CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212320Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 212320
Review #1

Drug Name/Dosage Form	Accrufer (ferric maltol) Capsules
Strength	30 mg
Route of Administration	Oral
Rx/OTC Dispensed	R_x
Applicant	Shield TX (UK) Ltd
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	27-Sept-18	All
Amendment	15-Oct-18	Process, Facilities
Amendment	9-Nov-18	Process
Amendment	14-Feb-19	DP
Amendment	8-Apr-19	DP

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Rohit Tiwari	Su Tran
Drug Product	Rajiv Agarwal	Anamitro Banerjee
Process and Facility	Huiquan Wu	Bogdan Kurtyka
Microbiology	n/a	n/a
Biopharmaceutics	Mei Ou	Banu Zolnik
Regulatory Business Process Manager	Kelly Ballard	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a
Environmental	Rajiv Agarwal	Anamitro Banerjee

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends APPROVAL of NDA 212320 for Accrufer (ferric maltol) Capsules, 30 mg. As part of this action, OPQ grants a (b) (4) retest period for the drug substance when stored (b) (4) and a 21-month expiry for the drug product when stored at 20 C to 25 C (68 F to 77 F); excursions permitted between 15 C to 30 C (59 F to 86 F). The Office of Pharmaceutical Quality (OPQ) has the following has the following Post-Marketing Commitment (PMC) to be conveyed to the applicant:

- PMC-1:
  1. Collect and submit multipoint dissolution profiles (5, 10, 15, 20 and 30 minutes) using the FDA's approved dissolution method (USP II (paddle) with sinker, 75 rpm, Tier 1: KCl/HCl Buffer, pH 1.2; Tier 2: KCl/HCl buffer with addition of Pepsin (700,000 to 750,000 unit/L, 900 mL) from newly manufactured commercial batches (minimum of six) and current stability registration batches.
  2. Include your proposal for the final acceptance criterion of the dissolution test of ACCRUFER capsules, 30 mg, which setting should be based on the newly collected data.
  3. If Tier 1 dissolution fails due to crosslinking, you may proceed to use Tier 2 dissolution testing with Pepsin as per USP. Provide evidence of cross-linking in gelatin capsules. Include photographic documentation or capsule switching test might be used to confirm crosslinking.

PMC Schedule Milestones: **Study Completion:** **September 2020**

The PMC report should be submitted to the Agency as a Prior Approval Supplement to NDA 212320 within twelve (12) months of the NDA's action date.

II. Summary of Quality Assessments

A. Product Overview

NDA 212320 was submitted for Accrufer (ferric maltol) Capsules, 30 mg in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act by Shield TX (UK) Ltd. Ferric maltol is an oral monotherapy indicated for the treatment of iron deficiency. Ferric maltol is intended to treat adults with iron deficiency (ID)/iron deficiency anemia (IDA), including those with previous intolerance to oral ferrous irons. Ferric maltol is a chemically stable complex of ferric iron and maltol. (b) (4) The ferric maltol is currently approved in the European

Union (EU) for the treatment of iron deficiency under the proprietary name Feraccru®. Feraccru® 30 mg capsules are commercially available in 12 countries.

Ferric maltol is a chemically stable complex of ferric iron and maltol that has poor flowability. The drug substance is manufactured by (b) (4) at a commercial batch size of (b) (4) The drug product is an immediate release, 30 mg oral dosage form that is presented as a red (b) (4), hard-gelatin capsules containing 30 mg of the active (in the form of 231.5 mg of ferric maltol), lactose monohydrate, sodium lauryl sulfate, colloidal (b) (4) crospovidone and magnesium stearate. The capsule body is imprinted with "30" in black ink. The 30 mg dose is equivalent to 231.5 mg of ferric maltol.

The recommended dosing regimen for Accrufer Capsules is 30 mg orally twice daily on an empty stomach. Treatment will vary based on the iron but will generally last at least 12-weeks.

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 2123320 and grants a (b) (4) re-test period for the drug substance and a 21-month expiration period for the drug product when stored at 20 C to 25 C (68 F to 77 F) in the proposed commercial packaging.

Proposed Indication(s) including Intended Patient Population	Indicated for the treatment of iron deficiency
Duration of Treatment	12+ weeks
Maximum Daily Dose	60 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance

Ferric maltol is a chemically stable complex of ferric iron and maltol. It is a dark reddish-brown solid that is slightly soluble in water, methanol, acetone and dichloromethane. Ferric Maltol is manufactured by (b) (4) The manufacturing process (b) (4). Ferric Maltol drug substance is produced at a commercial

batch size of (b) (4)

The controls for all CQAs are adequately described in the submission. It was concluded that the drug substance manufacturing process is described in sufficient detail to clearly delineate how impurities are formed, how changes in the process could potentially affect the formation, fate, and purge of impurities and why the proposed control strategy is suitable for the drug substance manufacturing process.

Polymorph screenings for the drug substance revealed 2 different crystalline forms (b) (4) Drug product containing (b) (4) was used in the pivotal Phase 1 studies and drug product containing (b) (4) were used in the Phase 3 studies that support this NDA ((b) (4) was used in study ST10-01-301/2 and (b) (4) was used in study ST10-01-303). It was concluded that polymorphic form has no impact on the performance of the drug product; however, the risk of the presence of the undesirable polymorphic form is mitigated as the polymorphic form is controlled in the drug substance specification. A summary of the results of the polymorphic studies is included in the drug substance review.

Specifications and acceptance criteria for the drug substance are consistent with ICH Q6A and are adequate to ensure the quality of the drug substance as it relates to the safety and efficacy of the drug product. All analytical methods are described in adequate detail and are appropriate for their intended use. All validation parameters (system suitability and system precision, specificity, linearity, range, precision, accuracy, ruggedness, robustness, and stability of solutions) are provided in the NDA and are adequate.

