0022	Received: 1/17/2017	Drug Substance, Facilities
SD#: 0024	Received: 1/23/2017	Drug Substance

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II			(b) (4)	12/1/2016	Reviewed by M. Cooper
	II					Reviewed by R. Frankewich for NDA but supplier withdrawn by applicant.
	III				N/A [1]	
	III				N/A [1]	
	III				N/A [1]	

[1] Adequate information in application or no changes to information since previous reviews.

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND		(b) (4)
IND	119258	BA/BE studies to support the current NDAs 208684 and 208585 for Deflazacort tablets and oral suspension, respectively
NDA	208685	Application for Deflazacort 208684 tablet formulation

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The Office of Product Quality (OPQ) review team recommends that the Agency **Approve** NDA 208685 for Emflaza® (deflazacort) oral suspension. From a quality perspective, the application, as amended, provides adequate information to ensure that the applicant can consistently manufacture a product that is suitable for use by the intended patients.

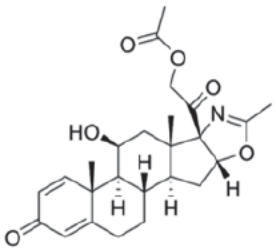
II. Summary of Quality Assessments

A. Product Overview

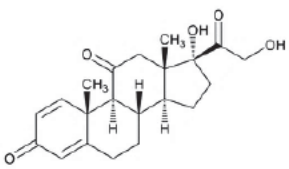
Duchenne muscular dystrophy (DMD) is a rare recessive X-linked disorder that results in progressive muscle weakness and loss of muscle mass, loss of movement, and ultimately death. The disease is caused by mutations in *DMD*, the gene encoding dystrophin, a sarcolemma protein critical to the structural stability of myofibers in skeletal and cardiac muscle. Dystrophin mutations induce a shift in the open reading frame of the dystrophin transcript, leading to the absence of functional dystrophin protein.

One drug, eteplirsen, was approved via the accelerated approval pathway for treatment of DMD in September 2016. Use of eteplirsen, an antisense oligonucleotide that targets specific *DMD* mutations, is limited to a small subset of patients and there is limited clinical evidence of effectiveness. Otherwise, treatment is limited to off-label use of corticosteroids such as prednisone to delay loss of muscle strength and supportive measures.

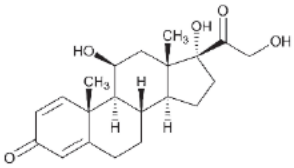
The applicant proposes use of deflazacort, a synthetic corticosteroid structurally similar to prednisone and prednisolone, for treatment of patients with Duchenne muscular dystrophy. Deflazacort is an acetate ester prodrug; the active moiety is the 21-hydroxy metabolite.



Deflazacort



Prednisone



Prednisolone

Deflazacort was first marketed outside the US, under the trade name Calcort, in 1982. It is currently available in several countries as tablets or oral suspension for treatment of a variety of indications responsive to glucocorticoids. (b) (4) Although physicians frequently use deflazacort as an alternative to prednisone to treat patients with DMD, it is not approved for this indication in any country.

Under NDA 208685, Marathon Pharmaceuticals proposes to market an oral suspension containing 22.75 mg/mL deflazacort. (b) (4) Marathon has contracted with (b) (4) to manufacture the suspension for the US market. The only change from the existing product is a switch from (b) (4) packaging.

Proposed Indication(s) including Intended Patient Population	Treatment of patients with Duchenne muscular dystrophy. The patient population is expected to be males ranging in age from children to young adults.
Duration of Treatment	Chronic
Maximum Daily Dose	The recommended doses (b) (4)
Alternative Methods of Administration	The applicant proposes immediate-release tablets NDA 208684. There are no other alternative routes of administration.

B. Quality Assessment Overview

Drug Substance

Deflazacort is a white (b) (4) powder that is poorly soluble in water and has a relatively high melting point between 254°C and 256°C. It is stable in the solid state (b) (4)

(b) (4) no polymorphic forms are described in the literature.

The bulk active ingredient (API) used to manufacture commercial product will be supplied by (b) (4). Due to its poor solubility, the API is (b) (4). Information regarding the characterization, manufacture, and control of the API is incorporated by cross-reference to (b) (4) drug master file (DMF) (b) (4). The DMF has been reviewed and deemed adequate to support approval of the NDA. [Refer to M. Cooper review dated 12/1/2016.] The applicant's NDA 208684 is also cross-referenced for drug substance information. The only information submitted directly to NDA 208685 is the drug product manufacturer's acceptance specification, with associated analytical procedures and validation information.

As the original NDA submission cross-referenced NDA 208684, a second API supplier, (b) (4) was listed. In response to an information request, the applicant clarified that while both (b) (4) would supply API for deflazacort tablets, only (b) (4) would supply API for manufacture of the oral suspension. At the Agency's recommendation, the applicant has formally withdrawn (b) (4) and related facilities from this application. It is noted that the applicant was aware of quality issues related to (b) (4) supply chain and chose to withdraw (b) (4) from the tablet NDA as well.

Drug Product

The proposed product is an aqueous suspension containing 22.75 mg/mL deflazacort. The suspension contains conventional pharmaceutical excipients (aluminum magnesium silicate, carboxymethylcellulose sodium, benzyl alcohol, sorbitol, polysorbate 80, acetic acid, and water) commonly used for this dosage form. All excipients comply with compendial standards.

