CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211379Orig1s000

PRODUCT QUALITY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

MEMORANDUM

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

DATE: October 10, 2019
FROM: Branch 2/DNDP1/ONDP/OPQ
SUBJECT: HEMADY
APPLICATION/DRUG: NDA 211379

Background:
NDA 211379 was submitted for Dexamethasone Immediate Release Tablets, 20 mg by Dexcel Pharma Technologies Limited in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act. On September 10, 2019, OPQ recommended approval NDA 211379. This recommendation was for (b) (4) as the proposed proprietary name; however, the final approved proprietary name for the product is HEMADY. This memo provides a correction to the name noted in the product quality executive summary for NDA 211379. Accordingly, OPQ recommends APPROVAL of NDA 211379 for HEMADY (dexamethasone) Immediate Release Tablets, 20 mg and grants a 36-month expiration period for the drug product when protected from light and stored at 20° to 25°C (68° to 77°F) excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. There are no outstanding issues and no post-approval quality agreements to be conveyed to the applicant.

Sherita McLamore, Ph.D.
Acting Quality Assessment Lead, Branch 2,
Division of New Drug Product I (DNDPI)
Office of New Drugs Products (ONDP)
Office of Pharmaceutical Quality/CDER/FDA

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/s/

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Recommendation: APPROVAL

NDA 211379
Review #1

Drug Name/Dosage Form	(b) (4) (dexamethasone) Tablets
Strength	20 mg
Route of Administration	Oral
Rx/OTC Dispensed	R_x
Applicant	Dexcel Pharma Technologies Limited
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	06-Sept-18	All
Amendment (SD)	11-Mar-19	DP, Process
Amendment (SD)	07-Jan-19	DP, DS, Process
Amendment (SD)	16-Jan-19	DP
Amendment (SD)	05-Apr-19	DP
Amendment (SD)	06-May-19	DP
Amendment (SD)	10-Dec-18	DP

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Rohit Tiwari	Su Tran
Drug Product	William Adams	Anamitro Banerjee
Process and Facilities	Zhaoyang Meng	Bogdan Kurtyka
Microbiology	n/a	n/a
Biopharmaceutics	Mei Ou	Banu Zolnik
Regulatory Business Process Manager	Rabiya Laiq	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a
Environmental	William Adams	Anamitro Banerjee

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	(b) (4)	n/a	8/15/2019	Adequate
(b) (4)	Type III	(b) (4)		n/a	No Review	Adequate information provided in the NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	11664	Decadron (dexamethasone)
NDA	20785	Thalomid (thalidomide)
NDA	21602	Valcade (bortezomib)

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends APPROVAL of NDA 211379 for (b) (4) (dexamethasone) Immediate Release Tablets, 20 mg. As part of this action, OPQ grants a (b) (4) month re-test period for the drug substance when stored at (b) (4) and a 36-month expiration period for the drug product when protected from light and stored at 20° to 25°C (68° to 77°F) excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. There are no outstanding issues and no post-approval quality agreements to be conveyed to the applicant.

II. Summary of Quality Assessments

A. Product Overview

NDA 211379 was submitted for Dexamethasone Immediate Release Tablets, 20 mg by Dexcel Pharma Technologies Limited in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act. Dexamethasone is a synthetic steroidal glucocorticoid that was approved in 1958 under the brand name Decadron (NDA 011664). Decadron was available in five strengths: 0.5, 0.75 1.5, 4 and 6 mg (withdrawn from the market in 2007). The proposed drug product is indicated for the treatment (b) (4) (b) (4) (b) (4) he Applicant submitted a major amendment to support a broader indication of dexamethasone as part of combination regimens (b) (4):

- Thalomid® (thalidomide, NDA 020785)
- Velcade® (bortezomib, NDA 021602)
- Revlimid® (lenalidomide, NDA 021880)
- Pomalyst® (pomalidomide, NDA 204026)
- Ninlaro® (ixazomib, NDA 208462)
- Farydak® (panobinostat, NDA 205353)
- Kyprolis® (carfilzomib, NDA 202714)

