

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208143Orig1s000

CHEMISTRY REVIEW(S)



QUALITY ASSESSMENT



NDA 208143
Review # 1
Review Date: November 25, 2015

Table with 2 columns: Field Name (Drug Name/Dosage Form, Strength, Route of Administration, Rx/OTC Dispensed, Applicant, US agent, if applicable) and Value (Readi-Cat 2 and Readi-Cat 2 Smoothie Suspension, 2.0 % w/v, Oral, Rx, Bracco Diagnostics, Inc., N/A)

Quality Review Data Sheet

- 1. LEGAL BASIS FOR SUBMISSION: 505(b)(2)
2. RELATED/SUPPORTING DOCUMENTS:
A. DMFs:
3. RELATED/SUPPORTING DOCUMENTS: The documents listed in Table 1 and Table 2 below were evaluated in this review:

Table 1 Drug Master Files (DMFs)

Table with 7 columns: DMF #, TYPE, HOLDER, ITEM REFERENCED, STATUS, DATE REVIEW COMPLETED, COMMENTS. Contains multiple rows of DMF data with some redacted information.

(b) (4)	Type IV	(b) (4)	adequate	29-Oct-2015	Reviewer Anne Marie Russell, Ph.D.
	Type IV		adequate	19-Nov-2015	Reviewer Anne Marie Russell, Ph.D.
	Type IV		adequate	19-Nov-2015	Reviewer Anne Marie Russell, Ph.D.
	Type IV		adequate	19-Nov-2015	Reviewer Anne Marie Russell, Ph.D.

¹ Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Table 2 Documents		
DOCUMENT	RECEIPT DATE	DESCRIPTION
EDR sequence 000	18-DEC-2014	Initial NDA submission
EDR sequence 004	29-JUL-2015	Response to IR#1

B. Other Documents: IND, RLD, or sister applications: N/A

4. CONSULTS: N/A

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Martin Haber	ONDP/DNDAPI
Drug Product	Anne Marie Russell, Ph.D.	Branch VI/Division II
Process	Li Shan Hsieh	OPQ/OPF/Process
Microbiology	Jessica Cole	OPQ/OPF/Microbiology
Facility	Thuy T. Nguyen	OPQ/OPF/DIA/BI
Biopharmaceutics	Fang Wu	OPQ/ONDP/DBP/Branch 3
Project/Business Process Manager		N/A
Application Technical Lead	Eldon Leutzinger	ONDP/Branch VII/Division II
Laboratory (OTR)		N/A
ORA Lead	Sharon Thomas	N/A
Environmental Assessment (EA)		N/A

Executive Summary

I. Recommendations: APPROVAL

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues

DRUG SUBSTANCE:

All of the Chemistry, Manufacturing and Controls Information on drug substance are found in NDA 208036 – refer to the Integrated Executive Summary for NDA 208036, and the CMC review of Drug Substance by Martin Haber, Ph.D. (ONDP/DNDAPI) for details on the issues and

their resolution. To briefly summarize, fundamental of the issues relating to establishment of drug product quality was the lack of characterization of barium sulfate drug substance, culminating in the absence of an understanding of (a) how **identity** will be confirmed in face of other (b) (4) sulfates, potentially occurring along with barium sulfate through association with the (b) (4) as it is obtained from the (b) (4), (b) how the **heavy metal impurity content** will be accurately determined, and (c) how **particle size (critical to clinical performance)** will be controlled. All of these issues, and others of lesser importance were fully resolved; see referenced OPQ reviews for details. Although Particle Size was addressed in the referenced reviews for drug substance, a brief re-discussion of it is included here, because of its criticality to clinical performance of the Readi-Cat 2 and Readi-Cat 2 Smoothie products.

Particle Size:

Barium sulfate is (b) (4) 2- (b) (4)

As a consequence, particle size is well-controlled to a (b) (4) level, resulting in a low risk of not meeting the critical particle size characteristics for clinical performance of barium sulfate suspensions.

