CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208844Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)

MEMORANDUM

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

DATE: 25 August 2016

TO: NDA 208844

FROM: Jessica G. Cole, PhD Acting Quality Assessment Lead
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THROUGH: Dupeh Palmer, PhD Microbiology Secondary Reviewer
Division of Microbiology Assessment/OPF/OPQ/CDER

cc: Frank Lutterodt Project Manager
Division of Medical Imaging Products/OND/ODEIV/CDER

SUBJECT: Product Quality Microbiology assessment of Microbial Limits for Varibar Pudding (proposed) barium sulfate paste 40% (w/v) [Submission Date: 14 December 2015, 27 January 2016, 20 July 2016]

The Microbial Limits specification for Varibar Pudding (proposed) barium sulfate paste 40% (w/v) is acceptable from a Product Quality Microbiology perspective. Therefore, this submission is recommended for approval. A single comment to be sent to the applicant is provided at the end of this review.

Varibar Pudding (proposed) barium sulfate paste 40% (w/v) is a non-sterile paste for oral administration supplied in a 230 mL multidose polyethylene tube. This NDA is the third product in a series of marketed but unapproved barium sulfate products that will be submitted to the Agency as contrast agents for gastrointestinal tract imaging. These products have extensive commercial use and NDA 208036 and NDA 208143 were approved in the bundled microbiology review in DARRTS dated 23 July 2015. Varibar Pudding has been marketed since the year 2000 and in 2008 Bracco acquired the EZ-EM product lines. Since 2008 there have been over (b) (4) units (See Module 3.2.P.2 submitted 20 July 2016) sold using the same microbiological control mechanisms described below.

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Table 1- Drug product composition (Sponsor Table A Module 3.2.P.1.2)

Component number	Component Name	Percent composition (% w/v)	Amount (g) per unit (230 mL)	Function	Grade
(b) (4)	Barium sulfate (b) (4)	40.0000[3]	92.000	Contrast agent	USP
	Sodium Benzoate			(b) (4)	USP/NF
	Potassium Sorbate				USP/NF
	Xylitol				USP/NF
	Citric Acid (b) (4)				USP
	Simethicone Emulsion (b) (4)				USP
	Polysorbate 80				USP/NF
	Glycerin				USP
	Xanthan Gum				USP/NF
	Carboxymethylcellulose Sodium				USP
	Maltodextrin				USP/NF
	Ethyl Vanillin				USP/NF
	Artificial Vanilla Flavor[3]				GRAS; 21CFR 172.5 compliant
	Saccharin Sodium				USP
	Purified Water				USP
					(b) (4)

The drug product is tested for Microbial Limits at release using method M10 which follows 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 Enumeration acceptance criteria are consistent with USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use). Method M10 was reviewed previously under NDAs 208036 and 208143 and found acceptable. The drug product will have (b) (4) CFU/g total aerobic microbial count, (b) (4) CFU/g total combined yeasts and molds and the absence of bile tolerant gram-negative bacteria (b) (4) *Staphylococcus aureus* (b) (4), *Pseudomonas aeruginosa* (b) (4), *Escherichia coli* (b) (4), and *Salmonella spp.* (b) (4). The microbiological test methods were verified to be appropriate for use with the drug product following procedures consistent with those in USP Chapters <61> and <62>. The sodium benzoate will be (b) (4) % (w/v) and the potassium sorbate will be (b) (4) % (w/v) for release and stability.

The drug product will also be tested for microbiological quality at expiry as part of the post-approval stability protocol. The initial stability batches will be tested at 3, 6, 9, 12, 18, 24 and 36 months for microbial quality but no preservative effectiveness studies are planned. Developmental studies described in report #1569 included analysis of preservative effectiveness below the minimum preservative levels from the specification. Lot #1569-01 was prepared with (b) (4) % sodium benzoate and (b) (4) % potassium sorbate, and the applicant states the acceptance criteria

were met but no additional information was provided. Only this single laboratory scale lot was studied. In use stability studies through 30 days evaluated the microbial content of the tubes but did not include USP<51> testing. Table D in Module 2.3.P.2.5 describes the raw material microbiology testing included for the barium sulfate, simethicone emulsion, xanthan gum, maltodextrin, vanilla flavor, and purified water.

REVIEWER COMMENT: A summary of the log reduction data obtained from antimicrobial effectiveness testing (AET) with lot 1569-01 was not provided but the test was stated to meet the USP requirements. Similar summary data were provided for and approved in NDAs 208036 and NDA 208143 so no additional information will be requested. NDA 208844 does not propose to conduct AET testing on stability or utilize more than one batch, yet both previously approved NDAs will test AET on at least one batch at expiry with three total batches. The preservative systems for these products are similar, and the manufacturer has significant manufacturing experience. Thus expiry testing will not be required for Varibar Pudding but the manufacturer will be advised to consider testing AET at expiry.

Burkholderia cepacia complex

The manufacturing process controls include [redacted] (b) (4) to exclude *S. aureus, E. coli, Salmonella spp., P. aeruginosa,* and *Burkholderia cepacia.* Document VA-1004 version 01 provides a Hazard Analysis and Critical Control Points (HAACP) risk assessment for the introduction of *B. cepacia* complex (BCC) into the final drug product. This risk assessment is similar to that provided NDAs 208036 and 208143 but is product specific. The applicant identified [redacted] (b) (4) It is assumed by this reviewer that the BCC method reviewed previously for NDAs 208036 and 208143 is also applicable here.

ADEQUATE

Reviewer Comments – The microbiological quality of the drug product is controlled via [redacted] (b) (4) and a suitable testing protocol. The following comment should be sent to the application for information only and no response is needed.

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Non-deficiency comment to be sent to the applicant:
The following comment is being provided as advice. The FDA recommends that all preserved drug products test at least one batch at expiry for antimicrobial effectiveness as preservative content does not always correlate with preservative effectiveness. Due to the extensive product history with Varibar Pudding, and adequate AET results at expiry for similar products, this testing is not required; however, it is recommended for all preserved drug products. For more information refer to Q1a Stability Testing of New Drug Substances and Drug Products. We recommend you address this in subsequent barium sulfate multiple dose product applications.

END

MEMORANDUM

Jessica Cole -S

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