CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213876Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 213876

Review # 1

Drug Name/Dosage Form	Hydrocortisone, Oral granules
Strength	0.5, 1, 2 and 5 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Diurnal Limited

SUBMISSIONS REVIEWED	DOCUMENT DATE
Original	11/29/2019
Quality Information	03/11/2020
Quality Response to Information Request	04/16/2020
Quality Response to Information Request	05/07/2020
Labeling Information	05/28/2020
Quality Response to Information Request	05/29/2020
Quality Response to Information Request	06/25/2020
Quality Response to Information Request	07/14/2020

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Daniel Jansen	Su Tran
Drug Product	Ali Mohammadi	David Claffey
Process/ Facility	Kejun Cheng	Aditi Thakur
Biopharmaceutics	Debasis Ghosh	Min Li
Regulatory Business Process Manager	Leeza Rahimi/Hamet Toure	
Application Technical Lead	Dhanalakshmi Kasi	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed
(b) (4)	Type II	(b) (4)	Drug Substance	Adequate	28 Apr 2018

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	8697	LD

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

The final OPQ recommendation is for Approval.

II. Summary of Quality Assessments

A. Product Overview

The drug product, Alkindi Sprinkle (hydrocortisone) oral granules is developed for use in neonates, infants and children <17 years old with adrenal insufficiency. This is a 505(b)(2) application for hydrocortisone oral granules relying on the safety and efficacy of the approved drug, Cortef® from Pfizer (NDA 8697) (see CDTL's review). The listed drug, hydrocortisone tablets was developed for adult population and is available in 5 mg,10 mg and 20 mg strengths. These unit strengths are higher than the therapeutic dose required for pediatric patients and the hydrocortisone tablets are crushed or split by a parent or pharmacist. This may result in inaccurate doses as well as a bitter taste of the crushed tablet. The proposed drug product, hydrocortisone oral granules contained in a hard capsule is developed in lower strengths, 0.5, 1, 2 and 5 mg to meet the pediatric population needs. The patients can use granules by pouring it onto tongue or in (b) (4) soft-foods (for example yogurt and puree).

The active pharmaceutical ingredient, hydrocortisone (b) (4) USP used in the drug product formulation is covered by DMF (b) (4). The drug substance meets the USP/EP monograph standards. The batch release data are adequate to support the use of hydrocortisone drug substance in the manufacture of hydrocortisone immediate release granules drug product. The storage condition for the drug substance is (b) (4) and the proposed retest period is (b) (4) months. The drug substance reviewer is recommending approval.

The proposed commercial manufacturing of hydrocortisone granules involves (b) (4) Drug product manufacturer is Glatt Pharmaceutical Services GmbH & Co. KG, FEI#3004146501. The facility team recommended PAI for this facility. Due to travel restrictions, the facility team opted for paper based 704(a)(4) review process. The records from the drug product manufacturer were evaluated by the ORA/Facility team and found acceptable. All other manufacturing facilities have been assessed and found acceptable based on profile, inspection history and district file review. The proposed commercial batch size is (b) (4)

The applicant developed an in-house dissolution method to perform in vitro dissolution test for granules. (b) (4) . The applicant revised their acceptance criterion for dissolution as NLT (b) (4) %(Q) in 45 min based on biobatch dissolution and the release specification is updated accordingly. The dissolution data from co-administered soft-food showed >80% dissolution

within 30 minutes in all scenarios. Hence, the compatibility study demonstrated that co-administered fluid/soft food is not likely to have any effect on the in vitro dissolution performance of the product. The biopharmaceutics team recommended approval for NDA 213876.

B. Quality Assessment Overview

Drug Substance

DMF [redacted] is referenced for all CMC information on the drug substance. DMF holder and the API supplier is [redacted]. DMF [redacted] is adequate to support this application. The drug substance, hydrocortisone meets the specification and is adequate to ensure the quality of the drug substance as it relates to the safety and efficacy of the eventual drug product. The API is a BCS I compound with a high solubility, permeability [redacted] The particle size of the drug substance is tightly controlled by the release specification. Hydrocortisone is packaged in [redacted] The shelf life of [redacted] months at [redacted] is supported by stability data. The drug substance information is adequate to support approval of the NDA.

Drug Product

The drug product Alkindi Sprinkle (hydrocortisone) oral granules are contained in a capsule and specifically developed for pediatric population of children <17-year-old age. The drug product is administered directly or with drinks or soft-foods. The excipients used in the drug product are microcrystalline cellulose, hypromellose, magnesium stearate and ethyl cellulose and the capsule shell contains hypromellose. The excipients are tested by USP/NF Monographs. The drug product is tested for appearance, identification, assay, delivered assay, degradation products, dissolution, content uniformity, [redacted], and microbial limits. The degradation products controlled as per ICH Q3B and hydrocortisone USP monograph. Batch analyses show that manufactured batches met the drug product specification. In addition, delivered assay and food compatibility are critical quality attributes of the drug product. The delivered assay test ensures that the oral granules are transferred adequately from the hard capsule at release and stability. Food compatibility is tested by validated HPLC method to monitor the degradation products after granules are mixed with drinks or soft-foods. No significant change in degradation products is observed at 5 and 60 minutes. The drug products capsules are packaged in a HDPE bottle with [redacted] closure with integrated desiccant. The proposed shelf life is 36 months is supported by stability data.

C. Special Product Quality Labeling Recommendations: None

D. Final Risk Assessment:

Drug Product (hydrocortisone) oral granules

Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation
Identity of hydrocortisone	Method of manufacture, suitability of analytical methods	Low	(b) (4)	Low. Acceptable
Assay of hydrocortisone	Method of manufacture, suitability of analytical methods	Low		Low. Acceptable
Delivered Assay	Suitability of analytical methods	Medium		Low. Acceptable
Dissolution	Formulation, method of manufacture	Low		Low. Acceptable
Drug product impurities and Food compatibility	Suitability of analytical methods	Medium		Low. Acceptable
Microbial Limits	Components, manufacturing process.	Low		Low. Acceptable

***E.* Life Cycle Knowledge Information:** None

Application Technical Lead Name and Date: Dhanalakshmi Kasi, Ph.D.

