

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209210Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 20, 2017
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 209210
Product Name and Strength:	Bydureon Bcise (exenatide extended-release) suspension, 2 mg
Applicant/Sponsor Name:	AstraZeneca
Submission Date:	October 19, 2017
OSE RCM #:	2016-2936-2
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMO

Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised container label for Bydureon Bcise (Appendix A) to determine if it is acceptable from a medication error perspective. The professional sample carton and container labeling and the trade carton labeling for Bydureon Bcise were found acceptable; the revisions to the trade container label are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised trade container label for Bydureon Bcise is acceptable from a medication error perspective. We have no further recommendations at this time.

^a Conrad A. Review of Revised Label and Labeling for Bydureon Bcise (NDA 209210). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Oct 13. RCM No.: 2016-2936-1.

APPENDIX A. LABEL AND LABELING SUBMITTED ON OCTOBER 19, 2017

Container label



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/s/

ARIANE O CONRAD
10/20/2017

HINA S MEHTA
10/20/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and
Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatric and Maternal Health Memorandum

Date: October 17, 2017 **Date consulted:** January 11, 2017

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, M.D., MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

To: Division of Metabolism & Endocrinology Products (DMEP)

Drug: Bydureon BCise (exenatide extended-release) for injectable suspension

Drug Class: Anti-Hyperglycemic Agents, not oral

NDA: 209210

Applicant: AstraZeneca Pharmaceuticals LP (AZ)

Subject: Pregnancy and Lactation Labeling Conversion (PLLR)

Indication: BYDUREON BCise is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Materials Reviewed:

- DPMH consult request dated January 11, 2017 in DARRTS (Reference ID 4040742)
- Applicant's submission for NDA (b) (4) and Prescribing Information (PI) for BYDUREON BCise (exenatide extended-release) for injectable suspension (non-aqueous) dated December 21, 2016
- Qtern labeling review by Christos Mastroyannis, M.D., February 22, 2017, in DARRTS (Reference ID: 4057405)
- Bydureon (exenatide extended-release) for injectable suspension labeling review by Christos Mastroyannis, M.D., October 11, 2017, in DARRTS (Reference ID: 4165650)

Consult Question:

DMEP requests DPMH assistance with reviewing the applicant's Pregnancy and Lactation Labeling section to comply with PLLR format.

INTRODUCTION

On December 21, 2016, the applicant AZ submitted a New Drug Application (NDA 209210) for Bydureon BCise (exenatide extended-release (b) (4) suspension formulation for injection), as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Bydureon BCise contains the same active ingredient (i.e. exenatide) as the commercial products Byetta (exenatide) injection (NDA 021-773) and Bydureon (exenatide extended-release) for injectable suspension (NDA 022-220). The exenatide suspension in BCise consists of the same exenatide embedded microspheres as in NDA 022-200 (Bydureon) although in a different diluent; BCise exenatide suspension is Miglyol 812 (oil) and Bydureon is water.

The Division of Metabolism & Endocrinology Products (DMEP) consulted the Division of Pediatric and Maternal Health (DPMH) on January 11, 2017, to provide input for appropriate labeling of the pregnancy and lactation subsections of Bydureon BCise (exenatide extended-release) for injectable suspension to comply with the Pregnancy and Lactation Labeling Rule format.

This review provides recommended revisions and structuring of existing information related to the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections in labeling to provide clinically relevant information for prescribing decisions and to comply with current PLLR regulatory requirements.

BACKGROUND**Regulatory History**

On December 21, 2016, the applicant, AstraZeneca Pharmaceuticals LP (AZ), submitted NDA 209210 for marketing approval for Bydureon BCise under the 505(b)(1) pathway. Within the submission, AZ cross-references to other study reports and information previously submitted to other applications held by AZ (including NDA 022200 Bydureon, NDA 021773 Byetta). The nonclinical development program for Bydureon BCise was based primarily on toxicology studies intended to bridge the non-aqueous formulation of Bydureon BCise to the nonclinical data used to support the marketing applications for Bydureon and

Byetta. In particular, AZ needed to establish that the MCT (Medium Chain Triglyceride) vehicle did not exacerbate adverse events attributed to exenatide, and that subcutaneous MCT administration was not itself associated with new toxicity findings.^{1,2}