The manufacturing process for Deflazacort oral suspension involves (b) (4) the applicant has established appropriate process controls to ensure consistent product quality.

The proposed regulatory specification for Deflazacort oral suspension includes test parameters that are typical for the dosage form. All analytical procedures are adequately described, and have been appropriately validated. Omission of one test parameter, particle size distribution, has been justified by data that demonstrate a direct correlation between API particle size and particle size in the finished suspension.

The primary packaging for Deflazacort oral suspension consists of a 20 mL [redacted] bottle [redacted]. Each bottle contains 13 mL of the oral suspension and is co-packaged with two 1 mL oral dispensers.

Methods Verification

Methods verification for the HPLC method for determination of assay and related substances in the bulk API was submitted and Deflazacort *tablets* were submitted to the Division of Pharmaceutical Analysis (DPA) for verification under NDA 208684. As the assay method for the oral suspension is similar to the others, separate method verification for the oral suspension was not requested. DPA has determined that the methods are suitable for regulatory use but recommended minor modifications to both the API and tablet methods. Thus, standard language regarding cooperation with methods verification should be included in the action letter for this NDA, as well as for NDA 208684.

Facilities

All facilities that will be involved in commercial manufacture and testing of Deflazacort and Emflaza® (deflazacort) oral suspension are currently acceptable.

C. Special Product Quality Labeling Recommendations

The label administration instructions for the oral suspension recommend mixing the measured dose with 3 to 4 ounces of [redacted] juice, or [redacted] milk. Based on degradation observed during in-use studies, it is recommended that the dose should then be administered immediately.

D. Final Risk Assessment for Deflazacort Oral Suspension

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, Stability	Impurities due to: excipient reactions, oxidation, hydrolysis	L	An existing non-US formulation is proposed for marketing. The applicant has independently evaluated excipient compatibility.	Acceptable	
Physical stability (solid state)	Formulation, process parameters, moisture	L	Deflazacort exists (b) (4) form. (b) (4) .	Acceptable	
Physical stability (phase separation)	Formulation, process parameters	L	Choice of appropriate excipients (b) (4)	Acceptable	
Dosing Accuracy	Dosing device, formulation, process parameters, equipment/scale	M	Product will be copackaged with 1 mL calibrated delivery devices. Dosing accuracy was demonstrated at 0.1 mL, 0.5 mL, and 1 mL. Data from simulated in-use testing demonstrate that accuracy is not affected by repeated use (b) (4)	Acceptable	
Palatability	Formulation, excipient changes	M	Product (b) (4) will be mixed with juice or milk prior to administration.	Acceptable	

QUALITY ASSESSMENT

NDA 208685

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Microbial limits	Formulation, raw materials, process parameters, moisture	L	Product contains benzyl alcohol (b) (4) Product is tested at release and on stability for microbial limits per USP <61> and absence of *E. coli* and *Burkholderia cepacia* complex organisms per USP <62>	Acceptable	
Leachables	Formulation, raw materials, process parameters	M	Extractables study for glass bottle and (b) (4) closure did not detect any extractable compound above the analytical threshold. Only trace levels of (b) (4) were detected in an analysis of (b) (4) .	Acceptable	
Dissolution	Particle size, raw materials, process parameters, scale/equipment	M	(b) (4) method to assay dissolved drug	Acceptable	Avoid using off-line analytical method to prevent possible degradation

Martha Heimann

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(b) (4)

[redacted]

Labeling

Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EMFLAZA™ safely and effectively. See full prescribing information for EMFLAZA.

EMFLAZA™ (deflazacort) tablets, for oral use
EMFLAZA™ (deflazacort) oral suspension
Initial U.S. Approval: 2017

----------**INDICATIONS AND USAGE**----------
EMFLAZA is a corticosteroid indicated in the treatment of (b) (4) Duchenne muscular dystrophy. (1)

----------**DOSAGE AND ADMINISTRATION**----------
(b) (4)
[redacted]

----------**DOSAGE FORMS AND STRENGTHS**----------
- Tablets: 6 mg, 18 mg, 30 mg, and 36 mg (3)
- Oral Suspension: 22.75 mg/mL (b) (4) (3)

----------**CONTRAINDICATIONS**----------
- Hypersensitivity to deflazacort or any of the inactive ingredients in EMFLAZA (4)

----------**WARNINGS AND PRECAUTIONS**----------
(b) (4)
[redacted]

(b) (4)
[redacted]

- Behavioral and mood disturbances: May include euphoria, insomnia, mood swings, personality changes, severe depression, and psychosis. (b) (4) (5.5)

(b) (4)
[redacted]

- Ophthalmic effects: May include cataracts, infections, and glaucoma. Monitor intraocular pressure if (b) (4) is continued for more than 6 weeks (5.7)

(b) (4)
[redacted]

----------**ADVERSE REACTIONS**----------
- Most common adverse reactions (b) (4) 10% for EMFLAZA) are Cushingoid, (b) (4) weight increased, central obesity, (b) (4) and increased appetite. (6.1)

----------**DRUG INTERACTIONS**----------
(b) (4)
[redacted]

To report SUSPECTED ADVERSE REACTIONS, contact Marathon Pharmaceuticals, LLC at 1-866-562-4620 or DrugSafety@propharmagroup.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

(b) (4)
[redacted]

See 17 for PATIENT COUNSELING INFORMATION

Revised: 8/2016

Reviewer's Assessment: ***Adequate***

The package insert contains the proprietary and established name. The dosage form and strength is also present on the label. This is acceptable.

