

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208143Orig1s000**

**MICROBIOLOGY/VIROLOGY REVIEW(S)**



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

---

**DATE:** 21 July 2015

**TO:** Cathy Tran-Zwanz  
Regulatory Business Project Manager  
CDER/OPQ/OPRO

**FROM:** Jessica G. Cole, PhD  
Review Microbiologist  
CDER/OPQ/OPF/Division of Microbiology Assessment  
(301) 796-5148

**THROUGH:** Stephen Langille, PhD  
Microbiology Branch Chief  
CDER/OPQ/OPF/Division of Microbiology Assessment Branch 3

**SUBJECT:** NDAs: 208-143 and 208-036  
Submission Date: 16 and 18 December 2014  
Drug Product: Barium sulfate suspension, 2% w/v (Readi-Cat 2 and Readi-Cat 2 Smoothies) and barium sulfate for suspension 98% w/w (E-Z-HD)  
Applicant: Bracco Diagnostics

---

**The Microbial Limits specifications for Readi-Cat 2 and Readi-Cat 2 Smoothies (Barium sulfate suspension, 2% w/v) and E-Z-HD (Barium sulfate for suspension, 98% (w/w)) are acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.**

Readi-Cat 2 and Readi-Cat 2 Smoothies (Barium sulfate suspension, 2% w/v) are oral suspension drug products. E-Z-HD (Barium sulfate for suspension, 98% w/w) is a powder for suspension to be mixed with (b) (4) water and used immediately. The drug product compositions are shown in the following 3 tables and the two ready-to-use products contain multiple preservative agents.

**MEMORANDUM**

Table 1- Composition of Readi-Cat 2 (NDA 208-143 Module 3.2.P.1.2 Table A 18 December 2014 submission)

Component Number	Component Name	% w/v	Function	Grade
(b) (4)	Barium sulfate (b) (4)	2.0898	Contrast Agent (b) (4)	USP
	Xanthan Gum			NF
	Simethicone Emulsion			USP
	Potassium Sorbate			NF
	Sodium Benzoate			NF
	Citric Acid (b) (4)			USP
	Sorbitol Solution			USP
	Saccharin Sodium			USP
	Natural and Artificial Orange flavor <sup>a</sup>			N/A
	Natural and Artificial Vanilla flavor <sup>b</sup>			N/A
	Purified Water			USP (b) (4)

Table 2- Composition of Readi-Cat 2 Smoothies (NDA 208-143 Module 3.2.P.1.2 Table A 18 December 2014 submission)

Component Number	Component Name	Function	Grade	Composition % w/v			
				Banana	Creamy Vanilla	Berry	Mochaccino
<b>Base Formulation</b>							
(b) (4)	Barium sulfate (b) (4)	Drug Substance	USP (b) (4)	2.0898	2.0898	2.0898	2.0898 (b) (4)
	Xanthan Gum		NF				
	Simethicone Emulsion		USP				
	Potassium Sorbate		NF				
	Sodium Benzoate		NF				
	Benzic Acid		USP				
	Citric Acid (b) (4)		USP				
	Sodium Citrate		USP				
	Sorbitol Solution		USP				
	Purified Water (b) (4)		USP				
	Saccharin Sodium		USP				
	Artificial Vanilla Flavor		Food Grade				
	(b) (4)		Food Grade				
	Naturally (b) (4) Banana Flavor		Food Grade				
	Natural and Artificial Blueberry Flavor		Food Grade				
	Natural and Artificial (b) (4) Chocolate Flavor		Food Grade				
	Natural and Artificial Coffee (b) (4) Flavor		Food Grade				

**MEMORANDUM**

Table 3- Composition of E-Z-HD (NDA 208-036 Module 3.2.P.1.2 Table A 12 June 2015 submission)