The drug substance will be packaged (b) (4) . Registration stability studies were conducted on three batches 3 batches of the drug substance manufactured at the (b) (4) The samples were manufactured according to the commercial manufacturing scheme, packaged in the commercial container closure system and stored for up to (b) (4) Additionally, (b) (4) stability data were included for 3 representative batches that were manufactured by (b) (4) real-time data were included for the first 3 commercial batches manufactured at a (b) (4) scale. The (b) (4) batches were used to manufacture the Phase 3 clinical material. The stability data for the registration batches and for the supportive batches demonstrated no notable changes after up to (b) (4) of storage (b) (4) The applicant requested (b) (4) retest for drug substance when stored (b) (4) Based on the available long-term, accelerated, forced

degradation and stress data, the proposed retest of (b) (4) retest for the drug substance when stored at (b) (4) is acceptable.

NDA 212320 is recommended for approval from a drug substance perspective.

Drug Product

The drug product, Accrufer Capsule, is presented as a 30 mg, immediate-release hard gelatin capsule containing of Fe^{3+} in the form of 231.5 mg of ferric maltol together with lactose monohydrate, sodium lauryl sulfate, colloidal (b) (4) crospovidone and magnesium stearate in a (b) (4) hard gelatin capsule. The capsule body is imprinted with "30" in black ink. All excipients are compendial, commonly used in solid oral dosage forms and demonstrate good compatibility with the drug substance.

The drug product is manufactured by (b) (4) at a commercial batch size of (b) (4) which translates to (b) (4) capsules. The manufacturing process (b) (4) . The drug product is manufactured (b) (4)

The QTPP was defined and the CQAs were identified. The proposed process parameters and in-process controls were described in sufficient detail and justified. The applicant demonstrated the suitability of the manufacturing process for the drug product at commercial scale. The description of the manufacturing process includes appropriate in-process controls and operating parameters.

The drug product will be packaged in 90 cc, tamper evident, 56-count white, opaque, HDPE bottles with a child-proof, white, opaque polypropylene push-lock closure. The packaging components comply with applicable FDA indirect food additive regulations (21CFR177.1520) (b) (4)

The drug product specifications are consistent with ICH Q6A and are based on batch analyses and stability data. The drug product specifications included appearance, identification, assay, content uniformity, Fe (III) Iron content, maltol content, related substances, (b) (4), dissolution, and microbial limits. The drug product specification was devoid of testing for polymorphic form of the drug substance in the drug product and for elemental impurities. The dissolution profile demonstrated no difference between batches made from (b) (4). Accordingly, it was concluded that the drug substance in the drug product is stable with respect to polymorphic form and the omission of the test for polymorphic form is adequately

justified. The applicant tested eight batches of the drug product and included a risk assessment for elemental impurities (b) (4) The results demonstrated that (b) (4) for individual elements for a parenteral drug product. 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 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. The drug product specifications provide adequate controls to ensure the quality of the drug product throughout the product expiry.

Twenty-four months long-term and 6 months accelerated stability data are included for 3 pilot-scale batches ((b) (4) capsule) of the drug product (batches B08908, B08909 and B08915) packaged in the proposed commercial packaging and manufactured according to the proposed commercial manufacturing process. The applicant also included up to 36 months of supportive stability (see drug product review for details) All stability studies were executed in accordance with the ICH 1A and Q1B.

Based on the stability data provided, Shield TX proposed and the FDA accepts the expiration dating period of **21 months** for the drug product when stored at stored at controlled room temperature in the commercial packaging.

NDA 212320 is recommended for approval from a drug product perspective.

Biopharmaceutics

The biopharmaceutics review focused on (1) the acceptability of the proposed dissolution method and acceptance criterion for the routine QC testing of the proposed drug product at batch release and on stability and (2) site bridging in the drug product development.

Dissolution Specification and Method: The dissolution method includes a USP Apparatus II (Paddle) at 75 RPM. The tier 1 dissolution medium is 900 mL of KCl/ HCl Buffer pH1.2 and the Tier 2 dissolution medium is 900 mL of KCl/HCl Buffer with the addition of Pepsin (700,000 to 750,000 unit/L). The proposed dissolution acceptance criterion is Q= (b) (4) % in 30 minutes.

(b) (4) accordingly, the FDA recommended the development of a new dissolution method (pH 1.2). During the review cycle, very limited dissolution data were submitted using the newly developed acceptable dissolution method (pH 1.2). Additionally, due to the observed crosslinking, it was recommended that a Tier 2 dissolution method be implemented. The Applicant implement the Tier 2 dissolution and provided Tier 2 dissolution data which included the use of Pepsin and (b) (4) the Applicant was requested to remove (b) (4) and to provide complete dissolution profile data (5, 10, 15, 20 and 30 minutes) on newly

manufactured batches and the registration-stability batches to support the setting of the final dissolution acceptance criterion under a Post-Marketing Commitment (PMC). The proposed acceptance criterion (Q= (b) (4)% in 30 min) is considered acceptable on an interim basis for release and on stability because review of the dissolution data appeared to support a dissolution acceptance criterion of Q= (b) (4)% in (b) (4) Accordingly, under PMC # 3658, the Applicant agreed to provide multipoint dissolution profiles using the approved dissolution method from newly manufactured commercial batches (minimum of six) and current stability registration batches. As part of this PMC, the Applicant also committed to provide evidence of cross-linking in gelatin capsules. At the end of the study, the Applicant will propose a final dissolution acceptance criterion for the drug product.

Bridging of the Clinical Formulations:
The clinical development batches of the drug substance and drug product were all manufactured at (b) (4) The commercial drug product will be manufactured at (b) (4) using drug substance manufactured at (b) (4) however, the (b) (4) site will serve as a back-up site of manufacture of drug substance. To date, no commercial drug product has been manufactured using (b) (4) drug substance. To support the new drug substance site at (b) (4) and the additional drug product manufacturing site (b) (4) , the Applicant provided comparative dissolution profiles in multi pH media (pH 1.2, 4.5 and 6.8). The (b) (4) batch showed comparable dissolution profiles in pH 1.2, 4.5 and 6.8 to the (b) (4) batch. Accordingly, the comparative dissolution profiles support the manufacturing site change.

NDA 212320 is recommended for approval from a biopharmaceutics perspective with a requirement for the completion of PMC #3658 within 12 months of the NDA's action date.