Note that the dosage form and strengths should probably be listed as:

6 mg, 18 mg, 30 mg, and 36 mg tablets

22.75 mg/mL oral suspension

(b) "Full Prescribing Information" Section

3 DOSAGE FORMS AND STRENGTHS

Tablets

- 6 mg: White and round with "6" debossed on one side
- 18 mg: White and round with "18" debossed on one side
- 30 mg: White and oval with "30" debossed on one side
- 36 mg: White and oval with "36" debossed on one side

Oral Suspension

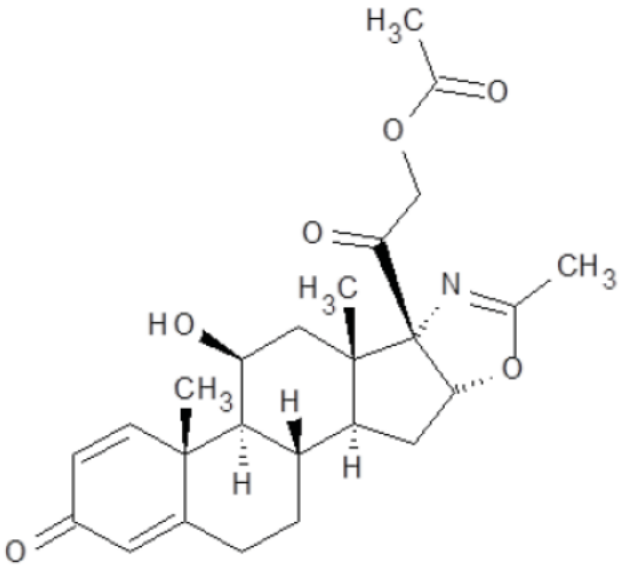
- 22.75 mg/mL: (b) (4) whitish suspension (b) (4)

Reviewer's Assessment: ***Adequate***

The dosage form and strength section contains the dosage form, strength, and identifying characteristics of the dosage form. However, the label contains excipient information which is not appropriate for this section.

11 DESCRIPTION

The active ingredient in EMFLAZA is deflazacort (a corticosteroid). Corticosteroids are adrenocortical steroids, both naturally occurring and synthetic. The molecular formula for deflazacort is $C_{25}H_{31}NO_6$. The chemical name for deflazacort is (11β,16β)-21-(acetyloxy)-11-hydroxy-2'-methyl-5'H-pregna-1,4-dieno[17,16-d]oxazole-3,20-dione, and the structural formula is:



Deflazacort is a white to off white, odorless fine powder and has a molecular weight of 441.517. Deflazacort is freely soluble in acetic acid and dichloromethane and soluble in methanol and acetone.

EMFLAZA is an immediate-release tablet in strengths of 6, 18, 30 and 36 mg and an immediate-release oral suspension in a strength of 22.75 mg/mL. Each tablet contains deflazacort and the following inactive ingredients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, and pre-gelatinized corn starch. The oral suspension contains deflazacort and the following inactive ingredients: acetic acid, aluminum magnesium silicate, benzyl alcohol, carboxymethylcellulose sodium, polysorbate 80, purified water, and sorbitol.

Reviewer's Assessment: ***Adequate***

The description section contains the proprietary and established name, the dosage form, drug product excipients, route of administration, active moiety expression of strength, therapeutic class, chemical name, structural formula, molecular weight.

The statement of strength may need to be reworded.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

EMFLAZA Tablets

- 6 mg are white, round with "6" debossed on one side. They are supplied as follows:

NDC 42998-501-01 Bottle of 100 tablets

- 18 mg are white, round with "18" debossed on one side. They are supplied as follows:
  NDC 42998-502-03 Bottle of 30 tablets

- 30 mg are white, oval with "30" debossed on one side. They are supplied as follows:
  NDC 42998-503-03 Bottle of 30 tablets

- 36 mg are white, oval with "36" debossed on one side. They are supplied as follows:
  NDC 42998-504-03 Bottle of 30 tablets

EMFLAZA Oral Suspension

- 22.75 mg/mL is a whitish colored suspension. Supplied as 13 mL in a 20 mL bottle packaged with two 1 mL oral dispensers.
  NDC 42998-505-21

Reviewer's Assessment: ***Adequate***

The how supplied section contains the following information: dosage form, strength, available units, and the identification of dosage form. This is acceptable.

16.2 Storage and Handling

Store at 20 to 25°C (68 to 77°F). See USP controlled room temperature.

Reviewer's Assessment: ***Adequate***

The storage and handling information is included; however, the excursion temperatures are not included.

Manufactured for:
Marathon Pharmaceuticals, LLC
Northbrook, IL 60062 USA

EMFLAZA Oral Suspension made in Spain

PC####X Month Year

(b) (4)

MARATHON
PHARMACEUTICALS, LLC

EMFLAZA™ (b) (4) trademarks of Marathon Pharmaceuticals, LLC.