Accordingly, the proposed product, Dexamethasone Immediate Release Tablets, 20 mg is indicated for the treatment of patients with multiple myeloma (MM), as part of combination regimens with anti-myeloma drugs. Dexamethasone is approved for the palliative management of leukemias and lymphomas. Presently, dexamethasone is not indicated for the treatment of multiple myeloma; however, it is routinely used off-label for the treatment of the disease and is commonly prescribed in combination with the anti-multiple myeloma products listed above. Accordingly, this NDA introduces a new tablet strength of dexamethasone (i.e. 20 mg vs the 6 mg highest approved strength) and a new indication (i.e. indicated for the treatment of multiple myeloma as part of combination regimens with anti-myeloma drugs). Dexamethasone was granted orphan drug designation for the treatment of multiple myeloma in March 2018.

Dexamethasone is a small chiral molecule that is manufactured by (b) (4) (b) (4) The sponsor references DMF (b) (4) for the manufacture and control of dexamethasone and includes the corresponding letter of authorization. The drug product is an immediate-release, solid, oral dosage form that is presented as a (b) (4), round, white, biconvex tablet debossed with "20" on one side. The drug product formulation includes 20 mg of the active, lactose monohydrate, corn starch, povidone (b) (4), sodium starch glycolate and magnesium stearate.

The recommended dosing regimen for Dexamethasone Tablets is 20 or 40 mg orally, once daily, on specific days of the treatment cycle depending on the treatment protocol.

Based on the information provided in this application (original submission and in responses to information requests), OPQ considers all review issues adequately addressed and potential risks to patient safety, product efficacy, and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 211379 and grants a (b) (4) month re-test period for the drug substance, a 36-month expiration period for the drug product when stored at controlled room temperature in the proposed commercial packaging.

Proposed Indication(s) including Intended Patient Population	Indicated for the treatment of patients with multiple myeloma as part of combination regimens with anti-myeloma drugs.
Duration of Treatment	Until disease progression or unacceptable toxicity
Maximum Daily Dose	40 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance

Dexamethasone is a small chiral molecule that is manufactured and release tested by (b) (4) Different BCS classifications are found in literature for dexamethasone: BCS class II or BCS class I/III substance.
Dexamethasone is a white to practically white non-hygroscopic crystalline solid that is practically insoluble in water, sparingly soluble in acetone, ethanol, and methanol; and slightly soluble in dichloromethane. Dexamethasone exhibits polymorphic behaviour. The Applicant notes that several polymorphic forms of dexamethasone are described in the literature; however, (b) (4) is considered as the most stable polymorph and is the only form consistently produced by the manufacturer. Complete chemistry manufacturing and control information for the drug substance is cross referenced in DMF (b) (4). DMF (b) (4) was reviewed in conjunction with this NDA and was deemed adequate to support the approval of the application. The Applicant indicates that a (b) (4) month retest has been adopted by the drug substance manufacturer.

NDA 211379 is recommended for approval from a drug substance perspective.

Drug Product and Process

The drug product, Dexamethasone Tablets, is presented as a 20 mg, immediate-release tablet containing the active, lactose monohydrate, corn starch, povidone (b) (4), sodium starch glycolate, and magnesium stearate. The tablets are a (b) (4) round, white, biconvex tablets debossed with "20" on one side. All excipients used in the manufacture of the drug product are compendial, commonly used in solid oral dosage forms, and demonstrate good compatibility with the drug substance.

The drug product is manufactured (b) (4) at a (b) (4)

The drug product will be packaged in 100 count 40 cc, white, white HDPE container with a 35-mm white (b) (4) child-resistant (b) (4) cap and a (b) (4) desiccant (b) (4) All packaging components comply with USP <661>. Bulk tablets are stored in a (b) (4) (b) (4)

The drug product specifications included appearance, identification, assay, content uniformity, individual and total degradants, (b) (4) dissolution, and microbial limits. The drug product specification was (b) (4) (b) (4) (b) (4) Accordingly, based on the applicant's justification and batch results the risk assessment is acceptable and a test for elemental impurities is not required in the drug product release specifications (see drug product review for details).