Component number	Component name	Percentage composition (% w/w)	Amount (g) per unit dose (340g)	Function	Grade
(b) (4)	Barium sulfate (b) (4)	88.6272	301.33	Contrast agent (b) (4)	USP
	Sorbitol				USP/NF
	Acacia (b) (4)				USP/NF
	Sodium citrate (b) (4)				USP
	Simethicone				USP
	(b) (4) Citric acid				USP
	Polysorbate 80				USP/NF
	Carrageenan				USP/NF
	Ethyl maltol				USP/NF
	Saccharin sodium				USP
	Natural and artificial strawberry flavor <sup>a</sup>				Food grade
	Natural and artificial cherry flavor <sup>b</sup>				Food grade

The drug product is tested for Microbial Limits at release and on stability using a method consistent with USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). The Microbial Limits acceptance criteria are consistent with USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use). The REDI-CAT 2 products (NDA 208-143) have a limit of (b) (4) CFU/mL total aerobic microbial count, (b) (4) CFU/g total yeast and mold count and the absence of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Salmonella spp.* The REDI-CAT 2 liquid drug products will be tested according to USP<51> on stability. For REDI-CAT 2, sodium benzoate levels must be (b) (4) % w/w ((b) (4) w/v) and potassium sorbate levels must be (b) (4) % w/w ((b) (4) % w/v). For REDI-CAT 2 smoothies, cumulative sodium benzoate and benzoic acid levels must be (b) (4) % w/w ((b) (4) w/v) and potassium sorbate levels must be (b) (4) % w/w ((b) (4) % w/v) for banana flavor and (b) (4) % w/w ((b) (4) % w/v) for all other flavors. Barium sulfate for suspension has a microbial release and stability specification of (b) (4) CFU/g TAMC, (b) (4) CFU/g TYMC, and the absence of *E. coli* in (b) (4). The Microbial Limits test methods were verified to be appropriate for use with the drug product following procedures consistent with those in USP Chapters <61> and <62>.

Information request sent in the 74-day letters (20 February 2015)  
 NDAs 208-143 and 208-036

We refer to document M-010 in Module 3.2.P.5.2. This document was provided in French and the English translation should be submitted.

Summary of response dated 11 June 2015 (NDA 208-036)

The English translation of M-010 rev. 1 was provided. The document describes microbial analyses performed at EZEM Canada. Samples are tested at a 1:10 or 1:50 dilution and the

## MEMORANDUM

pour plates are incubated 3-5 days at 33±2°C for TAMC and 5 days at 23±2°C for TYMC. Appropriate USP<62> methods were described for the detection of indicator organisms.

Information request dated 20 February 2015 (NDA 208-143)

Provide a summary of the product development studies that determined the appropriate preservative content for the formulations. Submit the USP<51> method summary and results from at least 3 batches of drug product. These summary results should confirm the preservative effectiveness from at least one batch at the minimum preservative contents from the product specification.

Summary of response dated 12 June 2015

The applicant prepared a laboratory batch of Readi-Cat 2 to evaluate the preservative effectiveness at the minimum (b)(4) concentration ((b)(4) % w/v) at product expiry. The (b)(4) concentration was (b)(4) % w/v. Results are provided in Report 1557 which documented acceptable USP<51> test results and (b)(4) CFU/g TAMC and TYMC with the absence of all specified organisms. Acceptable stability results were indicated on AET lots 00502005, 00502006, 00502007.

Reviewer Comment: Ideally the (b)(4) concentration would also have been evaluated at the lower limit of the stability specification (b)(4) w/v. However, the routine AET testing for Readi-Cat 2 on stability, combined with the data presented below for the Readi-Cat 2 smoothies ((b)(4) % w/v (b)(4) and (b)(4) % w/v (b)(4)), are sufficient to support approval. Accelerated stability results (30°C/75% RH) on three batches remained at (b)(4) w/w for (b)(4) at the 18 month time point, which suggests that this preservative will not decrease significantly over the 24 month shelf life. The level of (b)(4) fell slightly from (b)(4) w/w to (b)(4) w/w over the same time period. AET will occur at 24 months and will confirm the adequacy of the preservative system.