The applicant, as per the statistical reviewer Yoonhee Kim, Ph.D.,³ submitted three clinical studies: one phase II study (BCB110), and two Phase III studies (BCB118 and BCB120) for EQWS on December 2016 in support for approval for this NDA 209210. The two Phase III clinical studies used non-inferiority (NI) study design with 2 treatment arms and 3 treatment arms for BCB118 and BCB120 respectively. BCB118 is a randomized (EQWS: Byetta; 3:2), open-label, long-term, parallel-group, comparator-controlled, multicenter study to compare the glycemic effects, safety, and tolerability of EQWS to Byetta in subjects with T2DM. BCB120 is a randomized (EQWS: Sitagliptin: Placebo; 3:2:1), long-term, open-label, 3-arm, multicenter study to compare the glycemic effects, safety, and tolerability of EQWS to Sitagliptin (active control) and placebo in subjects with T2DM.

Bydureon (exenatide extended-release for injection), NDA 022200 was approved in the U.S. on January 27, 2012. On December 22, 2016, the applicant, AZ, submitted a supplemental New Drug Application (sNDA 022200/025) and proposed to include the efficacy data from the exenatide extended-release (Bydureon) and dapagliflozin (Farxiga) clinical study DURATION 8 (D5553C00003). DPMH completed a consult review for this sNDA 022200/025 on October 11, 2017, in DARRTS (Reference ID: 4165650).

Bydureon BCise Drug Characteristics⁴

- Bydureon BCise is an extended-release formulation of exenatide and is supplied as a sterile suspension of exenatide extended-release microspheres in an oil-based vehicle of medium chain triglycerides (MCT) in a single-dose autoinjector and to be administered by subcutaneous injection.
- [REDACTED] (b) (4)
- It is a 39-amino acid synthetic peptide, a glucagon-like peptide-1 (GLP-1) receptor agonist, that binds and activates the human GLP-1 receptor *in vitro*.
- [REDACTED] (b) (4)
- Exenatide promotes insulin release from pancreatic beta-cells in the presence of elevated glucose concentrations.
- Exenatide has a molecular weight of 4,186.6 Daltons [REDACTED] (b) (4)

¹ Hao H. Nonclinical primary review in DARRTS, September 28, 2017, Reference ID: 4160176

² Wange R. Nonclinical secondary review in DARRTS, September 29, 2017, Reference ID: 4160821

³ Kim Y, Primary statistical review in DARRTS, September 14, 2017, Reference ID: 4153028

⁴ Bydureon existing labeling, last approved September 24, 2015.

Background on Pregestational and Gestational Diabetes

The reader is referred to the DPMH review for Qtern⁵, a [dapagliflozin /saxagliptin/ fixed dose combination (FDC) tablet] by Christos Mastroyannis, M.D., for an extensive review of the published literature pertaining to Diabetes and Pregnancy.

REVIEW

Nonclinical Experience

Nonclinical data relevant to the safety and labeling of the current product, Bydureon BCise (EQWS), have been reviewed by the nonclinical team previously during the reviews of Byetta and Bydureon. Toxicity studies performed by the Applicant with EQWS included a single-dose, local tolerability study in rats, and 4-week and 13-week toxicity studies in monkeys. AZ does not report any toxicity during these studies, and MCT did not exacerbate any of the effects of exenatide. In addition, no systemic adverse findings, except injection site reactions consisting of edema, were observed. Dr. Wange in his review in DARRTS² concludes that “the toxicologic profile of EQWS appears to be indistinguishable from that of Bydureon and the MCTs present in Bydureon BCise do not constitute a safety risk”

Therefore, both DPMH and nonclinical team recommend that BCise carry the same labeling in the relevant subsections (i.e., 8.1, 8.2, 13.1 and 13.3) as that of the PLLR converted Bydureon labeling.

Applicant’s Pregnancy Reports during the Three Clinical Trials

The applicant states that pregnant and breastfeeding women were actively excluded from exenatide clinical studies (all formulations), and women who became pregnant while on study treatment were withdrawn from the study.

As per the applicant, one pregnancy was reported among the EQWS-treated subjects during the three clinical studies.

A 41-year-old, white, female woman in Study BCB118 was discontinued from EQWS treatment when she reported that she was pregnant. The subject gave birth to a normal, healthy baby 9 months later.

Published Literature and Database Review

For an extended review of exenatide, the reader is referred to the review by Christos Mastroyannis, M.D., in DARRTS, and dated October 11, 2017, Reference ID: 4165650.