Facilities
NDA 212320 included 8 facilities:

- (b) (4)

All facilities listed in NDA 212320 were deemed acceptable for the responsibility listed in the application (see facilities review for details). Accordingly, this application is recommended for approval from a compliance perspective.

Environmental Assessment

The applicant submitted a claim for categorical exclusion and a statement that this action will not significantly affect the quality of the human environment in accordance with 21 CFR 25.5(c) 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

33 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

LABELING (NDA 212320) ACCRUFER (ferric maltol)

R Regional Information

1.14 Labeling

Labeling & Package Insert

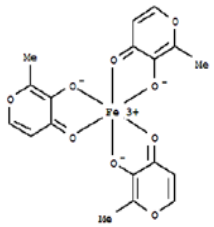
DESCRIPTION section:

(b) (4)

11 DESCRIPTION

ACCRUFER (ferric maltol) capsules, an iron replacement product for oral administration, contain 30 mg-iron and 201.5 mg maltol. Ferric maltol contains iron in a stable ferric state as a complex with a trimaltol ligand. Ferric maltol is 3-hydroxy-2-methyl-4H-pyrane-4-one iron (III) complex (3:1) and has the molecular formula $(C_6H_5O_3)_3Fe$ and a molecular mass of 431.2.

Each red capsule (b) (4) with "30", contains colloidal anhydrous silica, crospovidone (Type A), lactose monohydrate, magnesium stearate and sodium lauryl sulfate as inactive ingedients. In addition, the capsule shell contains FD&C Blue No. 1, FD&C Red No. 40, FD&C Yellow No.6, gelatin and titanium dioxide. The ink used for printing the marking contains ammonium hydroxide, ethanol, iron oxide black and propylene glycol.



Is the information accurate? ☒ Yes ☐ No
If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

HOW SUPPLIED section:

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ACCRUFER (ferric maltol) 30 mg iron capsules are supplied as 56 capsules in HDPE bottles with a child-proof polypropylene push-lock.

1 Bottle of 56-count 30 mg ferric iron capsules (NDC xxxxx-xxx-xx).

16.2 Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP controlled room temperature].

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of ACCRUFER is 30 mg twice daily, taken 1 hour before or 2 hours after meals. Do not open, break, or chew ACCRUFER capsules.

Treatment duration will depend on the severity of iron deficiency but generally at least 12 weeks of treatment is required. The treatment should be continued as long as necessary until ferritin levels are within the normal range.

3 DOSAGE FORMS AND STRENGTHS

Capsules: ACCRUFER contains 30mg iron, as ferric maltol, in red capsules (b) (4) with "30"

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)?

☒ Yes ☐ No ☐ N/A

If "No," explain.

R Regional Information

1.14 Labeling

Commercial packagings:

Immediate Container Label (56 capsules in bottle):

(b) (4)

Secondary Container Label: (Carton)

(b) (4)

Reviewer's Assessment:

1. CMC related coments on labels and labeling were communicated to the applicant in collaboration with DMEPA. Applicant has responded satisfactorily to the comments on 8-APR-2019.

2. The labeling of the physician's and container labels is now per labelling tool, guidances and CFR to have the most current information of the labels.

3. (b) (4)

(b) (4)

4. Per 21 CFR 201.56 all relevant information pertaining to the each section of the labeling have now been provided in the physician's labels.

5. A final version of the agreed upon PI (with DMEPA's editorial chages) will be reviewed by the ATL and included in their memo.

The container and physician's lables are adequate.

Conclusion: *Labels and Labeling are adequate from a CMC stand point.*

Primary Labeling Reviewer Name and Date:

Rajiv Agarwal, Ph.D, 10-APR-2019

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

Anamitro Banerjee, PhD,

Rajiv Agarwal

Digitally signed by Rajiv Agarwal
Date: 4/29/2019 01:48:27PM
GUID: 504fa29c0000100b83d3aaa4905783c1

Anamitro Banerjee

Digitally signed by Anamitro Banerjee
Date: 4/30/2019 07:15:01PM
GUID: 5075764700003844b7bc89632228509f

BIOPHARMACEUTICS

Application No: NDA 212320-ORIG-1 [505(b)(2)]
Drug Product Name / Strength: ACCRUFER (Ferric Maltol) capsules, 30 mg
Route of Administration: Oral
Applicant Name: Shield TX (UK) Limited
Biopharmaceutics Review Team:
Primary Reviewer: Zhuojun Zhao, PhD
Secondary Reviewer: Banu Zolnik, PhD

Product Background:
NDA 212320 was submitted as a 505(b)(2) NDA under the Federal Food, Drug and Cosmetic Act. The proposed ACCRUFER (Ferric Maltol) hard gelatin Capsules 30mg is an oral monotherapy intended to treat adults with iron deficiency (ID)/iron deficiency anemia (IDA), including those with previous intolerance to oral ferrous irons. The proposed ACCRUFER has the same formulation as the Applicant's EU approved product FERACCRU® (ferric maltol), 30 mg.

Review Summary:
The Biopharmaceutics review is focused on the evaluation of the adequacy of the overall information/data supporting the proposed dissolution method and acceptance criterion, as well as site bridging in the drug product development.

In Vitro Dissolution Method and Acceptance Criterion:
Based on the provided dissolution data, the dissolution method in the table below is found acceptable however, the proposed acceptance criterion (Q= (b)(4)% in 30 min) is acceptable on **an interim basis** because the initial assessment of the dissolution data supported the dissolution acceptance criterion of Q= (b)(4)% in (b)(4) as conveyed to the Applicant in IR letter dated February 11, 2019. **Under the PMC # 3658**, the Applicant agreed to collect and submit multipoint dissolution profiles using the approved dissolution method from newly manufactured commercial batches (minimum of six) and current stability registration batches and **propose a final dissolution acceptance criterion** for ACCRUFER capsules. When the PMC is submitted in 09/2020, FDA recommended initial dissolution acceptance criterion of Q= (b)(4)% in (b)(4) will be re-assessed based on the newly generated data.