The drug product specifications are consistent with ICH Q6A and are based on batch analyses and stability data. The drug product specifications provide adequate controls

to ensure the quality of the drug product throughout the product expiry. The proposed specification and acceptance criteria for the drug product, together with controls for impurities in the drug substance are adequate to ensure that the critical quality attributes of this product are well controlled.

Primary stability studies were conducted on 4 pilot scale batches of the drug product (batches H1716, H1641, H1642 and H1643). As discussed with the agency, 24 months of long-term and 6 months accelerated stability data are included for 3 batches of (b) (4) tablets (batches H1641, H1642 and H1643) together with 12 months of long-term and 6 months accelerated stability accelerated data for batch H1716 (b) (4) and represents the commercial product. All batches were packaged in the commercial container closure system (i.e. 100 count 40 mL HDPE bottle with the (b) (4) closure and (b) (4) desiccant) and manufactured according to the proposed commercial manufacturing process. The applicant included a comparative dissolution profile (b) (4) The comparison (b) (4) demonstrated that there were no significant differences in the product performance (b) (4)

Bulk stability studies were completed on batch H1716. (b) (4)

In addition to the long term and accelerated data, the applicant completed photostability and forced degradation studies for the drug product. All stability studies were executed in accordance with the ICH 1A and Q1B and no notable trends were observed under any storage condition

The Applicant proposed a 36-month expiry for the drug product and a when stored in the original c/c at controlled room temperature 20°C–25°C (68°–77°F) and protected from light. The Applicant proposed a (b) (4) holding time for bulk product (b) (4) (b) (4)

Based on the available stability data provided, Dexcel Pharma Technologies Ltd. proposed and the FDA accepts the a **36 month** expiration dating period for the drug product when protected from light and stored at 20°C to 25°C (68° to 77°F) excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature] and a (b) (4) hold time for the bulk tablets.

The following "Outstanding Issue" was included in the drug product review:

(b) (4)

(b) (4)

The following "Lifecycle Management Consideration" was included in the drug product review:

A potential change will be (b) (4)

(b) (4)

The ATL considers this recommendation superfluous for the following reasons:

(b) (4)

NDA 211379 is recommended for approval from a drug product perspective.

Biopharmaceutics

The biopharmaceutics review focused on (1) the acceptability of the proposed in vitro dissolution method and acceptance criterion for the routine QC testing of the proposed drug product at batch release and on stability and (2) bridging of the between the clinical and commercial formulations. The listed drug (Decadron) was discontinued therefore the sponsor conducted comparative bioavailability and in vitro dissolution studies of the drug product against West-Ward's Dexamethasone Tablets USP, 4 mg.

Dissolution Specification and Method: The dissolution method includes a USP Apparatus II (Paddles) at 50 rpm in 900 mL of 0.1N HCl at 37°C. The proposed dissolution acceptance criterion is Q= (b) (4)% in 15 minutes While the proposed dissolution method showed limited discriminatory ability, the drug product

demonstrated (b) (4) and consistent dissolution behavior of under multi-media and different dissolution conditions. Accordingly, the proposed dissolution method and acceptance criteria were deemed acceptable for batch release and stability testing for the drug product.

Bridging of the Clinical Formulations: The only difference noted between the clinical drug product and the commercial drug product is (b) (4) The clinical drug product included (b) (4) while the proposed commercial product does not. The biopharm team indicated that bridging of the clinical product to the commercial product was established based on the following:

1. dissolution profiles for clinical batches were comparable to profiles the for commercial batches under multi-media and different dissolution conditions
2. the products were manufactured at the same site
3. there were minor manufacturing process difference (b) (4)

For these reasons, it was concluded that the bridge between the clinical and commercial formulations is established and no additional *in vitro* or *in vivo* bridging studies were required.

Based on the information provided (i.e. dissolution profile data for pivotal clinical batches and stability data), the proposed dissolution method and acceptance criterion are deemed acceptable for batch release and stability testing for the drug products and NDA 211379 is recommended for approval from a biopharmaceutics perspective.