Pregnancy:

There are no published reports on pregnancy exposure to exenatide. AZ submitted a review of their PV database on exenatide-exposed pregnancies. There are reports of major congenital malformations and pregnancy losses. The number of cases is small and there is no pattern reported on these malformations. Therefore, a clear determination of any risk with use of exenatide during pregnancy cannot be concluded from the provided information. Limitations of these data include incomplete information, confounding, and small sample size. From the pregnancy

⁵ Qtern labeling review by Christos Mastroyannis, M.D., in DARRTS, February 22, 2017 and Reference ID: 4057405

registry in the 4 cases reported in the exenatide cohort, no adverse pregnancy outcomes were identified.

Lactation:

It is not known whether exenatide is present in human milk. AZ submitted a review of their PV database on exenatide and lactation. There was a total of 3 cases reporting exenatide exposure during breast feeding. Besides the one case of amniotic fluid volume decreased described with both maternal and breast feeding exposure, there were 2 reports, which described a drug exposure via breast feeding where no outcomes were provided. These reports were reviewed and no trends or safety issues were identified.

In conclusion, no new safety issues regarding exenatide exposure during breastfeeding were identified. There is no available information on the effects of the drug on the breastfed infant or the effects of the drug on milk production. The high molecular weight and short elimination half-life of exenatide suggest that transfer into milk would be small. Also, exenatide, being a peptide, would be digested in the stomach of the breastfed infant. Therefore, the breastfed infant would be exposed to a very small amount of exenatide.

Females and Males of Reproductive Potential:

No published information exists regarding the effects of exenatide on fertility in females and males of reproductive potential. The applicant did not provide any relevant human data.

No findings from AZ nonclinical studies of exenatide demonstrate an adverse effect on fertility.

Summary

In conclusion, the review of published literature, AZ's Global Patient Safety database, and data from the drug development program of Bydureon BCise on exenatide use during pregnancy and lactation, did not demonstrate clear association of any adverse outcomes. The human data also cannot confirm or refute the findings from nonclinical studies. No new safety issues regarding exenatide exposure during pregnancy or breastfeeding were identified.

CONCLUSIONS

The cumulative review of all articles and abstracts from literature search and case reports from the Global Patient Safety database of exenatide exposure during pregnancy and breastfeeding, did not demonstrate clear evidence of a causal relationship of any adverse outcomes.

Therefore, DPMH recommends the labeling for Bydureon BCise for the subsections 8.1, 8.2, 8.3 and 17 of the labeling be similar to Bydureon and as such it complies with the required PLLR format.

DPMH revised subsections 8.1, 8.2, 8.3 and 17 of labeling for compliance with the PLLR (see below). The below recommendations reflect discussions with the DMEP Nonclinical and Clinical teams. DPMH refers to the final NDA action for final labeling.

The Pregnancy and Lactation subsections of Bydureon BCise labeling were structured to be consistent with the PLLR as follows:

- **Pregnancy, Subsection 8.1**

- The “Pregnancy” section of Bydureon BCise labeling was formatted in the PLLR format to include: “Risk Summary”, “Clinical Considerations” and “Data” sections.
- **Lactation, Subsection 8.2**
- The “Lactation” section of Bydureon BCise labeling was formatted in the PLLR format to include the “Risk Summary” and “Data” sections.
- **Females and Males of Reproductive Potential, Subsection 8.3**
- Females and Males of Reproductive Potential section of Bydureon BCise labeling was omitted because there is nothing to report.
- **Patient Counseling Information, Section 17**
- The “Patient Counseling Information” section of labeling was updated to correspond with changes made to section 8.1 of the labeling.

RECOMMENDATIONS

DPMH has the following recommendations for Bydureon BCise labeling.

