Summary Review for Regulatory Action

Responsible Organization	Division of Medical Imaging Products (DMIP)
Date	02/27/2017
From	Libero Marzella MD, PhD
Subject	Division Director Summary Review
NDA	208143
Supplement	2
Applicant Name	Bracco Diagnostics Inc.
Date of Submission	05/04/2016
PDUFA Goal Date	03/03/2017
Proprietary Name **Established (USAN) Name**	Liquid E-Z-PAQUE Barium sulfate
Dosage Form **Strength**	Oral suspension in a single-use bottle Barium sulfate 213g in 355 ml (60% w/v)
Indication	Liquid E-Z-PAQUE is a radiographic contrast agent indicated for use in single contrast radiographic examinations of the esophagus, stomach, and small bowel to visualize the gastrointestinal (GI) tract in adult and pediatric patients
Regulatory Action	Approval

Material Reviewed/Consulted OND Action Package, including:		**Names of Discipline Reviewers**
OPQ/ONDP	Drug product	Anne Marie Russell, PhD
OPQ/OPF	Microbiology	Jessica Cole, PhD
OND/DMIP	Clinical	Brenda Ye, MD
OND/DMIP	Labeling	Michele Fedowitz, MD
PMHS	Pediatrics	Mona Khurana, MD
OPDP	Labeling	Zarna Patel, PharmD
DMEPA	Labeling	Leeza Rahimi, PharmD

DMEPA - Division of Medication Error and Analysis
OND - Office of New Drugs
ONDP - Office of New Drug Products
OPF - Office of Products and Facilities
OPQ - Office of Pharmaceutical Quality
OPDP - Office of Prescription Drug Promotion
PMHS - Pediatric and Maternal Health Staff

Reference ID: 4062577

Introduction

On May 4, 2016 Bracco Diagnostics (Applicant) submitted a 505(b)(2) efficacy supplement to their New Drug Application (sNDA 208143) for Liquid E-Z-PAQUE (barium sulfate) oral suspension, 60% (w/v). Liquid E-Z-PAQUE is intended for use in single contrast radiographic examinations of the esophagus, stomach, and small bowel to visualize the gastrointestinal (GI) tract in adult and pediatric patients.

The original application (NDA 208143) for READI-CAT 2 and READI-CAT 2 SMOOTHIE was approved for the use of a more dilute 2% (w/v) barium sulfate oral suspension for use for the delineation of the GI tract in adults and in pediatric patients of all ages.

Barium sulfate, the active ingredient, is opaque to x-rays and functions as a positive contrast agent. Barium sulfate has been in long-term clinical use for radiographic imaging of the gastrointestinal tract .The present sNDA cross-references NDA 208036 approved in January 2016 for data on the drug substance and for non-clinical and clinical information. This review summarizes my assessment of the approvability of this application based on the assessments by the FDA reviewers listed above.

Regulatory History

Liquid E-Z-PAQUE (barium sulfate) oral suspension is classified as a radiographic contrast agent. Liquid E-Z-PAQUE has been marketed since 1984 as an unapproved drug.

I reference the meeting minutes of the pre-investigational new drug application (Pre-IND) 115090. The Agency and the Applicant discussed the plan for the submission of new drug applications for the unapproved barium sulfate products and the anticipated submission schedule. An agreement was reached on the total number of applications and on the data and other information necessary for each application.

A total of (b) new drug applications and supplemental new drug applications are anticipated. It was determined that the information on the barium sulfate (b) (4) drug substance, the non-clinical and the clinical information would be filed to the initial NDA for E-Z-HD (208036). Subsequent applications would reference that NDA for this information.

Liquid E-Z-PAQUE has been manufactured by the same process using similar specifications and formulation since market introduction. This manufacturing history supports the clinical determination of safety and efficacy from studies in the scientific literature.

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1. Chemistry Manufacturing and Controls

I concur with the recommendation by the FDA reviewer Dr. Russell that the application be approved from the Drug Product Pharmaceutical Quality perspective.

Reference ID: 4062577

The comparability of the proposed commercial product with the unapproved historical product was an important review issue. In the absence of a reference listed drug, Dr. Russell determined that the commercial product is comparable to the unapproved product marketed since 2012 and is also qualitatively similar to the products marketed since 1984. The history of the quality of the comparable products supports the Agency's reliance on the safety and efficacy data from the scientific literature.

The drug substance, barium sulfate, is a mined mineral refined to remove impurities and (b) (4). The Applicant has committed to testing (b) (4) The drug product, Liquid E-Z-PAQUE, is a ready-to-use low viscosity barium sulfate suspension (60% w/v) for oral administration. The finished drug product dosage form is presented as a ready-to-use, unit dose in a 500mL bottle filled with 355 mL of product containing 213 grams of barium sulfate.