Reviewer's Assessment: *Adequate*

This section contains the (b) (4) name. However, it contains the phrase, (b) (4)

Immediate Container Label

(b) (4)

Reviewer's Assessment: *Adequate*

The label complies with regulatory requirements from a CMC perspective. It bears the "Rx only" statement, the NDC number, name of manufacturer, lot number, expiration date, net contents, strength, bar code, and the name (proprietary and established).

Carton Labeling

(b) (4)

[redacted]

Reviewer's Assessment: ***Adequate***

The label complies with regulatory requirements from a CMC perspective. It bears the "Rx only" statement, the NDC number, name of manufacturer, lot number, expiration date, net contents, bar code, strength, and the name (proprietary and established).

List of Deficiencies: None

Methods Verification Package - None

Reviewer's Assessment: Not Applicable

Comparability Protocols - None

Reviewer's Assessment: Not Applicable

Post-Approval Commitments

Reviewer's Assessment: Not Applicable

Lifecycle Management Considerations

Reviewer's Assessment:

Changes in particle size distribution of a suspension may occur due to various factors. The Applicant determined that the particle size distribution remains constant for the proposed drug product formulation and is therefore not monitoring particle size on release and stability. The Applicant only determined the particle size of the proposed drug product using the current manufacturing conditions. If changes are made to the manufacturing process or the formulation, the particle size should be analyzed to ensure that the drug product quality remains the same.

An in-process check of the final oral suspension is made for deflazacort content. (b) (4)

The Applicant currently does not have any controls for device (oral syringe) functionality. This is mitigated by results from the in-use oral dispenser study and the performance test study for the oral dispenser. This study determined that the oral dispenser can accurately provide doses of deflazacort suspension in 0.1 mL increments. However, if there are any changes to the oral syringe the Applicant should repeat the studies and include a release test for the device functionality.

List of Deficiencies - None

Primary Drug Product Reviewer Name and Date: Andrei Ponta, Ph.D.

Secondary Reviewer Name and Date:

Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 12/08/2016 02 05:46PM
GUID: 50816dbc000085595ca3284bbca465a8

Andrei Ponta

Digitally signed by Andrei Ponta
Date: 12/08/2016 01 58:56PM
GUID: 53b58e0b00004a630e714ee170af4c26

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MICROBIOLOGY

Product Background:

NDA: 208685

Drug Product Name / Strength:
Proprietary: Emflaza
Non-proprietary: Deflazacort
22.75 mg/mL supplied as 13 mL in a 20 mL bottle

Route of Administration: Oral suspension

Applicant Name:
Name: Marathon Pharmaceutical, LLC
Address: 1033 Skokie Boulevard, Suite 600, Northbrook, IL 60062
Representative: Matthew A. Lee, Phar.D., Director, Regulatory Affairs
Telephone: (312)777-3754
Fax: (312)777-3718

Manufacturing Site:
(b) (4)
SPAIN

Method of Sterilization: N/A. Drug product is non-sterile.

Review Summary:
The submission is recommended for approval on the basis of sterility assurance.

List Submissions being reviewed (table):

Submit	Received	Review Request	Assigned to Reviewer
6/9/2016	6/9/2016	N/A	6/29/2016
9/9/2016*	9/9/2016	N/A	N/A

*IR response

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: None

Product Quality Microbiology Assessment

All of the information in this review relates to patient risk associated with a non-sterile liquid suspension for oral administration.

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – Non sterile oral suspension packaged in a 20 mL (b) (4) glass bottle.

- **Drug product composition** –

Component	Quantity in mg per mL of Suspension	Function
Deflazacort	(b) (4)	
Aluminum magnesium silicate		
Carboxymethylcellulose sodium		
Benzyl alcohol		
Sorbitol (b) (4)		
Polysorbate 80		
Acetic acid		
Water, purified		

- **Description of container closure system** –

Deflazacort suspension is packaged in a 20 mL (b) (4) glass bottle sealed with a (b) (4) cap. Container closure met the requirement of USP <671> for tight containers.

Component	Materials	Manufacturer
20 mL (b) (4) Glass Bottle	Type III glass, (b) (4)	(b) (4)
		(b) (4)

Note to reviewer: The drug product is non-sterile (b) (4) The sponsor had described the container/closures adequately.

Reviewer's Assessment:
The drug product composition and container-closure system were adequately described. The container-closure system is adequate for the liquid drug product oral route of administration.

ADEQUATE

(b) (4)

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Stability data for four lots are provided. Testing for *B. cepacia* was initiated in August 2015. Lots tested before that did not include the testing for *B. cepacia*.

Lot #	Test	0 month	24 month	36 month
7098	TAMC	<5	NT	<5
	TYMC	<10	NT	<5
	E. coli	Absent	NT	Absent
7096	TAMC	<5	NT	<5
	TYMC	<10	NT	<5
	E. coli	Absent	NT	Absent
0917	TAMC	<5	NT	NA
	TYMC	<5	NT	NA
	E. coli	Absent	NT	NA
3028	TAMC	<5	NT	NA
	TYMC	<5	NT	NA
	E. coli	Absent	NT	NA
	B. cepacia	Absent	NT	NA

NT: Not Tested; NA: Not Available

Reviewer's Assessment: The submitted stability protocol, commitment and data comply with the Guidance for Industry: (1) Q1A(R2) Stability Testing of New Drug Substances and Products.