FULL PRESCRIBING INFORMATION: CONTENTS

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited data with exenatide, the active ingredient in BYDUREON BCISE, in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy (*see Clinical Considerations*). Based on animal reproduction studies, there may be risks to the fetus from exposure to BYDUREON BCISE during pregnancy. BYDUREON BCISE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Animal reproduction studies identified increased adverse fetal and neonatal outcomes from exposure to exenatide extended-release during pregnancy or from exposure to exenatide, (b) (4)

(b) (4) during pregnancy and lactation. (b) (4)

(b) (4)

(b) (4) Based on animal data, advise a pregnant woman of the potential risk to a fetus.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk:

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, still birth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal Data

Pregnant rats given subcutaneous doses of 0.3, 1, or 3 mg/kg exenatide extended-release every 3 days during organogenesis had systemic exposures (b) (4) times human exposure, respectively, at the maximum recommended human dose (MRHD) of 2 mg/week BYDUREON BCise based on plasma exenatide exposure (AUC) comparison. Reduced fetal growth at all doses and skeletal ossification deficits at 1 and 3 mg/kg occurred at doses that decreased maternal food intake and body weight gain. In studies evaluating reproduction and development in pregnant mice and rabbits, maternal animals were administered exenatide, the active ingredient in BYDUREON BCise, by subcutaneous injection twice a day. Differences in embryo-fetal developmental toxicity from subcutaneously injected exenatide extended-release and exenatide were not evaluated in mice, rats, or rabbits.

In pregnant mice given 6, 68, 460, or 760 mcg/kg/day exenatide during fetal organogenesis, skeletal variations associated with slowed fetal growth, including changes in number of rib pairs or vertebral ossification sites, and wavy ribs were observed at 760 mcg/kg/day, a dose that produced maternal toxicity and yielded systemic exposure 200 times the human exposure resulting from the MRHD of BYDUREON based on AUC comparison.

In pregnant rabbits given 0.2, 2, 22, 156, or 260 mcg/kg/day exenatide during fetal organogenesis, irregular fetal skeletal ossifications were observed at 2 mcg/kg/day, a dose yielding systemic exposure up to (b) (4) times the human exposure from the MRHD of BYDUREON based on AUC comparison.

In maternal mice given 6, 68, or 760 mcg/kg/day exenatide from gestation day 6 through lactation day 20 (weaning), an increased number of neonatal deaths were observed on postpartum days 2 to 4 in dams given 6 mcg/kg/day, a dose yielding a systemic exposure equivalent to the human exposure from the MRHD of BYDUREON based on AUC comparison.

8.2 Lactation

Risk Summary

There is no information regarding the presence of exenatide in human milk, the effects of exenatide on the breastfed infant, or the effects of exenatide on milk production. Exenatide, the active ingredient in BYDUREON BCISE, was present in the milk of lactating mice. However, due to species-specific differences in lactation physiology, the clinical relevance of these data are not clear (*see Data*). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for exenatide and any potential adverse effects on the breastfed child from exenatide or from the underlying maternal condition.

Data

In lactating mice subcutaneously injected twice a day with exenatide, the active ingredient in BYDUREON BCISE, the concentration of exenatide in milk was up to 2.5% of the concentration in maternal plasma.

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/s/

CHRISTOS MASTROYANNIS
10/18/2017

TAMARA N JOHNSON
10/19/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 13, 2017
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 209210
Product Name and Strength:	Bydureon Bcise (exenatide extended-release) suspension, 2 mg
Applicant/Sponsor Name:	AstraZeneca
Submission Date:	October 13, 2017
OSE RCM #:	2016-2936-1
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMO

Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised carton labeling and container labels for Bydureon Bcise (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised professional sample carton and container labeling and trade carton labeling for Bydureon Bcise are acceptable from a medication error perspective. However, this review identified a deficiency with the NDC numbers on the trade container label and we provide one recommendation in Section 3.

^a Conrad A. Label and Labeling and Human Factors Review for Bydureon Bcise (NDA 209210). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Sept 08. RCM No.: 2016-2936 and 2017-211.

3 RECOMMENDATIONS FOR ASTRAZENECA

The container label for one unit of the Bydureon Bcise device and the carton labeling for four Bydureon Bcise devices should have different NDC numbers. In the submission, both NDCs use -04 as the package configuration (xxxx-xxxx-04). Revise the NDC for the Bydureon Bcise container label so that the package configuration is different from the carton containing four units. You can consider using -01 to indicate one unit on the Bydureon Bcise container label.

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/s/

ARIANE O CONRAD
10/13/2017

HINA S MEHTA
10/13/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: October 12, 2017

To: Richard Whitehead, Regulatory Project Manager, Division of Metabolism and Endocrinology Products (DMEP)

Monika Houstoun, Associate Director for Labeling, (DMEP)

From: Domenic D'Alessandro, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for BYDUREON BCISE (exenatide extended-release) injectable suspension for subcutaneous use

NDA: 209210

In response to the DMEP consult request dated January 10, 2017, OPDP has reviewed the proposed product labeling (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for the original NDA submission for BYDUREON BCISE.