Apparatus	Rotation Speed	Medium	Volume	Cumulative % of Drug Dissolved (Label Claim) INTERIM
USP II (Paddle) with sinker	75 RPM	Tier 1: KCl/HCl Buffer, pH 1.2 Tier 2: KCl/HCl Buffer, with addition of Pepsin (700,000 to 750,000 unit/L)	900 mL	NLT (b)(4)% (Q) at 30 minutes

As part of the PMC, the Applicant also committed to provide evidence of cross-linking in gelatin capsules and include photographic documentation or capsule switching test might be used to confirm crosslinking if Tier 1 dissolution fails due to crosslinking.

Site Bridging:
The Applicant provided adequate comparative dissolution data to support the additional drug substance site (b) (4) and the drug product site (b) (4)

RECOMMENDATION:
Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 212320 for ACCRUFER (Ferric Maltol), 30 mg, is recommended for **APPROVAL** with a Post-Marketing Commitment (PMC No 3658).

BIOPHARMACEUTICS ASSESSMENT

List of Submissions being reviewed:

Submissions Reviewed	Document Date
Original Submission	9/27/2018
IR Response	2/25/2019, 4/8/2019 and 6/13/2019
T-Con	6/5/2019

I. Drug Substance

The Applicant identified two crystalline forms of the drug substance, (b) (4) . The Applicant states that the polymorphic form has no impact on the quality of the drug product as confirmed by the consistency of the batch analysis data for drug product produced from (b) (4) drug substance. Batches using (b) (4) were utilized in the pivotal Phase III IBD studies (ST10-010-301/2) and batches using (b) (4) were utilized in the pivotal Phase III CKD study (ST10-01-303).

The manufacturing process (b) (4)

II. BCS Designation

BCS designation is not requested in the application.

Drug Substance Solubility:

The Applicant provided the solubility of Ferric Maltol (b) (4) over the physiologic pH range in Table 1.

Table 1. Solubility of Ceritinib drug substance

Medium	(b) (4)
Water	
pH 4.0	
pH 6.5	
FaSSIF (pH6.5)	
FeSSIF (pH 5)	
FaSGF (pH 1.6)	

FaSSIF = fasted simulated small intestinal fluid;
FeSSIF = fed simulated small intestinal fluid;
FaSGF= fasted simulated gastric fluid

III. Formulation:

Table 2 summarizes the qualitative and quantitative composition of the proposed ACCRUFER (Ferric Maltol) Capsules, 30 mg.

Table 2. Composition of the Proposed ACCRUFER (Ferric Maltol) Capsules, 30 mg

Material	Specification	Per Capsule (mg)	Percent	Function
Ferric Maltol	In-House	231.5	(b) (4)	Drug substance
Lactose Monohydrate	NF/Ph Eur	(b) (4)		(b) (4)
Sodium Lauryl Sulfate	NF/Ph Eur			
Crospovidone	NF/Ph Eur			
(b) (4) Colloidal	NF/Ph Eur			
Magnesium Stearate	NF/Ph Eur			
Total				
(b) (4) Shell (b) (4) (b) (4)	In-House			
Total Capsule Weight		414.6		

Capsule Body and Cap Composition		
Material[1]	**Per Capsule (mg)**	**Percent**
(b) (4) FD&C Blue No.1, (b) (4)	(b) (4)	
(b) (4) FD&C Red No.40, (b) (4)		
Titanium dioxide, (b) (4)		
(b) (4) FD&C Yellow No.6, (b) (4)		
Gelatin (NF)		

IV. Dissolution Method:

(b) (4) the Applicant was recommended to redevelop a dissolution method for the proposed drug product[1]. The proposed dissolution method for the US product (b) (4) are summarized as follows:

Parameters	Proposed Method for US	(b) (4)
USP Apparatus type	USP II (Paddle) with sinker	
Rotation	75 RPM	
Medium	Tier 1: KCl/HCl buffer, pH 1.2 Tier 2: with addition of pepsin (700,000 to 750,000 unit/liter)	
Volume	900 mL	

As requested in FDA's meeting on IND 114832[1], the Applicant provided the dissolution development report in Module 3.2.P.2.2 as detailed below:

[1] DARRTS: IND 114832, COR-MEET-03 (Meeting Minutes), final date 07/29/2019
[2] Detailed information is attached in Appendix I.

(b) (4)

[redacted]

Reviewer's Assessment:

Based on the Applicant's study results with varying dissolution parameters, the selection of the dissolution condition for Tier 1 is acceptable.

Due to the observed crosslinking, the Applicant was recommended to use enzyme as Tier 2 dissolution method (Appendix IV). The Applicant submitted Tier 2 dissolution data using Pepsin and (b) (4) The inclusion of (b) (4) in the Tier 2 dissolution method is not acceptable. The Applicant was requested to remove the (b) (4). In a teleconference held on June 5, 2019, the Applicant agreed to remove the (b) (4) In response dated June 13, 2019 (Appendix V), the Applicant proposed to implement the following Tier 2 condition: KCl/HCl Buffer, with addition of Pepsin (700,000 to 750,000 unit/L), the proposed Tier 2 is found acceptable.

Dissolution Method Validation:

The Applicant provided the Method validation report for dissolution test (Tier 1) (\\cdsesub1\evsprod\nda212320\0001\m3\32-body-data\32p-drug-prod\ferric-maltol-capsules-all\32p5-contr-drug-prod\32p53-val-analyt-proc\32p53-app3-report-rad-17-012-01.pdf), which shows the method was validated for specificity, linearity, accuracy, precision, robustness and solution stability. The CMC reviewer will review the validation results.