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	ALKINDI® Sprinkle	Adequate
Established name(s)	Hydrocortisone	Adequate
Route(s) of administration	Oral granules	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Oral Granules, 0.5 mg, 1 mg, 2 mg, 5 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Do not swallow the capsule. Do not chew or crush the granules.	Adequate

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

<table>
<tr><th>Item</th><th>Information Provided in the NDA</th><th>Assessor's Comments</th></tr>
<tr><td colspan="3">DOSAGE FORMS AND STRENGTHS section</td></tr>
<tr><td>Available dosage form(s)</td><td>Oral granules</td><td>Adequate</td></tr>
<tr><td>Strength(s) in metric system</td><td>0.5, 1, 2, 5 mg</td><td>Adequate</td></tr>
<tr><td>If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance</td><td>N/A</td><td>N/A</td></tr>
<tr><td>A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting</td><td>ALKINDI Sprinkle are oral granules contained within capsules and are available as follows:

<table><tr><th>Strength</th><th>Description</th></tr><tr><td>0.5 mg</td><td>INF-0.5" in red ink imprinted on capsules</td></tr><tr><td>1 mg</td><td>INF-1.0" in blue ink imprinted on capsules</td></tr><tr><td>2 mg</td><td>INF-2.0" in green ink imprinted on capsules</td></tr><tr><td>5 mg</td><td>INF-5.0" in gray ink imprinted on capsules</td></tr></table></td><td>Adequate</td></tr>
<tr><td>Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"</td><td>N/A</td><td>N/A</td></tr>
<tr><td>For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.</td><td>N/A</td><td>N/A</td></tr>
</table>

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	ALKINDI Sprinkle	Adequate
Dosage form(s) and route(s) of administration	Oral granules	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	N/A
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	microcrystalline cellulose, hypromellose, magnesium stearate, and ethyl cellulose	Adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	Glucocorticoid	Adequate
Chemical name, structural formula, molecular weight	11β,17α,21-trihydroxy-pregn-4-ene-3,20-dione $C_{21}H_{30}O_5$, 362 $g \cdot mol^{-1}$	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	Hydrocortisone is a white or almost white powder soluble in the pH range of 1- 7.	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	N/A

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

<table>
<tr><th>Item</th><th>Information Provided in the NDA</th><th>Assessor's Comments</th></tr>
<tr><td colspan="3">HOW SUPPLIED/STORAGE AND HANDLING section</td></tr>
<tr><td>Available dosage form(s)</td><td>Oral granules</td><td>Adequate</td></tr>
<tr><td>Strength(s) in metric system</td><td>0.5, 1, 2, 5 mg</td><td>Adequate</td></tr>
<tr><td>Available units (e.g., bottles of 100 tablets)</td><td>Amount in bottle: 50 capsules</td><td>Adequate</td></tr>
<tr><td>Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number</td><td>
<table>
<tr><th>Strength</th><th>Description</th><th>NDC</th></tr>
<tr><td>0.5 mg</td><td>INF-0.5" in red ink imprinted on capsules</td><td rowspan="4">(b) (4)</td></tr>
<tr><td>1 mg</td><td>INF-1.0" in blue ink imprinted on capsules</td></tr>
<tr><td>2 mg</td><td>INF-2.0" in green ink imprinted on capsules</td></tr>
<tr><td>5 mg</td><td>INF-5.0" in gray ink imprinted on capsules</td></tr>
</table>
</td><td>Adequate</td></tr>
<tr><td>Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"</td><td>N/A</td><td>N/A</td></tr>
<tr><td>For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.</td><td>N/A</td><td>N/A</td></tr>
</table>

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

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Store in the original bottle in order to protect from light. Once the bottle has been opened, use the capsules within 60 days.	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	desiccant	Adequate
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at controlled room temperature (USP) 20°C to 25°C (68°F to 77°F).	Adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	N/A
	(b) (4)	Adequate

1.2.5 Other Sections of Labeling

1.2.6 Manufacturing Information After Section 17 (for drug products)

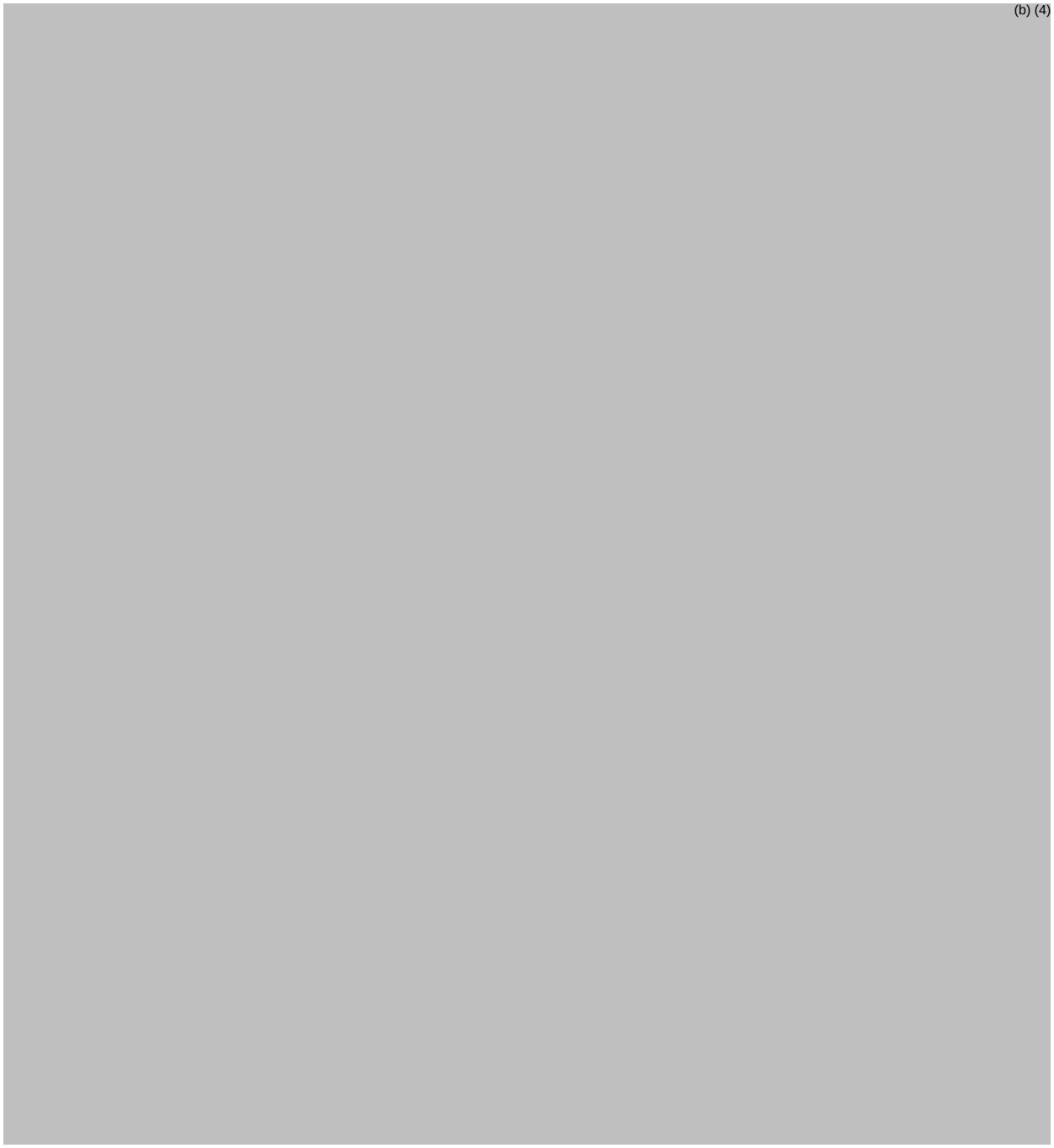
Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Alkindi Sprinkle is manufactured for Diurnal Limited by Glatt Pharmaceutical Services GmbH & Co. KG Werner-Glatt-Strasse 1, Binzen, Baden-Wuerttemberg, 79589, Germany, and is packaged by Delpharm Lille SAS, Parc d'Activités Roubaix-Est, 22 rue de Toufflers CS 50070, Lys Lez Lannoy, France.	Adequate