PI and Medication Guide/IFU: OPDP's comments on the proposed labeling are based on the draft PI, Medication Guide, and IFU received by a link to SharePoint via electronic mail from DMEP on October 6, 2017, and are provided below. Reference is made to the Division of Medical Policy Program's (DMPP) review of the Medication Guide/IFU dated October 5, 2017. We agree with DMPP's comments and offer the following additional comments.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on June 16, 2017, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Domenic D'Alessandro at (301) 796-3316 or Domenic.dalessandro@fda.hhs.gov.

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/s/

DOMENIC G DALESSANDRO
10/12/2017

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: October 5, 2017

To: Jean-Marc Guettier, MD
Director
Division of Metabolism and Endocrinology Products (DMEP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Aman Sarai, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)

Drug Name (established name): BYDUREON BCISE (exenatide extended-release)

Dosage Form and Route: injectable suspension for subcutaneous use

Application Type/Number: NDA 209210

Applicant: AstraZeneca Pharmaceuticals

1 INTRODUCTION

On December 20, 2016, AstraZeneca submitted for the Agency's review a new drug application for BYDUREON BCISE (exenatide extended-release) injectable suspension for subcutaneous use. This is a 505(b)(1) application with a proposed indication for BYDUREON BCISE as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

This review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on January 13, 2017 for DMPP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for BYDUREON BCISE (exenatide extended-release) injectable suspension for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on September 8, 2017.

2 MATERIAL REVIEWED

- Draft BYDUREON BCISE (exenatide extended-release) MG and IFU received on December 20, 2016, revised by the Review Division throughout the review cycle, and received by DMPP on September 25, 2017.
- Draft BYDUREON BCISE (exenatide extended-release) Prescribing Information (PI) received on December 20, 2016, revised by the Review Division throughout the review cycle, and received by DMPP on September 25, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG and IFU document using the Arial font, size 10.

In our review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU is consistent with the Prescribing Information (PI)
- rearranged information due to conversion of the PI to Physicians Labeling Rule (PLR) format
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG and IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the MG and IFU is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
10/05/2017

MARCIA B WILLIAMS
10/05/2017

LABEL AND LABELING AND HUMAN FACTORS RESULTS REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	September 8, 2017
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 209210
Product Name and Strength:	Bydureon Bcise (exenatide extended-release) suspension, 2 mg
Product Type:	Single Ingredient, Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	AstraZeneca
Submission Date:	December 21, 2016 and June 16, 2017
OSE RCM #:	2016-2936 and 2017-211
DMEPA Primary Reviewer:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader:	Hina Mehta, PharmD
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS

1 REASON FOR REVIEW

The Division of Metabolic and Endocrinology Products (DMEP) requested that DMEPA review the human factors (HF) validation study report and proposed labels and labeling submitted under NDA 209210 for Bydureon Bcise (exenatide extended-release) as part of the evaluation of the 505(b)(1) submission. Bydureon Bcise contains exenatide, which is the same active ingredient as the commercially available Byetta (NDA 021773) and Bydureon (NDA 022200).

1.1 PRODUCT INFORMATION

Byetta (exenatide, NDA 021773) was approved on April 28, 2005. Bydureon (exenatide extended-release, NDA 022200) was approved on January 27, 2012 in the vial/syringe presentation (a single-dose tray containing 2 mg vial, a vial connector, and a prefilled diluent syringe). The Bydureon Pen was approved under the NDA 022200/S-08 on February 28, 2014 (a single-dose pen containing 2 mg of exenatide and diluent). Bydureon and Bydureon Pen require mixing prior to administration and they are administered subcutaneously once weekly.

AstraZeneca submitted NDA 209210 for Bydureon Bcise, an exenatide extended-release suspension, available in a single-dose autoinjector that delivers a single dose of 2 mg subcutaneously once weekly. AstraZeneca plans to add this product to the existing product line of Bydureon and Bydureon Pen. The Bydureon Bcise autoinjector is designed as a more convenient method of delivery for Bydureon. Of note, the Bydureon Bcise autoinjector has a locking needle shield that covers the used needle once the injection has completed to minimize the risk for unintentional needle sticks.