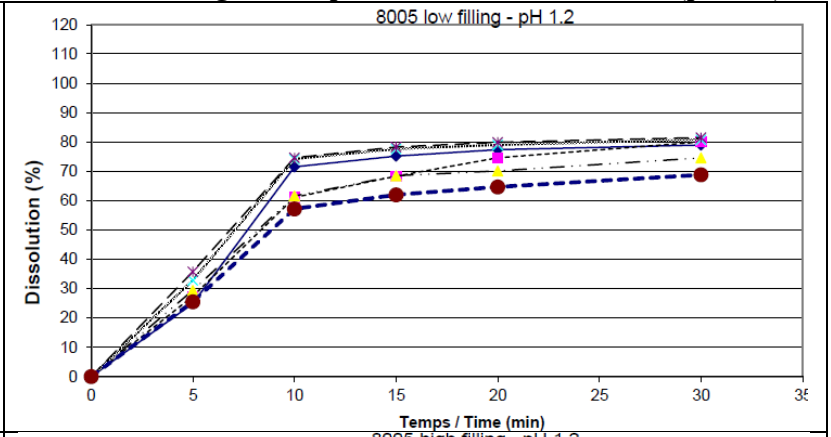
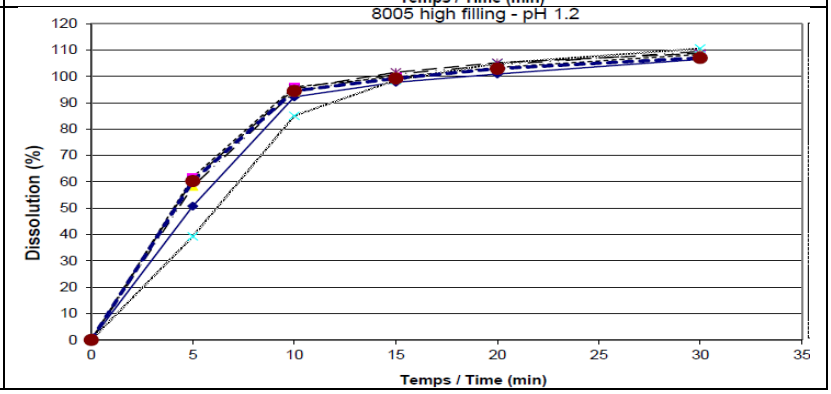
Discriminating Power of the Dissolution Method[5]:

Filled Weight:

The Applicant compared capsules manufactured with low and high filled weight. The capsules were filled manually in order to obtain (b) (4)% difference in comparison to the target weight ((b) (4) mg): low capsules ((b) (4) mg to (b) (4) mg) and high capsules ((b) (4) mg to (b) (4) mg).

[5] \\cdsesub1\evsprod\nda212320\0001\m3\32-body-data\32p-drug-prod\ferric-maltol-capsules-all\32p2-pharm-dev\pharmaceutical-development-22-app4.pdf

Table 8. Dissolution Profiles Using the Proposed Dissoltuion Method (pH 1.2)

Low filling	
High filling	

As shown in Table 8, with capsules filled at 80% of the target value, dissolution values were near to 80% and not 100%; with capsules filled at 110% of the target value, dissolution values were near to 110% and not 100%.

Reviewer's Assessment:

The Applicant has adequately demonstrated the suitability of the dissolution method (Tier 1) for batch release and stability testing. The dissolution method showed discriminating ability towards filling weight only, as no other variables were assessed.

The proposed dissolution method (i.e. US Apparatus II with sinker at 75 rpm using 900 mL KCl/HCl buffer pH 1.2) is found acceptable for the QC of the proposed drug product.

Dissolution Acceptance Criterion:

The Applicant stated that older batches (including pivotal clinical batches) cannot be used to set dissolution criteria for release by generating comparative dissolution profiles due the significant changes in dissolution profile over time.

The Applicant initially proposed a dissolution acceptance criterion of Q= (b) (4)% at 30 minutes using the proposed dissolution method based on the dissolution profiles (Appendix II) of test samples (Table 9).

Table 9. Samples used in Dissolution Study

Bulk Batch Number	Supplier	API Supplier	Date of Manufacture	Expiration date
8004	(b) (4)		Jun/2018	N/A
8005			Jun/2018	N/A
B14232			May/2016	Aug/2017*
B17466			Aug/2017	Feb/2019
B19301			May/2018	Feb/2020

*expired before the date of analysis

Reviewer's Assessment:

The initially proposed acceptance criterion of Q= (b) (4)% at 30 minutes was not acceptable. Based on the dissolution data from Batch B19301, B17466, 8004 and 8005, dissolution data supported the dissolution acceptance criterion of Q= (b) (4)% in (b) (4) as conveyed to the Applicant in IR letter dated February 11, 2019. However, since the Applicant did not have any dissolution profiles with Tier 2 dissolution method with pepsin only, the Applicant newly proposed a dissolution acceptance criterion of Q (b) (4)% in 30 minutes in IR response dated June 13, 2019 (Appendix V).

A revised dissolution acceptance criterion of NLT (b) (4)% (Q) in 30 minutes **is acceptable on an interim basis**. Under the PMC # 3658, the Applicant agreed to collect and submit multipoint dissolution profiles using the approved dissolution method from newly manufactured commercial batches (minimum of six) and current stability registration batches and propose a final dissolution acceptance criterion for ACCRUFER capsules (Appendix VI and VII).

Biowaiver Request:

The Applicant is seeking approval for only one dosage strength (30 mg) and thus biowaiver request is not applicable for the application.

Bridging of Manufacturing Sites:

Clinical development batches (drug substance and drug product) were all manufactured at (b) (4). The proposed commercial US product will be manufactured at (b) (4) using drug substance manufactured at (b) (4) will be retained as a back-up site of manufacture of drug substance; to date no (b) (4) finished product has been manufactured using (b) (4) drug substance.

To support the new drug substance site at (b) (4) and the additional drug product manufacturing site (b) (4) the Applicant agreed to provide dissolution profiles in three pH media (1.2, 4.5 and 6.8) for (b) (4) batches (8004 and 8005) (using drug substance manufactured at (b) (4)) and the two most recently manufactured (b) (4) batches (B17466 and B19301) (using drug substance manufactured at (b) (4)) in Pre-NDA meeting dated February 5, 2018.

The Applicant states that the (b) (4) batches were newly released and (b) (4) batches B 14232 and B17466 were 26 months and 11 months old, and thus only one (b) (4) batch

B19301 was used to generate dissolution profiles to compared with (b) (4) batches 8004 and 8005.