ADEQUATE

R REGIONAL INFORMATION

R.1 Executed Batch Record

The batch record for exhibit batch lot # 2000010833 is provided.

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)
MODULE 1

A. PACKAGE INSERT

Store at 20 to 25°C

Reviewer's Assessment: There is no concern to the package insert of the product.

ADEQUATE

Primary Microbiology Reviewer Name and Date:

Yuansha Chen, Ph.D.

CDER/OPQ/OPF/DMA

10/19/2016

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

Neal J. Sweeney, Ph.D.

CDER/OPQ/OPF/DMA

10/18/16

Neal Sweeney

Digitally signed by Neal Sweeney
Date: 10/19/2016 04:48:03PM
GUID: 508da70c00028f5119acd77351f33159

Yuansha Chen

Digitally signed by Yuansha Chen
Date: 9/16/2016 08:50:29AM
GUID: 545289f5000727e1136ef94794e114b8

BIOPHARMACEUTICS

NDA: 208685-ORIG-1

Drug Product Name/Strength: Deflazacort Oral Suspension 22.75 mg/mL supplied as 13 mL in a 20 mL bottle

Route of Administration: Oral

Applicant Name: Marathon Pharmaceuticals LLC.

Drug Product Background:

EMFLAZA™ is a corticosteroid indicated in the treatment of patients with Duchenne muscular dystrophy. The recommended dose of EMFLAZA is 0.9 mg/kg/day administered orally as a single daily dose. EMFLAZA Oral Suspension should be shaken well before (b) (4) administration. One oral dispenser for dosing is co-packaged with the product. The second dispenser is reserved as a replacement in case the first one is damaged or lost. After withdrawing the appropriate dose into the oral dispenser, the EMFLAZA Oral Suspension can be slowly added into 3 to 4 ounces of (b) (4) juice, or (b) (4) milk, mixed well, and then administered immediately.

The oral suspension is manufactured by (b) (4) is the commercial manufacturing site. The source of the active pharmaceutical ingredient for the oral suspension is (b) (4)

Review Summary:

Submission: *Marathon Pharmaceuticals LLC., submitted NDA-208685 for EMFLAZA™ (deflazacort) Oral Suspension 22.75 mg/mL supplied as 13 mL in a 20 mL bottle under 505 (b)(1) of the Federal Food, Drug, and Cosmetic Act.*

Assessment: *The following dissolution method and acceptance criterion agreed to with the Applicant to be implemented for the drug product:*

Apparatus:	*USP Type II (Paddle)*
Speed:	*25 rpm*
Medium:	*SGF buffer pH 1.2*
Volume:	*500 mL*
Temperature:	*37 °C*
Dissolution acceptance criterion:	*Q (b) (4)% in 15 minutes*

The dissolution method is coupled with an automated on-line UV spectroscopy method to assay the dissolved drug. The proposed dissolution method is acceptable.

Recommendation: *From the Biopharmaceutics perspective, NDA 208685 for Deflazacort Oral Suspension 22.75 mg/mL supplied as 13 mL in a 20 mL bottle is recommended for* ***APPROVAL****.*

List Submissions being reviewed:

- Original NDA 208685 and NDA 208684 submitted on Jun 09, 2016.

- Applicant's Response dated Sep 23, 2016 to Information Response dated Sep 18, 2016.

Highlight Key Outstanding Issues from Last Cycle: None. This is the first review cycle.

Concise Description of Outstanding Issues: None.

BCS Designation

The Applicant did not request a BCS designation for deflazacort.

Solubility: It is reported by the Applicant that deflazacort API is practically insoluble in water (0.1 mg/mL at 37 °C). It is soluble in DMSO (88 mg/mL at 25 °C) and ethanol (12 mg/mL at 25 °C). It is slightly soluble in methanol and acetone. It is freely soluble in acetic acid and dichloromethane (Page 5, Components of the Drug Product, Module 3.2.P.2). A solubility study of deflazacort was done in USP buffer pH 1.2, pH 4.5 and pH 6.8 covering the physiological pH range (Table 1).

Table 1. Solubility of deflazacort in different aqueous solutions (Page 97, Module 2.7.1 in NDA-208684).

	Solubility results - 37°C - magnetical stirring 1H and 24H Filtration on glass fiber filter 1µm				
		Deionized water	USP buffer pH 1.2	USP buffer pH 4.5	USP buffer pH 6.8
[c] mg/mL	1 Hour	0.119	0.521	0.116	0.100
	24 Hour	0.141	0.522	0.137	0.139

Permeability: No data were provided for the permeability of deflazacort in this NDA.