1.2 REGULATORY HISTORY

DMEPA reviewed the human factors study for the autoinjector and the proposed labeling submitted by AstraZeneca on December 21, 2016. The protocol for the human factors validation study was submitted to FDA under IND 107815^a and we provided comments to AstraZeneca.^b We confirmed that the comments included in two of the three reviews completed by DMEPA^c were implemented. The comments provided in our final review of the protocol^d were not sent to AstraZeneca in error; therefore, the comments from that review

^a AstraZeneca Pharmaceuticals. Protocol for Human Factor Summative Use Testing for exenatide extended-release injectable suspension (IND 107815). Gaithersburg (MD): AstraZeneca Pharmaceuticals; 2015 Jun 30.

^b White M. COR-INDAD-02 Advice/Information Request for exenatide extended-release suspension. Silver Spring (MD): FDA, CDER, OND, DMEP (US); 2015 Sept 4. IND 107815.

White M. COR-INDAD-02 Advice/Information Request for exenatide extended-release suspension. Silver Spring (MD): FDA, CDER, OND, DMEP (US); 2015 Dec 4. IND 107815.

^c Vee S. Human Factors Protocol Review for exenatide extended-release suspension (IND 107815). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 Aug 14. RCM No. 2015-1578.

Vee S. Review of Human Factors Protocol Review Memo for exenatide extended-release suspension (IND 107815). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 Nov 9. RCM No. 2015-1578-1.

^d Garrison N. Review of Human Factors Protocol Review Memo for exenatide extended-release suspension (IND 107815). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 Mar 9. RCM No. 2015-1578-3.

were not implemented when the study was conducted. However, we determined that the changes recommended in that final review of the protocol would not adversely affect the study results because the comments did not represent content changes to the product labeling (e.g., request to clarify an aspect of the study protocol and minor wording changes to the “Common Questions and Answers” section of the IFU).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
Information Request	D
Labels and Labeling	E

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the human factors validation study results. We also performed a risk assessment of the proposed labeling to identify areas of vulnerability that may lead to medication errors and other areas of improvement.

3.1 HUMAN FACTORS VALIDATION STUDY

Methodology

We reviewed the methodology in our previous reviews of the protocol. All of the participants, except for the 15 pharmacist participants^e, completed two differentiation tasks, the simulated injection task, and post scenario assessments of the IFU and carton/container labeling. The study moderators did not specifically direct participants to use the IFU until the labeling assessment, with the exception of those participants who independently said they would call their doctor or pharmacist for assistance during the simulated injection task.

^e Pharmacist participants completed one differentiation task with the product carton, the simulated dosing tasks, and the IFU assessment only.

Results

We have provided a summary of the errors in the following sections.

1. Differentiation

- A. Product differentiation: Six participants (one untrained healthcare practitioner and five untrained lay users) selected the Bydureon Pen or the Bydureon “Single Tray” instead of the Bydureon Bcise autoinjector when presented with comparator devices. In addition, one lay user selected the Trulicity pen based on a personal preference for that product’s appearance. AstraZeneca determined that these errors occurred because the participants did not read the entire proprietary name on the prescription or pharmacy label and failed to notice the ‘Bcise’ modifier in the name. Thus, AstraZeneca classified each error as a study artifact. Based on the subjective feedback from the participants, we determined that these errors did not occur because of difficulties with differentiation. Of note, all of the pharmacist participants correctly selected the Bydureon Bcise autoinjector on the simulated prescription. In addition, we determined that patients may not routinely have more than one presentation of Bydureon available at a time; therefore, it is unlikely that this error would occur in real-world use. As the Bydureon Bcise autoinjector will be added to the product line with Bydureon Pen and Bydureon “Single Tray”, there is the potential that the wrong presentation is selected; however, patients would still receive the correct drug product. Thus, we do not have any recommendations for additional differentiation to mitigate the risk of these errors.
 - B. Carton differentiation: Three participants (untrained lay users) selected the carton that corresponded with the incorrect device selected in the previous task. Patients may not routinely have more than one presentation of Bydureon at one time; therefore, it is unlikely that this error would occur in real-world use. Of note, all of the pharmacist participants selected the correct carton based on the simulated prescription. This indicates that pharmacists will dispense the correct product if the prescription clearly indicates the desired product (i.e., Bydureon Bcise); thus, we determined that the errors that were noted with other user groups did not occur due to difficulties with differentiation.
2. Simulated Injection: Table 2 lists the critical tasks where failures occurred, the number of errors that occurred during the task categorized by user group, our analysis of the errors, and a summary of our recommendations for each error.