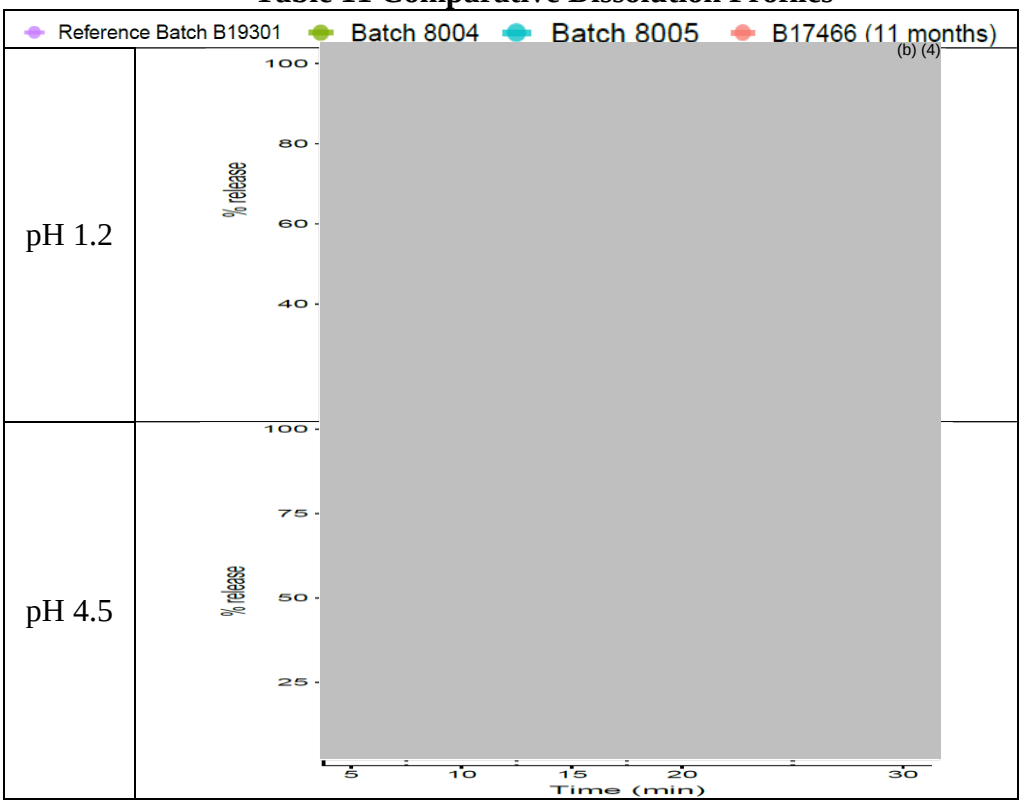
The Applicant performed the comparative dissolution studies in Appendix II[6] and provided calculated *f*2 values in Table 10.

Table 10 The Applicant's Calculated *f*2 Values Using (b) (4) Batch B19301 as Reference

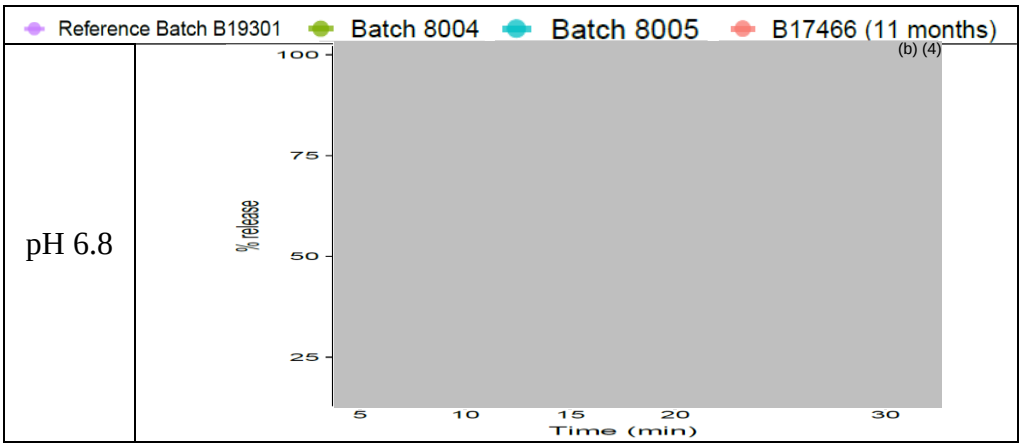
Batch 1	**Batch 2**	**f2**		
		pH 1.2	pH 4.5	pH 6.8
8004 (b) (4)	B19301 (b) (4)	56	63	51
8005	B19301	66	37	35

Based on the provided dissolution data, the reviewer generated the comparative dissolution profile comparison in mean values in **Table 11**.

Table 11 Comparative Dissolution Profiles



[6] \\cdsesub1\evsprod\nda212320\0001\m3\32-body-data\32p-drug-prod\ferric-maltol-capsules-all\32p2-pharm-dev\pharmaceutical-development-22-app4.pdf



Reviewer's Assessment:

(b) (4) Batch 8004 showed comparable dissolution profiles in pH 1.2, 4.5 and 6.8 to the (b) (4) Batch B19301. Comparative dissolution profiles in pH 1.2 supports the manufacturing site change.

Although not needed to support the manufacturing site change, similarity values less than 50 in pH 4.5 and 6.8 was observed. Therefore, the Applicant requested to provide the reasons for dissolution profile comparisons between the batches 8005 and B19301 manufactured at (b) (4) (commercial site) and (b) (4) (clinical manufacturing site), respectively do not meet the f2 similarity requirements in pH 4.5 or pH 6.8 to support the addition of (b) (4) In addition, based on the reviewer calculated f2 similarity test, dissolution profile comparisons between the two (b) (4) commercial batches (8004 and 8005) also did not meet the f2 similarity requirement in pH 4.5 or pH 6.8. The Applicant was requested to provide reasons for the observed inconsistent dissolution profiles of (b) (4) Batch 8005 in IR letter dated February 11, 2019 (Appendix III).

***f*2 Value (8004 vs 8005)**		
pH 1.2	pH 4.5	pH 6.8
49.57	43.92	46.24

In the Applicant's response dated February 25, 2019, the Applicant stated that the failure was due to non-validated pH conditions. The Applicant's response is found acceptable because 1) only pH 1.2 dissolution profile comparison is needed to support manufacturing site change; 2) lower solubility of API was reported in pH 4.0 or pH 6.8 shown in Table 1 and 3; 3) f2 values comparing to (b) (4) Batch B19301 are over 50.