Dissolution Method and Acceptance Criterion

Dissolution method:

The proposed dissolution method for the proposed Deflazacort Oral Suspension 22.75 mg/mL is as follows (Page 113, Module 2.7.1 in NDA-208684):

Apparatus:	USP Type II (Paddle)
Paddle Speed:	25±2 rpm
Medium:	Simulated Gastric Fluid (SGF) buffer pH 1.2
Volume:	500 mL
Sample:	1.0 mL introduced slowly in the dissolution medium with a syringe
Temperature:	37 ±1 °C

With respect to the selection of the dissolution medium, the Applicant states that sink conditions are fulfilled in USP buffer pH 1.2 and just at the solubility limit for deionized water, USP buffer pH 4.5 and USP buffer pH 6.8 (Page 97, Module 2.7.1 in NDA-208684). The Simulated Gastric Fluid (SGF) buffer (pH 1.2) was utilized as dissolution medium for Deflazacort Oral Suspension. However, in NDA-208684 for Deflazacort tablets, it is reported that significant degradation of deflazacort (b) (4) was observed in 0.01 N HCl dissolution medium, and less degradation of deflazacort was observed at higher pH dissolution media (pH 4.5 and pH 6.8) (Figure 1). Therefore, the Applicant was asked in an Information Request dated Sep 18, 2016 to clarify the use of SGF, pH 1.2, as the dissolution medium for the oral suspension. In the Applicant's Response dated Sep 23, 2016, the Applicant stated that, an **automated on-line UV spectroscopy method**, with minimum time lag between the suspension dissolution sample pull time and its UV analysis, was utilized for analyzing deflazacort suspension dissolution samples, consequently minimizing any degradation effect. According to the Applicant, an off-line HPLC method is used in the quantitation of deflazacort in dissolution samples in NDA 208684.

With respect to the selection of the dissolution apparatus, various dissolution techniques (USP II, USP IV) were compared in order to evaluate their suitability with regards to results obtained and ease of operation. The Applicant states that USP IV seems feasible but some variability was noted (Page 101, Module 2.7.1 in NDA-208684), and the dissolution profiles obtained with USP apparatus II were very fast with the different standard media tested between pH 1.2 (b) (4) (Page 106, Module 2.7.1 in NDA-208684). The Applicant states that USP apparatus II with 500 mL of SGF buffer (pH 1.2) at 25 rpm and 1 mL of sample introduced slowly in the dissolution medium is convenient in order to control the quality of the Deflazacort oral suspension (Page 113, Module 2.7.1 in NDA-208684).

Figure 1. Dissolution profiles of Deflazacort Oral Suspension in different pH media (Page 17, Drug Product, Module 3.2.P.2).

The Applicant also states that small changes in temperature (b) (4) or agitation speed (25 rpm– (b) (4) resulted in an increase in deflazacort release rate at the early time points.

Effect of critical quality attributes on drug release profiles

It is reported by the Applicant that the proposed dissolution method is discriminating for API particle size (b) (4) (Page 15, Module 3.2.P.2, Manufacturing process development) (Figure 2). Therefore, the Applicant states that (b) (4) deflazacort API is a requirement for the manufacture of deflazacort suspension (Page 18, Drug Product, Module 3.2.P.2).

Figure 2. Influence of API particle size on dissolution profiles of deflazacort oral suspension using the proposed dissolution method (Page 18, Drug Product Module 3.2.P.2).

Reviewer's Assessment: The proposed dissolution method for Deflazacort Oral Suspension is acceptable.

Dissolution acceptance criterion:

Two batches (batch numbers 3021 and 3028) of deflazacort suspension were used in clinical studies.

Table 2. Dissolution profiles of deflazacort oral suspension (batch no.: 3021) using the proposed dissolution method (Page 20, Module 2.7.1 in NDA-208684).

Batch Number	Conditions	Number of Runs	Results			
			Collection Times	Mean % Dissolved	Individual Values	RSD
3021	Apparatus II Paddle, 25 RPM 500 mL SGF pH 1.2	12	3 min 6 min 9 min 12 min 15 min 30 min 45 min	(b) (4)		

Dissolution data for the clinical batch of 3028 was not provided originally. Therefore, the Applicant was asked in the Information Request dated Sep 18, 2016 to provide the dissolution data for the clinical batch of 3028. In the Applicant's Response dated Sep 23, 2016 to this Information Request, the Applicant stated that the clinical batch of 3028 was

withdrawn from clinical distribution due to improperly sealed suspension bottles attributed to incorrect closing torque specification and application of the (b) (4) cap; a replacement clinical batch of 3066 has been studied (Figure 3).

Figure 3. Dissolution profile for clinical batch 3066 at 3 months @ 25 °C/60% RH (Page 3, the Applicant's Response dated Sep 23, 2016 to the Information Request dated Sep 18, 2016).

The Applicant originally did not propose a dissolution acceptance criterion for the QC of Deflazacort oral suspension.

Therefore, the Applicant was asked in the Information Request dated Sep 18, 2016 to provide a dissolution acceptance criterion for the proposed drug product. In the Applicant's Response dated Sep 23, 2016 to this Information Request, the Applicant proposed the dissolution acceptance criterion for batch release and stability testing as follows:
Q = (b) (4)% in 15 minutes.

In the Applicant's Response dated Sep 23, 2016, the Applicant also stated that dissolution is included as a QC test for batch release testing in the specifications table as well as the stability protocol.

The dissolution method is validated for specificity, linearity and range, accuracy, precision, filter validation, stability of analytical solution, and robustness.

Reviewer's Assessment: The proposed dissolution acceptance criterion (Q = (b) (4)% in 15 minutes) for Deflazacort Oral Suspension 22.75 mg/mL is acceptable.