Facilities

There were 5 facilities included in this application:

(b) (4)

All facilities listed in NDA 211379 were deemed acceptable for the responsibility listed in the application. Accordingly, NDA 211379 is recommended for approval from a compliance perspective.

Comparability Protocol

A comparability protocol that provided for the (b) (4) (b) (4) was included in the original submission of this NDA but was later withdrawn (b) (4) (b) (4)

(b) (4)

	Container closure system submitted with NDA 211379	Container closure system covered by comparability protocol
Tablet count	100 tablets	<100 tablets
Bottle	40 ml white HDPE bottle.	40 ml white HDPE bottle.
Cap	35 mm (b) (4) child-resistant cap (b) (4) (b) (4)	35 mm (b) (4) child-resistant cap (b) (4) (b) (4)
Desiccant	(b) (4) desiccant (b) (4) (b) (4)	(b) (4) desiccant (b) (4) (b) (4)

Environmental Assessment

The applicant submitted a claim for categorical exclusion and a statement of no extraordinary circumstances under 21 Code of Federal Regulations (CFR) Sections 25.31(b). The categorical exclusion cited is appropriate based on the estimated amount of drug to be produced for direct use. The claim of categorical exclusion is therefore acceptable and granted.

C. Special Product Quality Labeling Recommendations (NDA only)

n/a

D. Final Risk Assessment (see Attachment)

Attached.

Sherita McLamore

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William Adams

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Anamitro Banerjee

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LABELING

NDA 211379 Review #1
Drug Product: Hemady™ (dexamethasone) Tablets, 20 mg for Oral Use
Route of Administration: Oral
Applicant Name: Dexcel Pharma Technologies Ltd (Or-Akiva, Israel)

Review Recommendation: Approval

Review Summary:

Submissions Reviewed	Document Date
SD-001: new NDA	09/06/18
SD-002: labeling	12/10/18
SD-004: labeling	01/07/19
SD-008: bottle and carton labels	04/05/19
SD-009: IR response – labels and labeling	05/06/19
SD-011: labeling	06/27/19
SD-012: labeling	07/03/19
DMEPA Review – trade name accepted	09/06/19
SD-016: bottle and carton labels	09/09/19

R Regional Information

1.14 LABELS and LABELING

Amendment SD-009
Comments 1. The proposed tablet count per bottle is not consistent with the dosing regimens described in section 2 of the Prescribing Information (PI) (b) (4)

(b) (4)

Response 1

Dexcel states that the 100-count package is to be marketed as a drug supply [multiple patient package] intended to be repackaged. Therefore, the statement in package insert section 16.2, "Dispense in a tight, light-resistant, child resistant container.", is appropriate. Revised labels and labeling without the proposed tradename (found unacceptable in letter dated 04/12/19) are included in this amendment.

Comment 2. Based on the information and conclusions in NDA modules 3.2.P.2 and 3.2.P.8, the storage statement on the bottle label, the carton label and package insert section 16.2 should be revised as follows:

a. In Section 16.2, modify the storage statement to "Store at 20° to 25°C (68° to 77°F) excursions permitted 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]."
b. In Section 16.2 and carton container, add "(b) (4)

c. The statement (b) (4) should be deleted from the bottle and carton labels.

Response 2

2a: The storage statement has been revised as requested.

2b,c. Reference is made to response 1 (above).

draft BOTTLE LABEL (Amendment SD-016)

(b) (4)

Reviewer's Assessment: Acceptable

CMC information is complete and acceptable; see comments and conclusion to the package insert regarding the storage statement "Dispense in" statement for the pharmacy repackaging is supported by the stability studies. Noted that the (b) (4) statement has been deleted.

draft CARTON LABEL (Amendment SD-016)

(b) (4)

[redacted]

Reviewer's Assessment: Pending

CMC information is complete and acceptable; see comments and conclusion to the package insert regarding the storage statement "Dispense in" statement for the pharmacy repackaging is supported by the stability studies. Noted that the (b) (4) statement has been deleted.

draft PACKAGE INSERT (Amendment SD-012)