2.0 PATIENT LABELING

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

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label



3.2 Carton Labeling


(b) (4)

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	(b) (4)	Adequate
Dosage strength	0.5, 1, 2, 5	Adequate
Route of administration	Oral	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	N/A
Net contents (e.g. tablet count)	50	Adequate
"Rx only" displayed on the principal display	Rx only	Adequate
NDC number	NDC: 71863-109-50	Adequate
Lot number and expiration date	LOT: EXP: (b) (4)	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at controlled room temperature (US 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30 °C (59°F to 86°F). Store in the original bottle in order to protect from light.	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	N/A
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	N/A

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

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured for: eTon PHARMACEUTICALS Deer Park, IL 60010, USA Manufactured by: Glatt Pharmaceutical Services GmbH & Co. KG Werner-Glatt-Strasse 1 79589 Binzen, Germany	Adequate
Medication Guide (if applicable)	Capsules must be opened prior to administration. Do not swallow the capsule, risk of choking. Open capsule and sprinkle onto back of tongue, spoon, or soft food and administer immediately as instructed in the medication guide. Read the Medication Guide before use.	Adequate
No text on Ferrule and Cap overseal	N/A	N/A
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	N/A
And others, if space is available	N/A	N/A

Assessment of Carton and Container Labeling: ***Adequate***

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor Name and Date:

Ali Mohamadi, Ph.D.; 8/06/2020

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

David Claffey

Digitally signed by David Claffey
Date: 8/11/2020 10:00:43AM
GUID: 508da71e00029e20b201195abff380c2

Ali Mohamadi

Digitally signed by Ali Mohamadi
Date: 8/07/2020 11:28:51AM
GUID: 508da6ea0002750ec7c6cb7cfc37f10e

CHAPTER VI: BIOPHARMACEUTICS

Product Information	Diurnal Limited submitted an NDA under 505(b)(2) for Alkindi Sprinkle (Hydrocortisone) Oral Granules (Granules in capsule for opening) 0.5 mg, 1 mg, 2 mg, and 5 mg as a treatment for replacement therapy of adrenal insufficiency.
NDA Number	213876
Assessment Cycle Number	1
Drug Product Name/ Strength	Alkindi Sprinkle (Hydrocortisone) granules 0.5 mg, 1 mg, 2 mg, 5 mg
Route of Administration	Oral
Applicant Name	Diurnal Limited, UK
Therapeutic Classification/ **OND Division**	Division of Metabolism and Endocrinology Products
RLD/RS Number	Cortef™ (NDA 008697) Tablet; 5, 10, 20 mg (Pharmacia-Upjohn , currently Pfizer) (Approval Date: 12/15/1952)
Proposed Indication	Replacement therapy of adrenal insufficiency in infants, children and adolescents (from birth to <17 years old)

Assessment Recommendation: **Adequate**

Assessment Summary:

Diurnal Limited ("Applicant") submitted an NDA under 505(b)(2) regulatory pathway to market Alkindi Sprinkle (Hydrocortisone) Oral Granule (proposed name, also referenced as 'Infacort' in the submission) as a replacement therapy for adrenal insufficiency in infants, children and adolescents (from birth to <17 years old). The reference drug product is Cortef® (hydrocortisone tablets, 5 mg, 10 mg and 20 mg)(NDA 008697, Pharmacia Upjohn currently Pfizer, initially approved on 12/15/1952). The proposed product is designed as an immediate release product (multiparticulate taste-masked granules in capsule) at strengths of 0.5 mg, 1 mg, 2 mg and 5 mg and supplied in a transparent hard gelatin capsule shell (size 00) with color-coded imprint for each strength. The capsule acts as a container closure system for granules and per product labeling, it is not intended to be swallowed. During oral administration of granules, the contents of the capsule (granules) can be taken directly into the mouth with co-administered fluid or sprinkled onto soft-food before dosing. To avoid unintended buccal absorption and bitter taste, the taste masked granules should not be chewed. The capsules are packaged in HDPE bottle.

Biopharmaceutics review is focused on the assessment of the dissolution method and acceptance criterion for routine quality control of the granules at release and stability including the effect of co-administered fluids and soft-food on the performance of in vitro dissolution.