Reviewer's Overall Assessment:

The proposed dissolution method is the USP II/25 rpm/500 mL SGF buffer pH 1.2 for Deflazacort Oral Suspension and is acceptable for the quality control of the proposed immediate release drug product as part of the batch release and stability testing.

The dissolution acceptance criterion is NLT (b) (4) *% (Q) of the labelled amount of deflazacort dissolved in 15 minutes for batch release and stability testing of the proposed Deflazacort Oral Suspension 22.75 mg/mL and is acceptable.*

From the Biopharmaceutics perspective, NDA 208685 for Deflazacort Oral Suspension 22.75 mg/mL is recommended for ***APPROVAL****.*

Primary Biopharmaceutics Reviewer Name and Date:

Yang Zhao, Ph.D. *01/10/2017*
Biopharmaceutics Primary Reviewer
Division of Biopharmaceutics
Office of New Drug Products, OPQ

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
I concur with Dr. Yang Zhao's assessment and Approval recommendation for NDA 208685.

Okpo Eradiri, Ph.D. *01/24/2016*
Biopharmaceutics Lead (Acting)
Division of Biopharmaceutics
Office of New Drug Products, OPQ

Okponanabofa Eradiri

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Yang Zhao

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 24, 2017

FROM: Raymond P. Frankewich, Ph.D., Review Chemist, OPQ/ONDP/DNDAPI/Branch I

THROUGH: Kasturi Srinivasachar, Ph.D., Branch Chief, OPQ/ONDP/DNDAPI/Branch I

SUBJECT: Evaluation of Method Verification Results and Conclusions for NDA 208684 & 208685

TO: NDA 208684 and NDA 208685

Reviews for NDA 208684 and 208685 for Drug Product were finalized on December 8, 2016, and for Drug Substance on December 9, 2016. No deficiencies were established for Emflaza® (Deflazacort) Tablets (NDA 208684) and Emflaza® (Deflazacort) oral suspension (NDA 208685) in those reviews.

A Methods Verification Request was submitted for NDA 208684 & 208685 on July 7, 2016. Verification was requested for the following analytical procedures:

- HPLC Assay, Related Substance and Identification Test Method for deflazacort, (b) (4)
- HPLC Assay, Related Substance and Identification Test Method for deflazacort, (b) (4)
- Deflazacort Assay and Impurities, Identification by HPLC and Identification by UV for Deflazacort Tablets

Method Verification Report, dated October 31, 2016, was submitted the same day. The report was authored by staff from CDER/OPO/OTR/DPA (DPA). The conclusions of the report were as follows:

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

- *HPLC assay, related substances and identification test method for deflazacort (b) (4))*
- *HPLC assay, related substances and identification test method for deflazacort ((b) (4))*

The following methods were evaluated and are acceptable with modifications for quality control and regulatory purposes:

- *Deflazacort assay and impurities, identification by HPLC and identification by UV for deflazacort tablets*

It the report it is noted that for the method used for the tablets, an unidentified impurity peak is observed at (b) (4) minutes (RRT (b) (4)) when one of the standard preparations is chromatographed. The level of the impurity was (b) (4)%, which exceeds the acceptance criterion for Individual

Unidentified substances in the Related Substances section of the specification for drug product release (which is ≤ (b)(4)%). The report indicates that this unidentified impurity peak does appear in chromatograms in the validation report provided by the applicant. The following description of the unidentified impurity peak is excerpted from the report.

The firm does not identify this peak in Figure 2, page 12. However, it is present as an unknown impurity throughout the validation report. Sample solution stability studies on pg. 49-50 of the validation report show an increase over time at ambient conditions. By (b)(4) hours, the sample is twice the specification limit. DPA analyzed the sample within 12 hours of preparation at ambient conditions. The method does not include a statement about stability at room temperature while the analyst is preparing the sample. The only note states " ... sample solutions were shown to be stable (b)(4) hours when stored in refrigerator, protected by light."

The problem appears to be that the unidentified impurity increases significantly following standard preparation, indicating the standard preparation is less stable than ideal. It appears that this might be addressed by the applicant including a statement in the analytical procedure description to use the standard and sample preparations within a particular period of time. It is noted in the experimental results that the peak at RRT (b)(4) appeared in the chromatogram of the standard preparation. However, in the chromatograms provided in the analytical procedure description provided in sec. 3.2.P.5.2 of the NDA (and the validation report provided in sec. P.5.3) this peak appears in the chromatograms of both the standard and sample preparations.

In addition to this, it is noted that when the method for assay, related substances and identification by HPLC for deflazacort (b)(4) was performed, deflazacort did not dissolve in diluent (b)(4) as required in the method. By contrast, the method for assay, related substances and identification by HPLC for deflazacort (b)(4) specifies dissolving deflazacort (b)(4) before adding diluent. It was indicated that with the (b)(4) method, deflazacort did dissolve (b)(4). To resolve this issue, DPA recommended that instructions be included to dissolve deflazacort (b)(4) before adding diluent.

Consistent with the recommendations in the report, the following items were sent to the NDA applicant (Marathon Pharmaceuticals LLC) in an electronic communication dated January 10, 2017.

It is requested that the following issues regarding the analytical procedures used for control of deflazacort drug substance and Emflaza® (deflazacort) Tablets be addressed. These analytical procedures were submitted in NDA 208684 for Emflaza® (deflazacort) Tablets.