The drug product contains the following inactive ingredients: (b) (4) xanthan gum and carboxymethyl cellulose (b) (4) sorbitol) (b) (4) (polysorbate 80) (b) (4) simethicone) (b) (4) sodium citrate and citric acid (b) (4) saccharin and strawberry lemon (b) (4) sodium benzoate and potassium sorbate). The reviewer determined that the quality of the excipients is acceptable.

As a risk minimization step, the drug labeling contraindicates the use of Liquid E-Z-PAQUE in patients with known severe hypersensitivity to the drug substance or any of the excipients listed above. The drug labeling also specifically warns about the risks posed by the sorbitol ((b) (4) per unit dose) in Liquid E-Z-PAQUE in patients with hereditary fructose intolerance.

The OPQ reviewers determined that the specifications for pharmaceutical and microbiological quality are acceptable. The specifications are in general more robust than those in the USP monograph and are similar to those of other approved barium sulfate products. The OPQ reviewer determined that quality of the container closure is acceptable. The stability data were adequate to support the proposed 18 month shelf life of the product (b) (4).

I concur with the FDA reviewer Dr. Cole that the application be approved from the Drug Product Microbiological Quality Perspective.

The OPQ reviewer determined that the microbial limit specification is acceptable. The microbiological test methods were verified to be appropriate for use with the drug product. Product lots were tested for microbiological quality for up to 24 months and met acceptance criteria; a post-approval stability protocol for testing the drug product at expiry is in place.

Reference ID: 4062577

2. Nonclinical Pharmacology and Toxicology

The application references NDA 208036. No new preclinical data are submitted in the present submission and none are needed.

3. Clinical Pharmacology and Biopharmaceutics

The application references NDA 208036. No new pharmacology data are submitted in the present submission and none are needed.

4. Clinical Microbiology

This section is not applicable to this NDA.

5. Clinical/Statistical Efficacy

The application references NDA 208036. No new efficacy data are submitted in the present submission and none are needed.

6. Safety

The application references NDA 208036. No new safety data are submitted in the present submission and none are needed.

7. Advisory Committee Meeting

No advisory committee meeting was needed for this submission.

8. Pediatrics

This supplemental application requires a pediatric assessment under the Pediatric Research Equity Act (PREA) because the indication is new. The Applicant proposes the use of Liquid E-Z-PAQUE in all pediatric age groups.

I concur with the determination by the Pediatric and Maternal Health reviewer Dr. Khurana that Liquid E-Z PAQUE is fully assessed. The proposed indication and the formulation as an oral suspension for Liquid E-Z PAQUE in this sNDA are similar to the indication and formulation for READI-CAT 2 and READI-CAT 2 SMOOTHIE (see original NDA) which are approved for use in all pediatric age groups. The final pediatric labeling for Liquid E-Z PAQUE takes into account the recommendations made by Dr. Khurana.

Reference ID: 4062577

The efficacy of Liquid E-Z-PAQUE is based on successful opacification of the esophagus, stomach, and small bowel during single contrast radiographic procedures. The safety and the dosing and administration recommendations are based on clinical experience. Pediatric patients with a history of asthma or food allergies may be at increased risk for development of hypersensitivity reactions. Pediatric patients with cystic fibrosis or Hirschsprung disease are at risk for bowel obstruction after use of barium sulfate.

In pediatric patients the recommended doses of Liquid E-Z-PAQUE are based on physiologic GI volume. For the upper GI tract a volume sufficient to distend esophagus and stomach is recommended. For small bowel examinations the recommended doses are: 30 to 75 ml in newborns and in patients less than 2 years of age; and 75 to 480 ml in patients 2 to 17 years of age.

9. Other Relevant Regulatory Issues

I agree with the labeling reviews and recommendations for revisions made by the FDA primary reviewers (Drs. Fedowitz, Khurana, Patel, Rahimi, and Ye).

I conclude that, as revised, the prescribing information and the immediate container and carton labeling meet the regulatory format and content requirements (21 CFR 201.56-57) and raise no issues from the drug promotion or medication error perspective. I reference the appended documents for the final labeling developed by the Agency and the Applicant.

10. Decision/Risk Benefit Assessment

I concur with the FDA reviewers' recommendation to approve this application for Liquid E-Z-PAQUE for use in single contrast radiographic examinations of the esophagus, stomach, and small bowel to visualize the GI tract in adult and pediatric patients.

The opacification of the GI tract by barium sulfate enhances the visualization of normal and abnormal anatomy and provides clinically important diagnostic information. Based on long-term clinical experience, serious adverse reactions are rare and the risks are mitigated by labeling.

The drug substance, preclinical and clinical information referenced to NDA 208036, the new information on the pharmaceutical and microbial quality of the drug product demonstrate that the risk benefit of Liquid E-Z-PAQUE for the indicated use in adult and pediatric patients is favorable.

Reference ID: 4062577

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/s/

LIBERO L MARZELLA
02/28/2017