Since individual dose for children is 0.5 mg to 1 mg, currently available lowest strength for tablet is 5 mg which should be crushed or split before oral administration to children. For

children dosing as well as to avoid bitter tasting from crushed or split tablet, the proposed granule formulation for pediatric patient was investigated. The quality target product profile (QTPP) of the proposed product is listed as: (a) immediate release functionality, (b) taste masked formulation, (c) suitable for pediatric patients, (d) oral route of administration, (e) accurate dosing at low pediatric dose strengths, mixing and administration with suitable fluids and foods.

The granules with typical mean diameter of (b) (4) mm were prepared by (b) (4)

The Applicant developed an in-house dissolution method to perform in vitro dissolution test for granules. Hydrocortisone (API) is a BCS Class I drug (as claimed by the applicant) and it is soluble across the physiological range (pH1-7). For the development of dissolution method, (b) (4) were considered. (b) (4) Nevertheless, considering the high solubility nature of the drug substance, the proposed in vitro dissolution method deemed adequate as a Quality Control (QC) method. Since proposed acceptance criterion for dissolution (NLT (b) (4) %(Q) in 45 min) was considered permissive, we recommended a revised acceptance criterion for dissolution (NLT (b) (4) %(Q) in 45 min) based on biobatch dissolution data generated by the above QC method. The Applicant accepted the Agency's recommendation and updated the dissolution specification and related document in the NDA.

Table 1. Approved Dissolution Method and Acceptance Criterion

Source	USP Apparatus	Speed	Medium	Temperature	Volume (mL)	Proposed Acceptance Criterion	Approved Acceptance Criterion
In-House	II	75 rpm	pH 1.2, 0.1M HCl	37°C	700 mL	NLT (b) (4) %(Q) in 45 min	NLT (b) (4) %(Q) in 45 min

Since granules are designed for oral administration into the mouth and then wash down with fluids (e.g. breast milk, whole milk, formula milk) or mixed with soft-food (apple sauce, yoghurt) to assist dosing, the compatibility study was performed to assess the impact of the co-administered fluid/soft-food on in vitro dissolution of the product. The standard dissolution apparatus could not be used for in vitro compatibility study (b) (4) A mini paddle apparatus (a miniature version of USP II Apparatus, QC Method) was selected for the dissolution study with co-administered fluid/soft-food. The dissolution parameters include volume of dissolution medium (200 mL), pH of the dissolution medium (1.8 or 4.0), rotational speed (100 rpm), and temperature (37°C). The use of simulated gastric fluid as the dissolution medium is justified (b) (4) . The Applicant did not provide the data regarding the discriminating nature of this dissolution method. However, considering the high solubility

nature of the drug substance, the proposed mini-paddle dissolution method appears to be adequate. The dissolution data with fluids showed 75-80% dissolution in 30 minutes for 0.5 mg dose but slightly less for 5 mg dose. The lower values for max dose could be attributed to coning effect as well as other physiological conditions. The dissolution data from co-administered soft-food showed >80% dissolution within 30 minutes in all scenarios. Hence, the compatibility study demonstrated that co-administered fluid/soft-food is not likely to have any effect on the in vitro dissolution performance of the product.

Risk Assessment for Dissolution:

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
(b) (4)				

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Original Application (SR#001)	11/29/2019
Amendment (SR#007)	05/07/2020
Amendment (SR#010)	06/25/2020

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

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): N/A

B.1 BCS DESIGNATION

Assessment: The Applicant does not request a BCS designation in this application therefore BCS classification is not evaluated comprehensively. Based on the solubility and permeability data, it appears the claim of BCS class 1 is supported.

- **Solubility:** The drug substance has an aqueous solubility of [redacted] (b) (4) mg/mL over the pH range 1-8 [redacted] (D) (4) . The Applicant indicated that hydrocortisone is a **BCS Class I** substance (highly soluble) and it met the criteria that the highest dose strength should be soluble in <250 mL of water over a pH range 1-7.5.
- **Permeability:** High based on P_{eff} (effective permeability coefficient) in rats and its low-dose bioavailability of 96%
- **Dissolution:** See the Biopharm Review below.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Dissolution Method: The Applicant developed in-house dissolution method to perform in vitro dissolution test for granules.

Dissolution Method Development:

[redacted] (b) (4)

[1] NDA213876 (213876 - 0004 - (4) - 2020-03-11 - ORIG-1 /Multiple Categories/Subcategories) - Pharmaceutical Development (Alkindi, Granules) (#40)

(b) (4)

Proposed Dissolution Method:

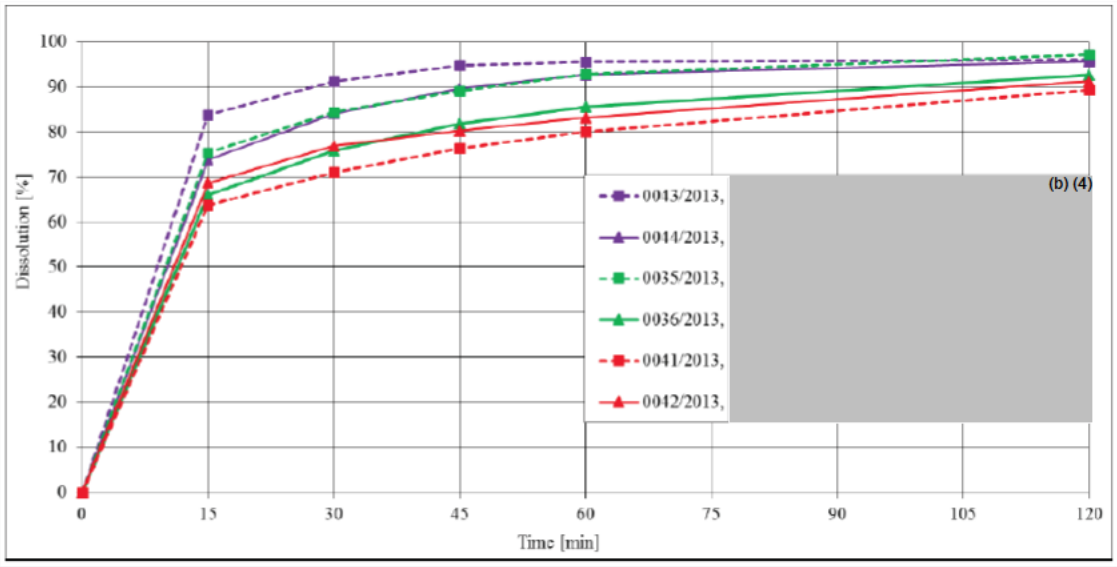
Source	USP Apparatus	Speed	Medium	Temperature	Volume (mL)	Sampling Times
In-House	II	75 rpm	pH 1.2, 0.1M HCl	37°C	700 mL	10. 15, 20, 30 45, 60, 120 min

a) Discriminating Power of the Proposed Dissolution Method

- **Formulation Changes:** To verify discriminatory nature of the proposed QC dissolution test, batches of the finished product containing various levels of the coatings (seal-coat and taste-mask coat) were evaluated during the development stage. (b) (4)