HIGHLIGHTS OF PRESCRIBING INFORMATION

Header

Hemady™ (dexamethasone), Tablets, 20mg for Oral Use

----DOSAGE FORMS AND STRENGTHS ----

Tablet, 20 mg

FULL PRESCIPTPION INFORMATION

3 DOSAGE FORMS AND STRENGTHS

(b) (4) Tablets (b) (4) white, round, biconvex tablets (b) (4) 20 mg (b) (4) embossed with "20" on one side (b) (4)

11 DESCRIPTION

Hemady™ (dexamethasone, USP) is an anti-inflammatory, 9-fluoro-glucocorticoid. The chemical name is 9-fluoro-11β,17,21trihydroxy-16α-methylpregna-1,4-diene-3,20-dione. Dexamethasone has the following structural formula is:

[molecular structure]

The molecular formula for dexamethasone is $C_{22}H_{29}FO_5$. The molecular weight is 392.47 g/mol. Dexamethasone is a white to practically white, odorless, crystalline powder. It is stable in air. It is practically insoluble in water.

(b) (4)

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Hemady™ is supplied as a white, round, biconvex, tablet embossed "20" on one side.

NDC 64239-300-10: Bottle of 100 Tablets

16.2 Storage

(b) (4)

Store at 20 to 25°C (68 to 77°F) excursions permitted 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].
Dispense in a tight, light-resistant, child resistant container.

17 PATIENT COUNSELING INFORMATION

Rx Only
Manufactured for:
Dexcel Pharma Technologies Ltd
1 Dexcel St, Or-Akiva, 3060000, Israel
~~Distributed by:~~
~~XXX~~

Reviewer Assessment:
Highlights
Header: Acceptable. No objection to the proposed trade name.
Dosage Forms and Strengths: Acceptable

Full Prescribing Information

Section 3: Acceptable

Section 11: Not Acceptable

New NDA version was revised based on the 2017 Velcade package insert and provided in amendment SD-002. This version does not include the Ingredient information per USP <1091>; included in the Velcade package insert. Noted that this part is not present in any version of the package insert in amendments SD-001, SD-002, SD-004, SD-011 or SD-012. Request that the package insert be revised to include this information.

Section 16.1: Acceptable

Section 16.2: Acceptable.

Storage statement revised based on proposed storage statement conclusions in modules 3.2.P.2.4 and 3.2.P.8.1, and reorganized in amendment SD-012.

* module 3.2.P.2.4: Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature] with excursions permitted to 15° to 30°C (59° to 86°F).

* module 3.2.P.8.1: Store at controlled room temperature 20°–25°C (68°–77° F). Protect the tablets from light. Store in original bottle.

The reorganized storage temperature statement is Acceptable.

Deletion of the '(b) (4) statement is Acceptable since the primary container is an opaque HDPE bottle.

The repackaging statement is Acceptable.

Section 17: Acceptable

The "manufactured by" statement is accurate, thus acceptable.

The (b) (4) statement was to be included on the bottle and carton label for consistency; DMEPA agreed. Deletion of the statement in the current version is acceptable since the statement is optional.

List of Deficiencies:

Revise section 11 of the package insert to include the ingredient information per USP <1091>.

"Hemady™ is a tablet for oral administration containing 20 mg dexamethasone USP. The inactive ingredients are corn starch NF, lactose monohydrate USP, magnesium stearate NF povidone USP, and sodium starch glycolate NF."

Primary Labeling Reviewer:

William Adams, CMC-DP reviewer/ONDP 09/12/19

Secondary Reviewer:

Anamitro Banerjee, Ph.D., Branch Chief/ONDP 09/12/19

William Adams

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Anamitro Banerjee

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BIOPHARMACEUTICS

NDA: 211379 [505(b)(2)]
Drug Product Name / Strength: (b) (4) (dexamethasone) Tablets, 20 mg
Route of Administration: Oral, Immediate Release Tablets
Applicant Name: Dexcel Pharma Technologies Limited
Proposed Indication: (b) (4)
Submission Dates: 09/06/2018
Primary Reviewer: Mei Ou, Ph.D.
Secondary Reviewer: Banu Zolnik, Ph.D.