DRUG PRODUCT:

The Readi-Cat 2 products were developed and marketed in 1985, Readi-Cat 2 Smoothie (banana flavored) in 1998, followed by berry flavor in 2002, vanilla flavor in 2005, and mochaccino flavor in 2009. These products came after E-Z-EM, which was developed and marketed in 1980; it was discontinued in the U.S. in 2013. Although there have been changes in the products since 1985 (source of barium sulfate, manufacturing site, formulation, the latter including preservatives, saccharin, citric acid/sodium citrate), **the quality history in referenced literature provided by Bracco indicates that the formulation, particle size and viscosity were similar from 1985 (time of introduction) until 2015.** Specifications for viscosity and pH were constant throughout this period. Averages of (b) (4) doses have been administered annually during this period (1985 – 2015). Hence, **it is concluded that the quality of the proposed commercial products (Readi-Cat 2 and Readi-Cat 2 Smoothie) are comparable to the products over the period from 1985 to 2015.**

The quality of the excipients in the formulation of the proposed commercial E-Z-HD is established by the standards in the USP/NF, and is documented with the respective USP specifications and Certificates of Analysis. The quality of the flavorings were established subsequently with information provided (as requested) in DMF's, thus completing the quality assurance of the formulation composition. An expiration date of 2 years at 25⁰C is given to the proposed commercial Readi-Cat 2 and Readi-Cat 2 Smoothie products on the basis of acceptability of the stability data provided. **In conclusion, the proposed commercial Readi-Cat 2 and Readi-Cat 2 Smoothie products meet acceptable quality standards for human use.**

2. Action letter language, related to critical issues such as expiration date
N/A
3. Benefit/Risk Considerations

Based on the a satisfactory purity and quality profile for barium sulfate drug substance, good control of particle size, batch history for the Readi-Cat 2 products, and a satisfactory stability

profile, evaluation of the final risk for purity and quality is acceptable from a chemistry, manufacturing and controls standpoint.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

Barium sulfate - information in NDA 208036 – see the Integrated Executive Summary for this information.

B. Drug Product [Established Name] Quality Summary

Readi-Cat 2 and Readi-Cat 2 Smoothie are white, low viscosity, flavored barium sulfate suspensions presented as a single-use 450 mL fill in a (b) (4) HDPE bottle with a white polypropylene stripped cap and a (b) (4) aluminum induction seal. Readi-Cat 2 contains Barium Sulfate in (b) (4) a strength of 2g/100 mL (2.0898%), with *inactive ingredients* (Xanthan Gum, Simethicone Emulsion, Potassium Sorbate, Sodium Benzoate, (b) (4) Citric Acid, Sorbitol Solution, Purified Water), (b) (4) (Saccharin Sodium) and *flavorings* (Natural & Artificial Orange, (b) (4)). Readi-Cat 2 Smoothie (b) (4) barium sulfate at 2 g/100 mL) contains Sodium Citrate in addition to the same inactive ingredients as Readi-Cat 2, and the flavoring composition shown in the table below:

Readi-Cat 2 Smoothie Products (BASE FORMULATION + FLAVORING)

Product	Flavoring
Banana Smoothie Readi-Cat 2	Artificial (b) (4) Banana Flavor
Creamy Vanilla Smoothie Readi-Cat 2	Artificial Vanilla Flavor
Berry Smoothie Readi-Cat 2	Natural and Artificial Berry Flavor
Mochaccino Smoothie Readi-Cat 2	Natural and Artificial (b) (4) Chocolate Flavor Natural and Artificial Coffee (b) (4) Flavor

Quality Standards for Readi-Cat 2 products are established through the (1) quality of the ingredients, (2) batch history and (3) stability. The first (quality of ingredients) is comprised of two parts: active ingredient (barium sulfate) and inactive ingredients (in table). Except for Particle Size, the CQA's for active ingredient (barium sulfate) has previously been discussed. I have separated Particle Size, treating it underneath its own heading, because of its criticality to clinical performance.

INACTIVE INGREDIENTS:

Flavorings are separated out and dealt with under a separate heading, because of the inactive ingredients, it is only the flavorings that had initial issues regarding their quality controls. Quality Standards for inactive ingredients (other than flavorings) are provided by (1) USP specifications, along with (2) certificates of analysis, both provided in the NDA.

FLAVORINGS:

Information on all flavorings is found in DMF's. Reviews of these DMF's (under separate cover; Anne Marie, Ph.D.) reveals no issues for quality.