Fig 2. In vitro dissolution profiles of prototype product (granules) containing different % seal coat (SC) levels (b) (4) In vitro dissolution was conducted in 700 mL 0.1M HCl at 75 rpm (Apparatus 2, paddle).

[2] NDA213876 (213876 - 0004 - (4) - 2020-03-11 - ORIG-1 /Multiple Categories/Subcategories) - Pharmaceutical Development (Alkindi, Granules) (#42)



Based on the above in vitro dissolution profiles for granules containing different taste masking coat weight gain (b) (4) and varying seal coat weight gain (b) (4) the proposed dissolution method can detect formulation changes. For example, when the level of coating is higher (thicker), the dissolution rate is reduced. (b) (4) was selected for the final formulation.

- **Changes in Manufacturing Process Conditions:** The Applicant did not provide any information on the dissolution method to discriminate changes in the manufacturing process conditions. (b) (4) However, comparative dissolution profiles of the products in QC Media (pH 1.2) showed similarity (f2>50). Therefore, the dissolution method can't discriminate changes in the manufacturing process parameters. Based on additional dissolution data using other dissolution mediums (pH 4.5 and pH 6.8), all batches of granules produced at different scales have equivalent in vitro dissolution performance.

b) Analytical Method for Dissolution: The Applicant employed HPLC-UV method for the analysis of hydrocortisone. Dissolution method is evaluated by the use of the method of external standards.

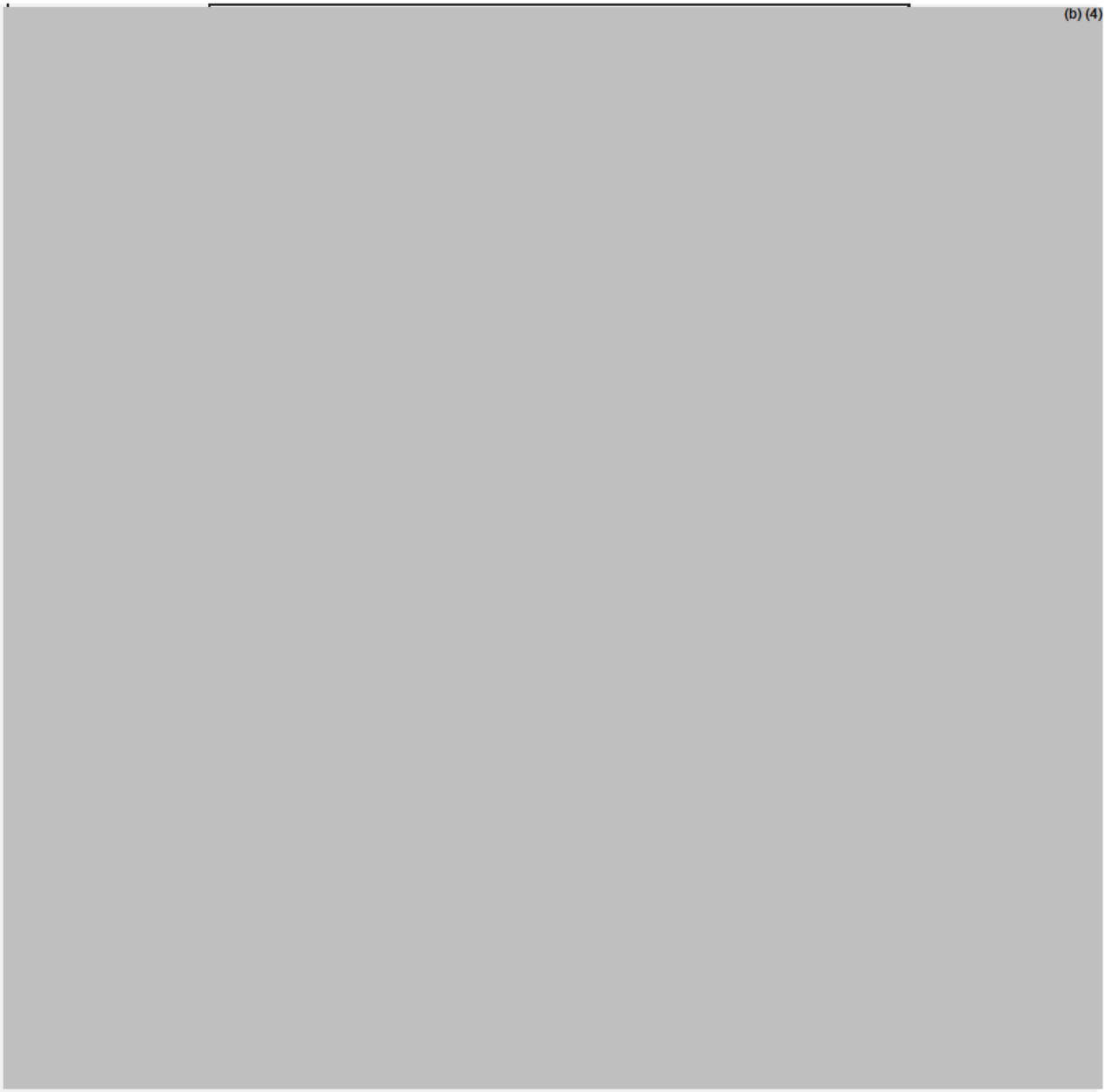
(b) (4)

c) **Validation of Analytical Procedures for Dissolution:** The validation of HPLC-UV method is provided according to the Guideline of ICHQ2(R1). For assessment of validation of HPLC-UV method, see DS/DP review.

d) **Dissolution Data and Specification:** In the original submission, the applicant did not provide individual dissolution data from Biobatch #0848/2017 or batches of other strengths used to demonstrate similarity.