Based on the reasons above the new drug substance site at (b) (4) and the drug product manufacturing site (b) (4) is found acceptable based on the comparative dissolution profiles in pH 1.2 per SUPAC IR guidance.

R Regional Information

Comparability Protocols: N/A

Lifecycle Management Considerations: N/A

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APPENDIX II: Comparative Dissolution Profiles (Using USP II with sinker at 75 RPM)

pH 1.2

Dissolution media at pH 1.2				Batch B19301	
Vessel number	Sampling time (min)				
	5	10	15	20	30
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Minimum					
Maximum					
Average	**63%**	**86%**	**93%**	**97%**	**101%**
RSD	**14%**	**10%**	**7%**	**6%**	**5%**
f2 similarity factor	**N/A (batch reference)**				

Dissolution media at pH 1.2				Batch 8004	
Vessel number	Sampling time (min)				
	5	10	15	20	30
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Minimum					
Maximum					
Average	**54%**	**77%**	**86%**	**91%**	**97%**
RSD	**13%**	**11%**	**9%**	**7%**	**4%**
f2 similarity factor	**56**				

Dissolution media at pH 1.2				Batch 8005	
Vessel number	Sampling time (min)				
	5	10	15	20	30
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Minimum					
Maximum					
Average	**57%**	**93%**	**98%**	**100%**	**102%**
RSD	**23%**	**6%**	**3%**	**3%**	**3%**
f2 similarity factor	**66**				

Dissolution media at pH 1.2				Batch B17466	
Vessel number	Sampling time (min)				
	5	10	15	20	30
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Minimum					
Maximum					
Average	**35%**	**60%**	**68%**	**75%**	**84%**
RSD	**28%**	**23%**	**19%**	**14%**	**11%**
f2 similarity factor	**31**				

pH 4.5

Dissolution media at pH 4.5				Batch B19301	
Vessel number	Sampling time (min)				
	5	10	15	20	30
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Minimum					
Maximum					
Average	**35%**	**71%**	**81%**	**85%**	**89%**
RSD	**37%**	**20%**	**14%**	**11%**	**9%**
f2 similarity factor	**N/A (batch reference)**				

Dissolution media at pH 4.5				Batch 8004	
Vessel number	Sampling time (min)				
	5	10	15	20	30
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Minimum					
Maximum					
Average	**< 50% (34%)**	**67%**	**75%**	**78%**	**81%**
RSD	**21%**	**13%**	**11%**	**10%**	**9%**
f2 similarity factor	**63**				

Dissolution media at pH 4.5				Batch 8005	
Vessel number	Sampling time (min)				
	5	10	15	20	30
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Minimum					
Maximum					
Average	**< 50% (15%)**	**55%**	**63%**	**67%**	**71%**
RSD	**45%**	**22%**	**19%**	**17%**	**15%**
f2 similarity factor	**37**				

Dissolution media at pH 4.5				Batch B17466	
Vessel number	Sampling time (min)				
	5	10	15	20	30
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Minimum					
Maximum					
Average	**< 50% (16%)**	**27%**	**37%**	**48%**	**58%**
RSD	**40%**	**53%**	**50%**	**44%**	**32%**
f2 similarity factor	**22**				

pH 6.8

Dissolution media at pH 6.8				Batch B19301	
Vessel number	Sampling time (min)				
	5	10	15	20	30
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Minimum					
Maximum					
Average	**< 50% 38%**	**69%**	**81%**	**85%**	**88%**
RSD	**25%**	**19%**	**12%**	**10%**	**8%**
f2 similarity factor	**N/A (batch reference)**				

Dissolution media at pH 6.8				Batch 8004	
Vessel number	Sampling time (min)				
	5	10	15	20	30
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Minimum					
Maximum					
Average	**< 50% 42%**	**64%**	**70%**	**72%**	**75%**
RSD	**19%**	**16%**	**16%**	**14%**	**13%**
f2 similarity factor	**51**				

Dissolution media at pH 6.8				Batch 8005	
Vessel number	Sampling time (min)				
	5	10	15	20	30
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Minimum					
Maximum					
Average	**< 50% (27%)**	**51%**	**58%**	**62%**	**67%**
RSD	**44%**	**36%**	**28%**	**25%**	**24%**
f2 similarity factor	**35**				

Dissolution media at pH 6.8				Batch B17466	
Vessel number	Sampling time (min)				
	5	10	15	20	30
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Minimum					
Maximum					
Average	**< 50% (33%)**	**54%**	**65%**	**70%**	**75%**
RSD	**34%**	**29%**	**27%**	**26%**	**25%**
f2 similarity factor	**44**				

APPENDIX VII: Biopharmaceutics PMC (uploaded in DARRTS)

POST-MARKETING COMMITMENT (PMC) DEVELOPMENT
PRODUCT QUALITY-BIOPHARMACEUTICS

This template should be completed by the Biopharmaceutics Reviewer (ONDP/OPQ) and included for *each* type of Biopharmaceutics PMC in the Action Package. Refer to #3 for the list of PMC types.

PMC No: 3658
Application No: NDA 212320

Product Name: ACCRUFER (ferric maltol) Capsules, 30 mg

PMC Description:

1. Collect and submit multipoint dissolution profiles (5, 10, 15, 20 and 30 minutes) using the FDA's approved dissolution method (*USP II (paddle) with sinker, 75 rpm, Tier 1: KCl/HCl Buffer, pH 1.2; Tier 2: KCl/HCl buffer with addition of Pepsin (700,000 to 750,000 unit/L, 900 mL)* from newly manufactured commercial batches (minimum of six) and current stability-registration batches.
2. Include your proposal for the final acceptance criterion of the dissolution test of ACCRUFER capsules, 30 mg, which setting should be based on the newly collected data.
3. If Tier 1 dissolution fails due to crosslinking, you may proceed to use Tier 2 dissolution testing with Pepsin as per USP. Provide evidence of cross-linking in gelatin capsules. Include photographic documentation or capsule switching test might be used to confirm crosslinking.