EXECUTIVE SUMMARY

The proposed drug product, (b) (4) (dexamethasone) Tablets, 20 mg, is an immediate release (b) (4) tablet for oral administration. There are three listed drug (LD) products of this 505(b)(2) application, which are: i) Decadron® (dexamethasone, NDA 011664, by Merck, approved on 10/30/1958, discontinued since 2007), ii) Thalomid® (thalidomide, NDA 020785, by Celgene, approved on 07/16/1998), and iii) Velcade® (bortezomib, NDA 021602, by Millennium Pharmaceuticals, Inc., approved on 05/13/2003). The reference standard (RS) product, Dexamethasone Tablets, 4 mg [under ANDA 084612, by West-Ward Pharmaceuticals (previously, Roxane Laboratories, Inc.), approval on 07/19/1978] is used as reference in the pivotal bioavailability/bioequivalence (BA/BE) study (study 160458), which is under purview of the Office of Clinical Pharmacology.

In previous communications cross referenced to IND 128569 [one Type-B pre-IND meeting dated 01/14/2016 (meeting minutes dated 01/23/2016[1]), one Type-B pre-NDA meeting dated 08/17/2017[2], and one Type-B pre-NDA meeting dated 11/08/2017 (meeting minutes dated 11/13/2017[3])], the requests of developing in vitro dissolution method and the information of selecting dissolution acceptance criterion had been conveyed to the Applicant.

In the current NDA 211379 submission dated on 09/06/2018, the Biopharmaceutics Review focuses on the evaluation of: i) the in vitro dissolution method and acceptance criterion of the proposed drug product; ii) the need of in vitro bridging between the clinical formulation and commercial formulation.

[1] IND 128569, a Type B pre-IND meeting, meeting minutes dated 01/23/2016: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af803cbe62
[2] IND 128569, a Type B pre-NDA meeting, preliminary comments dated 08/17/2017: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80455003
[3] IND 128569, a Type B pre-NDA meeting, meeting minutes dated 11/13/2017: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af804694eb

In Vitro Dissolution Testing of the Finished Product:
Although the proposed dissolution method showed very limited discriminating ability, because of the relative high solubility of drug substance, and the consistent and (b) (4) (b) (4) dissolution behavior of the drug product under multi-media and different dissolution conditions, the proposed dissolution method is acceptable as a quality control (QC) test of the finished drug product for batch release and stability testing.

The final approved *in vitro* dissolution method and acceptance criterion for the finished drug product are presented below:

USP Apparatus	II (Paddle)
Rotation Speed	50 rpm
Medium and Volume	Dilute HCl (1:100), degassed, 900 mL
Temperature	37 ± 0.5°C
Acceptance Criterion	Q = (b) (4)% in 15 minutes

Formulation Bridging:
Because of the differences between the clinical formulation (b) (4) and the commercial formulation (b) (4) bridging is established with the following data/information: (i) similar dissolution profiles using the dissolution method of USP Apparatus I Basket, 50 rpm, 900 mL of diluted HCl (1:100); (ii) (b) (4) and similar dissolution profiles using the same proposed dissolution QC method of USP Apparatus II Paddle, 50 rpm, 900 mL of diluted HCl (1:100); (iii) the same manufacturing site; (iv) minor manufacturing process difference (b) (4) Therefore, no additional *in vitro* or *in vivo* bridging studies are needed.

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 211379 for the proposed (b) (4) (dexamethasone) Tablets, 20 mg, is recommended for **APPROVAL**.

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Banu Zolnik

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Sherita McLamore

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ATTACHMENT I: Final Risk Assessment

A. Final Risk Assessment – **NDA 211379 for** (b) (4) **(dexamethasone) Tablets**,

a) Drug Product

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 (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	(b) (4)	Acceptable	Controls are in place, continue stability monitoring post approval
Physical stability (solid state)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	M		Acceptable	
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	M		Acceptable	Controls are in place.
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment	L		Acceptable	Controls are in place, continue stability monitoring post approval
Dissolution – BCS Class II & IV	• Formulation • Raw materials • Exclude major ref ormulations • Process parameters • Scale/equipments • Site	M		Acceptable	Controls are in place, continue stability monitoring post approval

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/s/

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