Following comment was sent to the firm on 4/30/2020:

(b) (4)



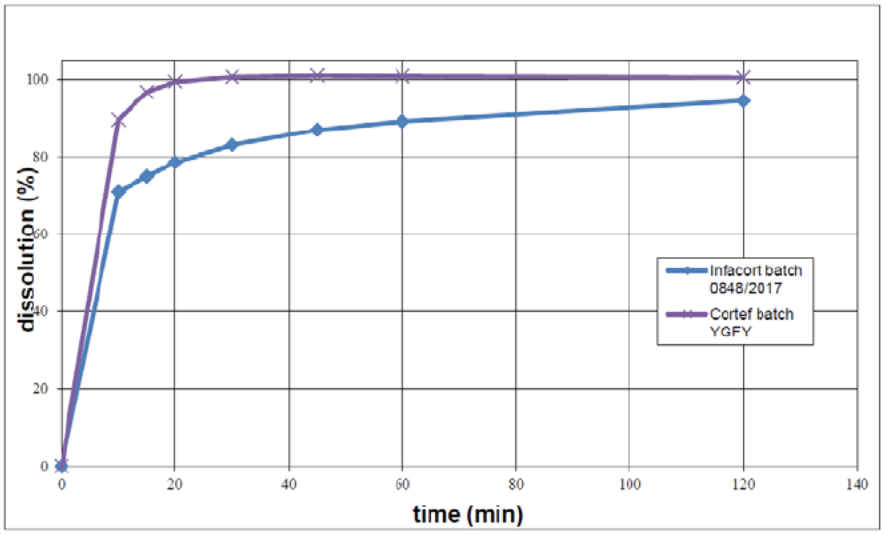
e) Comparative Dissolution Profiles:

The BE study was conducted to demonstrate the bioequivalence of the proposed product (batch#1019/2017)[3] and listed product (LD). The bioequivalence study was reviewed by clinical pharmacology team and determined that Test and Ref products are bioequivalent.[4] Comparative in vitro dissolution profiles of US biobatch (#0848/2017) 5 mg (4x5 mg) vs 20 mg US hydrocortisone reference (Pharmacia and Upjohn) Cortef batch #YGFY used in the BE study were provided. Results are shown for dissolution testes in media at three different pH values (pH 1.2, pH, pH 4.5 and pH 6.8). Following is the dissolution profile of Test and Reference product in QC medium (pH 1.2).[5]

[3] Batch#1019/2017 is a sublot of Batch#0848/2017 (bulk capsule batch)
[4] Clinical Pharmacology Review in DARRTS (5/22/2020)
https://darrts fda.gov//darrts/faces/ViewDocument?documentId=090140af8056749f&_afrRedirect=814516444973564
[5] NDA213876 (213876 - 0009 - (9) - 2020-05-29 - ORIG-1 /Quality/Response To Information Request) - Pharmaceutical Development (Alkindi, Granules)

pH 1.2 (QC)

Figure 3.2.P.2.2.1-3: Comparative Dissolution Profiles in pH 1.2 (QC media) for the Infacort 007 Drug Product Biocquivalence batch and 20mg hydrocortisone tablets (n=12). *In vitro* dissolution was conducted in 700ml 0.1M HCl (pH 1.2) at 75rpm (Apparatus 2, paddle)



The Applicant also provided f2 similarity results in different pH media conditions comparing Infacort#007 US biobatch 0848/2017 (5 mg) to other strengths (0.5 mg, 1.0 mg 2.0 mg).

Table 1: USbiobatch#0848/2017 (5 mg) vs other strengths: f2 similarity study (as submitted)

***In vitro* dissolution media pH conditions**	**f2 Similarity values**			**Acceptance Criteria (f2 >50)**
	0320/2013	**0377/2015**	**0321/2013**	
pH 1.2 (QC media)	61	52	61	Complies
pH 4.5	65	86	62	Complies
pH 6.8	58	50	58	Complies

Reviewer's Comment: The dissolution profiles of US biobatch in different pH medium including QC medium (pH 1.2) were found to be similar with batches of all other strengths (0.5 mg, 1.0 mg, 2.0 mg).

f) Information Request

See **Appendix 1**.

B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA *(e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)*

Assessment: *N/A*

B.4 APPLICATION OF DISSOLUTION/IVIVC IN QbD

Assessment: *N/A*

B.5 MODIFIED RELEASE ORAL DRUG PRODUCTS – *In-Vitro Alcohol Dose Dumping*

Assessment: *N/A*

B.6 IN-VITRO SOFT-FOOD INTERACTION STUDY

Assessment: `

The proposed product (granules) is intended to be administered to young children (newborns <28 days old; infants and toddlers >28 days to 23 months; pre-school children 2-6 years old). The granules are designed for oral administration into the mouth and washed down immediately with fluids or mixed with a spoonful of soft-food and washed down with fluids immediately following administration. The granules are supplied in a hard gelatin transparent capsule but the capsule acts as a container closure system only. Compatibility of the granules with administration fluids including breast milk, whole milk, formula (artificial) milk and water was provided. In support of compatibility, in vitro dissolution tests and compatibility studies were performed. Part of the compatibility study involves in-use stability (assay, degradation etc.) which was evaluated by drug product reviewer. See drug product review in Panorama for the adequacy of the compatibility information.

Dissolution Method Development for Co-administered Fluid/soft-food Compatibility Study:

(b) (4)

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[6] Klein, S and Shah, V.P; A standardized Mini Paddle Apparatus as an Alternative to the Standard Paddle, AAPS PharmSciTech, Vol 9, No.4, Dec 2008.