Information request dated 20 February 2015 (NDA 208-143)

Non-sterile aqueous drug products may potentially be contaminated with organisms in the *Burkholderia cepacia* complex (BCC). BCC strains have a well-documented ability to ferment a wide variety of substrates and are known to proliferate in the presence of many traditional preservative systems. Thus, despite the presence of otherwise adequate preservative systems, BCC strains can survive and even proliferate in product during storage. For a recent review of FDA's perspective on BCC please see *PDA J Pharm Sci Tech* 2011; 65(5): 535-43.

## MEMORANDUM

In order to control for the presence of BCC in your product you should consider the following:

1. Identify potential sources for introduction of BCC during the manufacturing process and describe the steps to minimize the risk of BCC organisms in the final drug product. We recommend that potential sources are examined and sampled as process controls. These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.
2. Provide test methods and acceptance criteria to demonstrate the drug product is free of BCC. Your test method should be validated and a discussion of those methods should be provided. Test method validation should address multiple strains of the species and cells should be acclimated to the conditions in the manufacturing environment (e.g., temperature) before testing.

As there are currently no compendial methods for detection of BCC, we have provided suggestions for a potential validation approach and some points to consider when designing your validation studies. However, any validated method capable of detecting BCC organisms would be adequate. It is currently sufficient to precondition representative strain(s) of BCC in water and/or your drug product without preservatives to demonstrate that your proposed method is capable of detecting small numbers of BCC. Your submission should describe the preconditioning step (time, temperature, and solution(s) used), the total number of inoculated organisms, and the detailed test method to include growth medium and incubation conditions. It is essential that sufficient preconditioning of the organisms occurs during these method validation studies to insure that the proposed recovery methods are adequate to recover organisms potentially present in the environment.

For more information, we refer you to *Envir Microbiol* 2011; 13(1):1-12 and *J. Appl Microbiol* 1997; 83(3):322-6.

### Summary of response dated 12 June 2015

The applicant provided a risk assessment for potential contamination of the Readi-Cat 2 products with BCC in document VA-969 v01. The hazard assessment included evaluation of each ingredient and process step for the potential of BCC contamination and persistence. Next, the lists of potential hazards were evaluated for which hazards were “reasonably likely to occur” and thus must be addressed with a critical control point. (b) (4)  
identified as raw materials and the product (b) (4) process steps have the potential to be contaminated with BCC.

**MEMORANDUM**

Table 4- Critical control points (3.2.P.2 VA-969 Table 6)

Table 6 CPP Summary
(b) (4)

(b) (4)
---------

Information request dated 08 and 10 July 2015 (NDA 208-036 and 208-143)

For the ongoing stability program and the post-approval stability program, provide a stability protocol, including storage conditions, time points and tests conducted, for the proposed shelf life of EZ-HD.

Summary of email response received 17 July 2015 (official response planned for late July 2015)

A single lot of EZ-HD is placed on stability annually (25°C/60% RH) and tested for TAMC, TYMC, and the absence of *E. coli* at 0, 12, 24, 36, 48, and 60 months. Two lots of Read-Cat 2 smoothie product are placed on stability annually (25°C/60% RH) with alternating flavors every 2 years. A single lot of Read-Cat 2 product is also placed on stability annually. The Read-Cat 2 stability studies include 0, 3, 6, 9, 12, 18, and 24 month sampling for TAMC, TYMC, and absence of *S. aureus*, *P. aeruginosa*, *E. coli*, and *Salmonella* spp. USP<51> testing is conducted at 0, 24, and 36 months. The banana smoothie stability specification also includes the absence of *Enterobacteriaceae* in addition to the other

**MEMORANDUM**

indicator organisms. Results for all lots are acceptable to date.

**ADEQUATE**

**Reviewer Comments – The microbiological quality of the drug products are controlled via suitable release and stability testing protocols.**

**END**

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

JESSICA COLE  
07/23/2015

STEPHEN E LANGILLE  
07/23/2015