BATCH HISTORY:

As a 505(b)(2) application, the problem is the absence of a reference listed drug. Consequently, Bracco is basing clinical efficacy and safety of their product on historical use and published literature. The Readi-Cat 2 products were developed and marketed in 1985, Readi-Cat 2 Smoothie (banana flavored) in 1998, followed by berry flavor in 2002, vanilla flavor in 2005, and mochaccino flavor in 2009. These products came after E-Z-EM, which was developed and marketed in 1980; it was discontinued in the U.S. in 2013. E-Z-EM is a barium sulfate suspension ((b)(4)% w/v) intended for use after dilution to a lower concentration ((b)(4)2%). Although there have been changes in the products since 1985 (source of barium sulfate, manufacturing site, formulation, the latter including preservatives, saccharin, citric acid/sodium citrate), the quality history provided by Bracco indicates that the particle size, formulation and viscosity were similar from 1985 (time of introduction) until 2015. Specifications for viscosity and pH (critical attributes) were constant through this period. Averages of (b)(4) doses have been administered annually during this period (1985 – 2015). Hence, **it is concluded that the quality of Readi-Cat 2 products (1985 – 2015) are comparable to the proposed commercial product.**

STABILITY:

There are data for 3 primary stability studies, and all met the specifications. There were no stability studies provided for the 4 flavors (Readi-Cat 2 Smoothies). In response to a request for stability data for Readi-Cat 2 Smoothies (4 flavors), 24 months of long-term data for Readi-Cat 2 Smoothie validation lots (#00500765 berry, #00500807 vanilla, #00500808 mochaccino), all packaged in the NDA configuration, showed no instability, except for (b)(4), but there were no out of specifications noted. **Based on an acceptable 18 months of long-term data and 6 months of accelerated data from three commercial batches, the proposed shelf-life of 24 months at 25°C is granted for Readi-Cat 2. An acceptable 24 months of long-term data from three commercial batches (one each of berry, mochaccino and vanilla flavors) and 12 months long-term data (one batch for banana flavor) supports a shelf-life of 24 months at 25°C for Readi-Cat 2 Smoothie.** Additionally, the microbiological quality of these products are controlled via suitable release and stability testing protocols (Jessica Cole, Ph.D.).

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Readi-Cat 2 and Ready-Cat 2 Smoothie suspension
Non Proprietary Name of the Drug Product	Barium Sulfate Oral Suspension (2.0%, w/v)
Non Proprietary Name of the Drug Substance	Barium sulfate
Proposed Indication(s) including Intended Patient Population	For use in Computed Tomography of the abdomen (b)(4)
Duration of Treatment	One-time use
Maximum Daily Dose	N/A
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

1. BCS Classification: N/A; the dissolution test is not necessary for barium sulfate suspension as an imaging contrast agent. There are no biopharm review issues for this NDA (Fang Wu, Ph.D.).
 - Drug Substance:

- Drug Product:

2. Biowaivers/Biostudies: N/A

- Biowaiver Requests
- PK studies
- IVIVC

E. Novel Approaches: N/A

F. Any Special Product Quality Labeling Recommendations

Some recommendations for labeling are provided in the drug product review (Anne Marie Russell, Ph.D., CMC Reviewer, DNDPII, Branch VII). However, labeling and package insert language is not final. Reviews of labeling, including revisions and negotiations will be handled through the clinical division (DMIP).

G. Process/Facility Quality Summary (see Attachment A)

The drug product manufacturer is E-Z-EM Canada, Inc. (b)(4) Anjou, Quebec, HIJ2Z4 Canada). Based on the results of three validation batches, it is concluded that the manufacturing process yielded a product consistently and reproducibly within the established product specifications. The preapproval inspection revealed no GMP deficiencies.

H. Life Cycle Knowledge Information (see Attachment B): N/A

Overall Drug Product Risk Assessment Summary					
From Initial Risk Identification			Review Assessment		
Attribute CQA	Factors that can impact CQA, or QS (1)	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation (4)	Lifecycle Considerations/ Comments
Drug substance (identity, heavy metals, particle [redacted])	See (2)	See (2)	See (2)	low risk	Commitment for heavy meals (b)(4)
Quality standards (QS) for inactive ingredients, other than flavorings	N/A	N/A	N/A, as QS met by USP specifications and COA's	No assignable risk, as QS established by USP specifications and COA's	(2)
Quality standards (QS) for flavorings	Absence of a QS (3)	-----	DMF's identified & info for QS is acceptable	QS info for all flavors is acceptable	None
					None

1) Quality Standard (QS) – a single attribute (QS ≡ CQA), or a set of attributes with established specifications (e.g., by USP or a COA).