(b) (4)

[redacted]

Proposed Dissolution Method for Compatibility Test:

Source	Apparatus	Speed	Medium	Temperature	Volume (mL)	Sampling Plan
In-House	Mini-Paddle (non-compendial)(DT 600, Erweka, Heusenstamm, Germany)	100 rpm	pH 1.8 or pH 4.0	37°C	200 mL	5, 10. 15, 30, 45, 60, 90, 120 mins

Dissolution Test Procedure: (b) (4)

(b) (4)

[redacted]

(b) (4)

[redacted]

Dissolution Study Results:

- ***With Co-administered Fluids:***

Dissolution of the granules (0.5 mg and 5.0 mg) when simulating co-administration with water, breast milks, formula milk 1 (baby formula) to neonates, formula milk 3 (infant formula) to infants and whole milk to pre-school children: Dissolution of the 0.5 mg dose in media and volumes intended to simulate initial gastric conditions after dose administration was complete in all scenarios, i.e. > 80% of the dose was released in the neonate and the infant scenario and >75% in the pre-school children setup within 30 mins. However, the results for the 5 mg dose were ~5-10% lower in all simulated age scenarios.

Representative Dissolution Profiles:

Figure 3.2.P.2.6-4: Dissolution of Infacort 0.5 mg when simulating co-administration of the Drug Product with water, breast milks and formula milk 3 (infant formula) to infants (mean of n=3 ± SD)

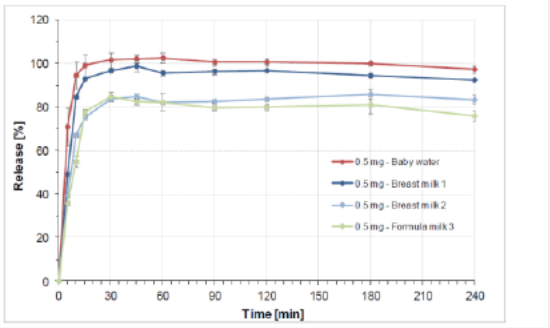
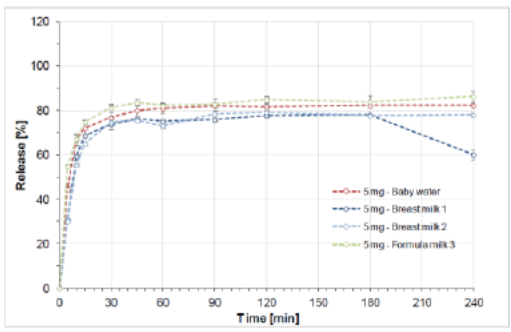


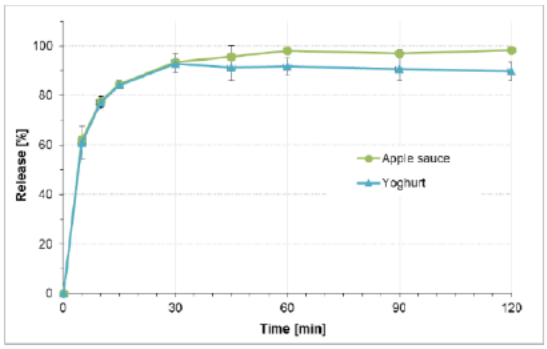
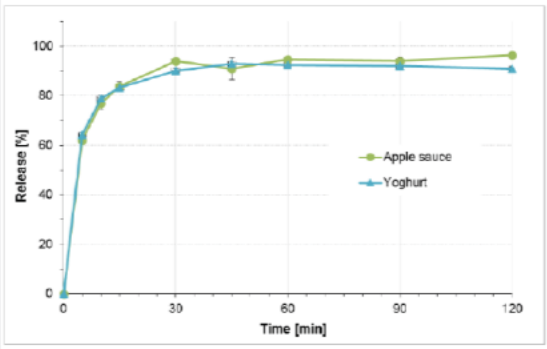
Figure 3.2.P.2.6-5: Dissolution of Infacort 5.0 mg when simulating co-administration of the Drug Product with water, breast milks and formula milk 3 (infant formula) to infants (mean of n=3 ± SD)



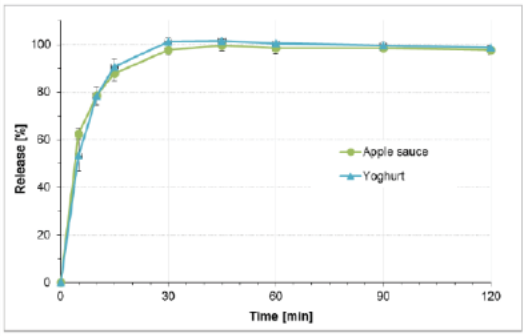
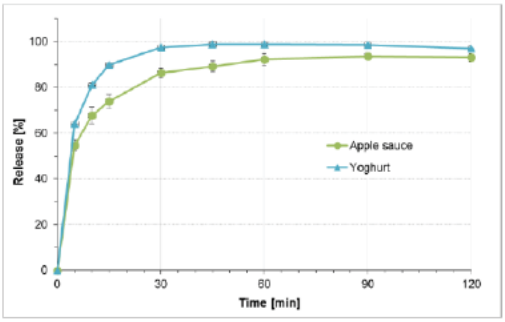
(b) (4) Nevertheless, the dissolution study showed that small differences could be observed in the total amount of drug dissolved when comparing the simulated administration of maximum (5 mg) and minimum (0.5 mg) doses in different administration fluids. (b) (4) The Applicant concluded that considering the variability, it is very unlikely that the composition of the co-administered fluid will affect in vivo dissolution and bioavailability.

- ***With Soft-foods***

Based on in vitro dissolution results obtained when ***simulating*** co-administration of proposed product (granules) 2.5 mg with a teaspoon of soft food followed by a small (35 mL) fluid volume to infants and pre-school children, >85% dissolution was noted after 30 min:

pH 1.8	pH 4.0
Figure 3.2.P.2.6-9: Dissolution profiles obtained when simulating co-administration of 2.5mg hydrocortisone with 1 teaspoon (5mL) of soft food + 35mL fluid in infants or pre-school children with a resting gastric fluid pH of 1.8 (mean of n=3 ± SD)	Figure 3.2.P.2.6-10: Dissolution profiles obtained when simulating co-administration of 2.5mg hydrocortisone with 1 teaspoon (5mL) of soft food + 35mL fluid in infants or pre-school children with a resting gastric fluid pH of 4.0 (mean of n=3 ± SD)
	