PMC Schedule Milestones:		
	Submission of PMC Report under a Prior Approval Supplement (PAS) to the NDA, including the requested dissolution data and proposed final dissolution acceptance criterion, within twelve (12) months from the NDA's action date	09/2020

Zhuojun Zhao

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Banu Zolnik

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Date: 7/02/2019 10:29:21AM
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POST-MARKETING COMMITMENT (PMC) DEVELOPMENT

PRODUCT QUALITY-BIOPHARMACEUTICS

This template should be completed by the Biopharmaceutics Reviewer (ONDP/OPQ) and included for *each* type of Biopharmaceutics PMC in the Action Package. Refer to #3 for the list of PMC types.

PMC No: 3658

Application No: NDA 212320

Product Name: ACCRUFER (ferric maltol) Capsules, 30 mg

PMC Description:

1. Collect and submit multipoint dissolution profiles (5, 10, 15, 20 and 30 minutes) using the FDA's approved dissolution method (*USP II (paddle) with sinker, 75 rpm, Tier 1: KCl/HCl Buffer, pH 1.2; Tier 2: KCl/HCl buffer with addition of Pepsin (700,000 to 750,000 unit/L, 900 mL)* from newly manufactured commercial batches (minimum of six) and current stability-registration batches.
2. Include your proposal for the final acceptance criterion of the dissolution test of ACCRUFER capsules, 30 mg, which setting should be based on the newly collected data.
3. If Tier 1 dissolution fails due to crosslinking, you may proceed to use Tier 2 dissolution testing with Pepsin as per USP. Provide evidence of cross-linking in gelatin capsules. Include photographic documentation or capsule switching test might be used to confirm crosslinking.

PMC Schedule Milestones:		
	Submission of PMC Report under a Prior Approval Supplement (PAS) to the NDA, including the requested dissolution data and proposed final dissolution acceptance criterion, within twelve (12) months from the NDA's action date	09/2020

1. **During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.**

- ☐ Need for drug (unmet need/life-threatening condition)
- ☒ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☐ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☐ Other

The Applicant's dissolution method (b) (4) was found not appropriate for the proposed drug product. Therefore, FDA requested the development of a new dissolution method (pH 1.2), which was found acceptable. However, during the original NDA's review cycle, very limited dissolution data were submitted using the newly developed acceptable dissolution method (pH 1.2). In addition, due to the observed crosslinking, the Applicant was recommended to implement Tier 2 dissolution method. However, because the Applicant submitted Tier 2 dissolution data using Pepsin and (b) (4) the Applicant was requested to remove the (b) (4) In a teleconference held on June 5, 2019, the Applicant agreed to remove (b) (4). As there is no dissolution profiles with Tier 2 dissolution method (pepsin only) were available, the Applicant also agreed to provide complete dissolution profile data (5, 10, 15, 20 and 30 minutes) on newly manufactured batches and the registration-stability batches to support the setting of the final dissolution acceptance criterion under a Post-Marketing Commitment. In the meantime, the proposed dissolution acceptance criterion of Q= (b) (4)% at 30 minutes is acceptable on an interim basis for release and on stability.

2. **Describe the specific review issue and the goal of the study.**

The following requests should be addressed in this Post-Marketing Commitment (PMC).

a) The PMC Report should include multi-point dissolution profiles (5, 10, 15, 20 and 30 minutes) using the newly developed and FDA's approved dissolution method from newly manufactured batches (minimum of six commercial batches) and current stability-registration batches.

Approved Dissolution Method for ACCRUFER Capsules, 30 mg			
Apparatus	**Rotation**	**Medium**	**Volume**
USP II (Paddle) with sinker	75 RPM	Tier 1: KCl/HCl Buffer, pH 1.2 Tier 2: KCl/HCL Buffer with addition of Pepsin (700,000 to 750,000 unit/L)	900 mL

b) The PMC should also include the Applicant's proposal for the final acceptance criterion of the dissolution test of ACCRUFER capsules, 30 mg, which setting should be based on the newly collected data.

c) If Tier 1 dissolution fails due to crosslinking, you may proceed to use Tier 2 dissolution testing with Pepsin as per USP. Provide evidence of cross-linking in gelatin capsules. Include photographic documentation or capsule switching test might be used to confirm crosslinking.

3. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMC study.

☒ Dissolution testing
☐ Assay
☐ Sterility
☐ Potency
☐ Product delivery
☐ Drug substance characterization
☐ Intermediates characterization
☐ Impurity characterization
☐ Reformulation
☐ Manufacturing process issues
☐ Other

Describe the agreed-upon study:

- The Applicant agreed to collect and submit multipoint dissolution profile data using the new FDA's approved dissolution method from at least 6 new-manufactured commercial batches and from current stability-registration batches. The Applicant also agreed that based on the new dissolution data, they will submit a proposal for the final acceptance criterion of the dissolution test of their drug product.

4. To be completed by ONDP/OPQ Supervisor:

☒ Does the study meet criteria for PMCs?
☒ Are the objectives clear from the description of the PMC?
☒ Has the Applicant adequately justified the choice of schedule milestone dates?
☒ Has the Applicant had enough time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

5. PMC Development Coordinator:

☒ This PMR/PMC has been reviewed for clarity and consistency, and it is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug products quality.

Director Concurrence (Signature):

Paul Seo, Ph.D.
Director, Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality, CDER

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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Sherita McLamore

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ATTACHMENT I: Final Risk Assessment

A. Final Risk Assessment – NDA 212320 (30 mg capsules)

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 and 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	L		Acceptable	Controls are in place.
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	Controls are in place.
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment	L		Acceptable	Controls are in place.
Dissolution	• Formulation • Raw materials • Exclude major reformulations • Process parameters • Scale/equipments • Site	M		Acceptable	Controls are in place, continue stability monitoring post approval
(b) (4)				(b) (4)	

Note: Although in Ferric maltol capsules, drug substance and all excipients (b) (4) particle size of the drug substance was considered a potentially critical parameter for the dissolution of the drug product to ensure the drug product quality. (b) (4)

Rajiv Agarwal

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Anamitro Banerjee

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