- 2) OPQ N208036 Integrated Quality Assessment final.pdf (Drug Substance).
- 3) Missing information on QS's for flavors ((b)(4) Chocolate (b)(4), Coffee (b)(4), Blueberry (b)(4)).
- 4) Final Risk Evaluation – low (and acceptable).

Application Technical Lead (ATL): Eldon E. Leutzinger, Ph.D., CMC Lead

Eldon E.
Leutzinger -A

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ASSESSMENT OF THE BIOPHARMACUETICS

Introduction:

Readi-Cat 2 and Readi-Cat 2 Smoothies are 2.0% w/v barium sulfate suspensions for oral administration. Barium sulfate, due to its high atomic number, is opaque to x-rays and therefore, acts as a positive contrast agent indicated for use in computed tomography (CT) to opacify the gastrointestinal (GI) tract and to locate and outline normal structures, or to distinguish between normal and abnormal anatomy. Barium sulfate has been used as a contrast agent for diagnostic radiographic imaging of the gastrointestinal tract since the early 1900s.

Drug Product:

Readi-Cat 2 is a formulation containing (b) (4) barium sulfate. Readi-Cat 2 contains one or more flavors (Natural and Artificial Orange and (b) (4) (Saccharin Sodium), (b) (4) (Sorbitol Solution), (b) (4) (Xanthan Gum), (b) (4) (Simethicone Emulsion), (b) (4) (Citric Acid (b) (4) (Potassium Sorbate and Sodium Benzoate) and purified water. Readi-Cat 2 are aqueous ready-to-use suspensions.

Readi-Cat 2 Smoothies are barium sulfate suspensions 2.0% w/v for oral administration. Barium Sulfate (b) (4) is the active ingredient in the formulation. The Readi-Cat 2 Smoothie drug products contain the following excipients: (b) (4) (Xanthan Gum), (b) (4) (Simethicone Emulsion), (b) (4) (Citric Acid (b) (4) (Potassium Sorbate and Sodium Benzoate and Benzoic Acid), (b) (4) (Sorbitol Solution), (b) (4) (Saccharin Sodium), flavoring agent for the Berry Smoothie (Natural and Artificial Blueberry (Berry) Flavor), flavoring agents for the Banana Smoothie (Artificial (b) (4) Banana (Banana) Flavor), flavoring agent for the Creamy Vanilla Smoothie (Artificial Vanilla Flavor (Vanilla)) and purified water. Readi-Cat 2 Smoothies are aqueous ready-to-use suspensions.

Readi-Cat 2 (barium sulfate oral suspension) drug product(s) composition is shown in the following table.

Biopharm Table 1. Readi-Cat 2 (barium sulfate oral suspension) Drug Product(s) Composition

Component Name	Function	Composition % w/v						
		Readi-Cat 1	Readi-Cat 2 Smoothies					
			Banana	Creamy Vanilla	Berry	Mochaccino		
								(b) (4)
Barium sulfate	(b) (4) Drug Substance	2.0898	2.0898	2.0898	2.0898	2.0898	2.0898	(b) (4)
Xanthan Gum								
Simethicone Emulsion								
Potassium Sorbate								
Sodium Benzoate								
Benzoic Acid								
Citric Acid	(b) (4)							
Sodium Citrate								
Sorbitol Solution								
Purified Water	(b) (4)							
Saccharin Sodium								
Artificial Vanilla Flavor	(b) (4)							
Naturally (b) (4) Banana Flavor								
Natural and Artificial Orange Flavor								
Natural and Artificial Blueberry Flavor								
Natural and Artificial (b) (4) Chocolate Flavor								
Natural and Artificial Coffee (b) (4) Flavor								

BCS Classification:

No BCS classification information is included in the submission.

Reviewer's Assessment:

According to the cross-reference to (b) (4) pharmaceutical grade barium sulfate previously submitted in NDA 208036, Module 3, section 3.2.S.2, Barium sulfate is practically insoluble in water and soluble in hot concentrated sulfuric acid.

33. Are the in-vitro dissolution test and acceptance criteria adequate for assuring consistent bioavailability of the drug product?

Barium sulfate (or sulphate) is an inorganic compound with the chemical formula BaSO₄. It is a white (b) (4) which is odorless and insoluble in water.

Reviewer's Assessment:

Considering Barium sulfate is insoluble in water and used as an imaging contrast agent, dissolution test is not necessary for Barium sulfate suspension.

34. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

Reviewer's Assessment:

There are no dissolution data in the submission for this NDA and the bridging, if any, will use comparisons of physicochemical properties. No biopharmaceutics review issues are identified.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Overall Assessment and Signature:

Dissolution test is not necessary for Barium sulfate suspension as an imaging contrast agent for NDA208143. There are no biopharm review issues for this NDA.

Fang Wu, Ph.D.
Primary Biopharmaceutics Reviewer
OPQ/ONDP/DBP

Fang
Wu -A

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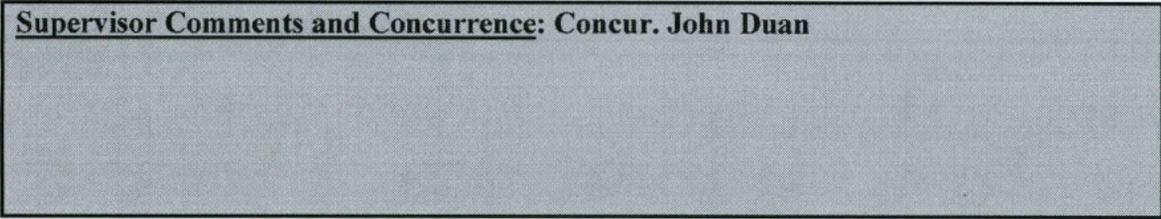
John Duan, Ph.D.
Secondary Biopharmaceutics Reviewer
& Branch Chief (Acting)
OPQ/ONDP/DBP

John Z.
Duan -S

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cc Sandra Suarez and Paul Seo

Supervisor Comments and Concurrence: Concur. John Duan



Primary Quality Review

ASSESSMENT OF THE DRUG SUBSTANCE

This NDA makes reference to Bracco's own N208036 (E-Z-HD) for drug substance as the same material is used for this NCE (new Chemical Entity) NDA. See CMC review by Martin Haber, Ph.D. of Barium Sulfate Drug Substance (b) (4) in N208036.

ASSESSMENT OF THE DRUG PRODUCT

2.3.P DRUG PRODUCT

Barium sulfate, the active ingredient, is opaque to x-rays and acts as a positive contrast agent for imaging. It has been used as a contrast agent for diagnostic radiographic imaging of the gastrointestinal tract since the early 1900s. The drug products, Read-Cat 2 and Read-Cat 2 Smoothie (four flavors), are a barium sulfate suspension (2% w/v) for oral administration. (b) (4)

[Redacted]

[Redacted] (b) (4)

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I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert: At this time, labeling and package insert language is not final. Labeling review, revisions and negotiations will be handled through the clinical team.

1. Package Insert

(a) “Highlights” Section (21CFR 201.57(a))

(Attach proposed text)

Item	Information Provided in NDA	Reviewer’s Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: Established Name:	
Dosage form, route of administration	Dosage: Route:	
Controlled drug substance symbol (if applicable)		
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths		

Conclusion:

(b) “Full Prescribing Information” Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer’s Assessment
Available dosage forms		
Strengths: in metric system		
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.		

Conclusion:

#11: Description (21CFR 201.57(c)(12))

(Attach proposed text)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name		
Dosage form and route of administration		
Active moiety expression of strength with equivalence statement for salt (if applicable)		
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.		
Statement of being sterile (if applicable)		
Pharmacological/ therapeutic class		
Chemical name, structural formula, molecular weight		
If radioactive, statement of important nuclear characteristics.		
Other important chemical or physical properties (such as pKa, solubility, or pH)		

Conclusion:

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

(Attach proposed text)

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form		
Available units (e.g., bottles of 100 tablets)		
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number		
Special handling (e.g., protect from light, do not freeze)		
Storage conditions		

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)		

Conclusion: TBD

2. Labels

1) Immediate Container Label



(b) (4)

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))		Acceptable
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		Acceptable
Net contents (21 CFR 201.51(a))		Acceptable
Lot number per 21 CFR 201.18		Acceptable
Expiration date per 21 CFR 201.17		Acceptable
"Rx only" statement per 21 CFR 201.100(b)(1)		Acceptable
Storage (not required)		Acceptable
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		Acceptable
Bar Code per 21 CFR 201.25(c)(2)**		Acceptable
Name of manufacturer/distributor		Acceptable
Others	The for use statement will be revised by clinical based on the final language in the PI	

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Acceptable. Submitted for Read-Cat 2 and Read-Cat 2 Smoothie flavors (creamy vanilla, banana, mochaccino and berry). Each flavor has its' unique label since the inactive ingredient list is different.