Regarding the analytical procedure for Deflazacort Assay and Impurities, Identification by HPLC and Identification by UV for Deflazacort Tablets:

1. *Identify the unknown peak which appears at RRT (b)(4) (approximately (b)(4) minutes) in both standard and sample preparations.*

2. *Since the unknown peak at RRT (b) (4) appears to increase after standard / sample solution preparation, amend the analytical procedure description with more specific information regarding solution stability. Specifically, include a statement in the analytical procedure description to use the standard and sample preparations within a particular period of time. A method verification study by FDA indicated that the peak at RRT (b) (4) was (b) (4)% (greater than the acceptance criterion for Individual Unidentified substances in the Related Substances section of the specification for drug product release ((b) (4)%)) when the standard solution was chromatographed within 12 hours of preparation.*

Regarding the analytical procedure for HPLC Assay, Related Substance and Identification Test Method for deflazacort, (b) (4):

3. *Include in the descriptions of preparations of sample and standard solutions instructions to dissolve deflazacort (b) (4) before adding diluent. FDA method verification study indicated that deflazacort did not dissolve in diluent ((b) (4) as instructed in the procedure description.*

Response was received in an Amendment to NDA 208684 dated January 17, 2017. Response to each item, followed by a brief evaluation of each response, is provided below.

Item #1. Identify the unknown peak which appears at RRT (b) (4) (approximately (b) (4) minutes) in both standard and sample preparations.

Response. The unknown peak which appears at RRT (b) (4) (approximately (b) (4) minutes) in both sample and standard preparations is discussed in Module 3.2.P.5.5 Characterization of impurities. Efforts are still ongoing to definitively identify this impurity. We are attempting to isolate the unknown compound from sample preparations. This work is not complete and efforts to isolate this unknown will continue. (See Module 3.2.P.5.5 Characterization of impurities, Attachment 1).

Evaluation. In sec. P.5.5 information collected regarding the unknown impurity at RRT (b) (4) is summarized. Some of the information is provided below.

Molecular Weight: (b) (4)

Possible Structures:

(b) (4)

Text from sec. P.5.5:
This impurity was detected in aged sample solutions and also during the forced degradation study in 1N HCl. Small amounts are detected in deflazacort tablet samples. Efforts are still ongoing to definitively identify this impurity. The mass spectrum of the HPLC peak, which was detected at retention time (b) (4) relative to the main component in the method used to control degradation products, included a protonated molecule signal at (b) (4) greater than that of deflazacort. This suggests that the unknown peak results from the addition of a (b) (4) group to the deflazacort structure. It is thought that the most likely structure is (b) (4) deflazacort shown above, but other possible structures, also shown above can't be ruled out based on the MS data. However, efforts to synthesize this compound have failed to produce samples that are stable enough to confirm identity.

It is not expected that any of the proposed structures would exhibit unusual toxicity, since the molecules contain no structural alerts. It is noted that this impurity has been evaluated as part of the drug product, and its levels are expected to be below the acceptance criterion for Individual Unidentified impurities ((b) (4)%). The response is acceptable and no further action is taken at this time.

Item #2. Since the unknown peak at RRT (b) (4) appears to increase after standard / sample solution preparation, amend the analytical procedure description with more specific information regarding solution stability. Specifically, include a statement in the analytical procedure description to use the standard and sample preparations within a particular period of time. A method verification study by FDA indicated that the peak at RRT (b) (4) was (b) (4)% (greater than the acceptance criterion for Individual Unidentified substances in the Related Substances section of the specification for drug product release ((b) (4)%)) when the standard solution was chromatographed within 12 hours of preparation.

Response. Storage conditions and times are for both the standard and the sample solutions are present both in the test method at the manufacturing site and the registration document, Module 32P52 Assay, impurities and identification by HPLC in the notes for the standard and sample solution preparation, sections 5 and 6. The notes for the standard and sample solution stipulate that the sample and standard solutions are protected from light and that a refrigerated auto-sampler is used to ensure the stability of the standard and sample solutions during analysis.

Evaluation. Standard solution preparation instructions (section 5) include the following notation:

NOTE 3: The standard solution was shown to be stable for 22 days when stored in the refrigerator, protected from light.

Sample preparation instuctions (section 6) include the following notation:

NOTE 2: The 6 mg, 18 mg and 30 mg and 36 mg sample solutions were shown to be stable for (b) (4) hours when stored in the refrigerator, protected from light.

The notations above clarify that the standard and sample solutions should be refrigerated and protected from light when stored. Response is acceptable. No further action is warranted at this time.

Item #3. Regarding the analytical procedure for HPLC Assay, Related Substance and Identification Test Method for deflazacort, (b) (4):
Include in the descriptions of preparations of sample and standard solutions instructions to dissolve deflazacort (b) (4) before adding diluent. FDA method verification study indicated that deflazacort did not dissolve in diluent (b) (4) as instructed in the procedure description.

Response. We will need to evaluate the change in the affected laboratories. Any change will need to be validated and submitted to the NDA prior to implementation.

Evaluation. The applicant has committed to evaluate the proposed change before amending the analytical procedure description. The applicant has committed to perform validation of the revised analytical procedure of necessary. Response is acceptable.

Kasturi Srinivasachar

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