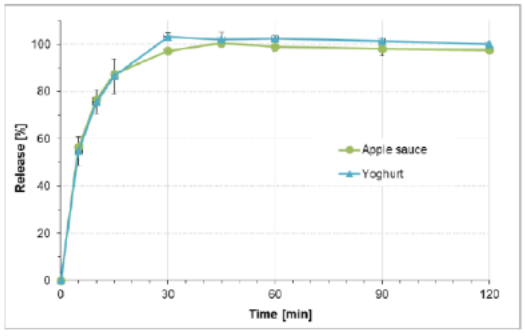
Based on in vitro dissolution results obtained when ***simulating*** co-administration of proposed product (granules) 2.5 mg with a teaspoon of soft food followed by a larger (85 mL) fluid volume to infants and pre-school children, >85% dissolution was noted after 30 min for all except apple sauce showed slightly less than 85% at pH 4.0.

pH 1.8	pH 4.0
Figure 3.2.P.2.6-11: Dissolution profiles obtained when simulating co-administration of 2.5mg hydrocortisone with 1 teaspoon (5mL) of soft-food + 85mL fluid in infants or pre-school children with a resting gastric fluid pH of 1.8 (mean of n=3 ± SD)	Figure 3.2.P.2.6-12: Dissolution profiles obtained when simulating co-administration of 2.5mg hydrocortisone with 1 teaspoon (5mL) of soft-food + 85mL fluid in infants or pre-school children with a resting gastric fluid pH of 4.0 (mean of n=3 ± SD)
	

Based on in vitro dissolution results obtained when ***simulating*** co-administration of proposed product (granules) 5 mg with a teaspoon of soft food followed by 170 mL fluid volume to school children, >85% dissolution was noted after 30 min.

pH 1.8

Figure 3.2.P.2.6-13: Dissolution profiles obtained when simulating co-administration of 5mg hydrocortisone with 1 teaspoon (5mL) of soft-food + 170mL fluid in school children with a resting gastric fluid pH of 1.8 (mean of n=3 ± SD)



Comparing the dissolution profiles of the simulated conditions for children of different age group and available gastric volumes, more than 80% dissolution occurs within 30 min in all cases. The

Applicant stated that no drug precipitation was observed during the 2-hour test period which also represent the maximum gastric residence time. Hence, commonly used soft-food like apple sauce and yogurt when co-administered with the granules has little or no influence on the dissolution rate of the product.

Reviewer's Comment on Compatibility Study:

- **On dissolution Method**: The proposed dissolution method was developed for the compatibility study of the product with co-administered fluid or soft food appears rational. The QC method uses USP II (paddle) with a speed of 75 rpm. In this case, the miniature version of the standard paddle apparatus needed 100 rpm to minimize coning effect. Literature[9] evidence suggests that the proposed increase of rotational speed to adjust low volume condition is acceptable. Considering gastric residence time for granules (including possible floating behavior of granules in gastric fluid), the selection of simulated gastric fluid (pH1.8 or 4.0) is adequate. While the Applicant reasoned the use of low volume of dissolution media and simulated gastric fluid conditions, the discriminating ability of the method is unknown. The proposed dissolution method does not consider other physiological factors like bile salts, gastric secretion, etc. for real-time data. Hence, considering the variability, the proposed dissolution method can be used for compatibility study.
- **On Compatibility Study**: Based on the dissolution study provided in the submission, the co-administered fluid study showed >75% to 80% dissolution in 30 minutes for 0.5 mg (minimum dose) but slightly less (5-10%) for 5 mg dose in all scenarios. The Applicant reasoned that such difference is possibly due to coning effect even at 100 rpm. In addition, the 5 mg dose is the highest available dose for granules which is higher than what is prescribed in replacement therapy for children. The Applicant stated that individual doses of 0.5 mg to 1 mg are common in small children. There are several variables which can't be appropriately incorporated in the design of in vitro dissolution study. Based on the floating nature of the granules in the gastric fluid, it may increase gastric residence time. Since 75-80% dissolution is accomplished in 30 minutes, the dissolution of the product is expected to be complete in gastric pH. So, considering the inherent variability of the system, it is expected that the co-administered fluid has little or no influence on the dissolution of the product in stomach pH (1.8 or 4.0). In case of soft-food study, >80% dissolution was accomplished in 30 minutes in all scenarios. This is true for both maximum (5 mg) and minimum (0.5 mg) doses. Hence, it can be assumed that there is no compatibility issues with the co-administered soft-food matrices.

Overall, the compatibility study demonstrated that co-administered fluid/soft-food is not likely to have any effect on the in vitro dissolution performance of the product.

B.7 IN-VITRO RELEASE TESTING (IVRT) FOR SEMI-SOLID PRODUCTS

Assessment: ***{Adequate/Inadequate} N/A***

B.8 IN-VITRO PERMEATION TESTING (IVPT) FOR TRANSDERMAL/TOPICAL PRODUCTS

Assessment: ***N/A***

[9] Klein, S. and V.P. Shah, A standardized mini paddle apparatus as an alternative to the standard paddle. AAPS PharmSciTech, 2008. 9(4): p. 1179-84.

B.9 IN-VITRO DISSOLUTION TESTING FOR ABUSE-DETERRENT PRODUCTS

Assessment: ***N/A***

B.10 IN-VITRO BE EVALUATION FOR PULMONARY PRODUCTS

Assessment: ***{Adequate/Inadequate} N/A***

B.11 EXTENDED RELEASE DOSAGE FORMS –*Extended Release Claim*

Assessment: ***{Adequate/Inadequate} N/A***

B.12 BRIDGING OF FORMULATIONS

Assessment: ***{Adequate/Inadequate} N/A***

B. 13 BIOWAIVER REQUEST

Assessment: ***{Adequate/Inadequate} N/A***

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: ***{Adequate/Inadequate} N/A***

Post-Approval Commitments

Assessment: ***{Adequate/Inadequate}None***

Lifecycle Management Considerations

None

BIOPHARMACEUTICS LIST OF DEFICIENCIES (Outstanding)

None

Primary Biopharmaceutics Assessor's Name and Date:
Debasis Ghosh, Ph.D.
July 28, 2020

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

Min Li, Ph.D.

July 28, 2020

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Debasis Ghosh

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Min Li

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