2) Cartons



(b) (4)



QUALITY REVIEW



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))		Acceptable
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		Acceptable
Net contents (21 CFR 201.51(a))		Acceptable
Lot number per 21 CFR 201.18		Acceptable
Expiration date per 21 CFR 201.17		Acceptable
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]		Acceptable
Sterility Information (if applicable)		Acceptable
“Rx only” statement per 21 CFR 201.100(b)(1)		Acceptable
Storage Conditions		Acceptable
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		Acceptable
Bar Code per 21 CFR 201.25(c)(2)**		Acceptable
Name of manufacturer/distributor		Acceptable
“See package insert for dosage information” (21 CFR 201.55)		Acceptable
“Keep out of reach of children” (optional for Rx, required for OTC)		Acceptable
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))		Acceptable

Conclusion: Acceptable. Submitted for Readi-Cat 2 and Readi-Cat 2 Smoothie flavors (creamy vanilla, banana, mocchaccino and berry). Each flavor has its' unique label since the inactive ingredient list is different.

II. Attachments: Lifecycle Knowledge Management

Drug Product Risk Assessment Summary					
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**
None identified for drug product - all critical quality attributes were for drug substance	N/A	N/A	Drug product physical characteristics which are critical to clinical performance are 1. Barium sulfate particle size which is controlled by drug substance specifications and 2. Low concentration, which is controlled by formulation and tested on release.	Acceptable	none

*Risk ranking applies to product attribute/CQA

**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval



III. OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT

Drug Product Reviewer's Assessment and Signature:

Primary Reviewer Anne Marie Russell, Ph.D.

Anne M. Russell -S

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Supervisor Comments and Concurrence:

Secondary Reviewer Danae Christodoulou, Ph.D. Branch Chief

Danae D. Christodoulou -S

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Note: additional reviewers can be added, as appropriate



QUALITY REVIEW



NDA 208143

ASSESSMENT OF THE FACILITIES

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

Manufacturer(s)

- Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation
		(b) (4)	Drug Substance	30	36	0	66	PAI Inspection

Reviewer's Assessment:

Establishment name	FEI Number	Responsibilities and profile codes	Current status	Initial Risks Identified	Final Recommendation
		(b) (4)	No FDA inspectional history	None	Acceptable

Drug substance manufacturer: (b) (4)

The pharmaceutical manufacturing process used to (b) (4)

(b) (4)

**2.3.P DRUG PRODUCT****2.3.P.3 Manufacture*****Manufacturer(s)***

2. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation
E-Z-EM Canada, Inc	3002808342	SES	Drug Product mfg	7	8	0	15	

Reviewer's Assessment:

Establishment name	FEI Number	Responsibilities and profile codes	Current status	Initial Risks Identified	Final Recommendation
E-Z-EM Canada Inc.	3002808342	Profile SES Manufacturing, analysis of finished drug product and API	Last inspection 9/20/2013 VAI	None	Acceptable

Drug Product Manufacturer: E-Z-EM Canada, Inc. located at (b) (4) Anjou, Quebec, H1J 2Z4, Canada. FEI: 3002808342. The drug product (Readi-Cat 2, Barium Sulfate Suspension) is manufactured, packaged, labelled, QC tested and released at E-Z-EM Canada. (b) (4)



QUALITY REVIEW



No current adverse quality trends in manufacturing and testing of these products were observed during the inspection. The inspection found the firm in general compliance, some minor discussion points were raised during the inspection, but no significant quality issues were noted.

Based on the Inspection Overview and associated Risk Assessment, the facility is adequate for production of the Read-Cat 2, Barium Sulfate Suspension.

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

Based on the Inspection Overview and associated Risk Assessment, (b) (4) is adequate for API production for Barium Sulfate USP.

Based on the Inspection Overview and associated Risk Assessment, E-Z-EM Canada, Inc. is adequate for production of the Read-Cat 2, Barium Sulfate Suspension.

Thuy T. Nguyen
Facility Reviewer
OPQ/OPF/DIA/BI

Thuy T.
Nguyen -S

Digitally signed by Thuy T. Nguyen -S
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ou=FDA, ou=People, cn=Thuy T.
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Supervisor Comments and Concurrence:

I concur with the facility reviewer's assessment.

Zhihao Peter Qiu, Ph.D.
Branch Chief, Division of Inspectional Assessment, OPF/OPQ

Zhihao
Qiu -S

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