Table 2: List of tasks where failures occurred and the number of failures that occurred during the task			
Task	# of Errors by User Group	Analysis of Error	Recommendations
Mix the medication by shaking	1 failure (untrained pharmacist)	Pharmacists would not be expected to prepare injections or complete medication administration tasks; thus, we do not expect for the pharmacist errors noted for mixing the medication for administration to impact the safe use of this product in actual use. The user population that would be expected to complete these tasks (i.e., HCPs, patients, & caregivers) did not experience failures with these two tasks.	We do not have any recommendations to mitigate the risk for these errors and we find the residual risk acceptable.
Check consistency of mixture to determine if well mixed; shake more if it is not mixed	1 failure (untrained pharmacist)		
Remove needle cap	8 failures: -1 untrained HCP -3 untrained, injection experienced lay users -1 trained, injection naive lay user -2 untrained, Bydureon Pen experienced lay users -1 trained, injection experienced lay user	AstraZeneca indicated that the needle cap is designed to be turned counterclockwise to unlock the device when the user is ready and recapping the autoinjector could inadvertently activate the autoinjector and dispense the dose of medication outside of the injection site. Participants were able to complete an injection of the product despite the initial difficulties with removing the needle cap after consulting the IFU.	We determined that the instructions in the IFU regarding cap removal could be improved to address the use errors observed in the study. Please see our recommendations for the IFU in Section 4.1 (sub-bullets 2a and 2d).
Complete the injection of well-mixed product	13 failures: -4 untrained pharmacists -4 untrained HCPs -2 untrained, injection experienced lay users -2 untrained, injection naive lay users -1 trained, injection naive lay user	Participants failed to shake the product well enough to mix the medication; they referred to the IFU but did not follow the mixing technique outlined (i.e., did not shake vigorously enough or long enough) prior to injecting the pad. Failure to prepare a well-mixed product could result in a clinically relevant under dose of Bydureon. AstraZeneca acknowledged that the IFU and product labels did not adequately communicate the recommended mixing process; however, it does not appear that changes were made to the IFU to clarify this information.	We determined that the instructions regarding the recommended mixing technique (i.e., how to shake the medications) could be unclear to readers and we recommend modifications to the IFU to improve clarity of this information. Please see our recommendations for the IFU in Section 4.1 (sub-bullets 2b and 2c).

Inject the dose	5 failures: -1 untrained HCP -3 untrained, injection experienced lay users -1 untrained, Bydureon Pen experienced lay user	Two participants initially tried to complete the injection with the cap on but were able to self-correct after referring to the IFU. A third participant initially failed to orient the device correctly when she picked it up from the table but the participant immediately self-corrected before the moderator intervened; however that was counted as a failure for the task. The final two participants (both untrained patients) recapped the autoinjector during a prior task and inadvertently activated the device, resulting in the release of medication and deployment of the needle shield. This error would result in a delay in therapy, as users would need another autoinjector. Of note, these participants were able to complete the tasks for a second injection without assistance. Thus, we did not have any concerns about these errors.	We do not have any recommendations to mitigate the risk for these errors and we find the residual risk acceptable.
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Hold needle in skin for complete injection	5 failures: -1 untrained HCPs -1 untrained pharmacist -1 untrained, injection experienced lay user -1 trained, injection naive lay user -1 untrained, injection naive lay user	Participants failed to hold the autoinjector in the injection pad for the recommended 15 seconds and experienced a wet injection. They immediately realized the mistake after the stream of medication was observed and referred to the IFU. Thus, they were able to identify the error immediately and determine the actions that should be taken to perform the task correctly. In response to our April 11, 2017 information request, AstraZeneca indicated that the autoinjectors are designed to deliver the labeled dose between 4 and 9 seconds. The applicant recommends 15 seconds for this task to minimize the risk of an under dose associated with this varied timeframe for delivery. Errors with this task would result in a clinically relevant under dose of Bydureon. However, because the participants that removed the needle too soon were able to determine the reason for their wet injections, we determined that this error would likely result in a one-time under dose. Thus, we determined that the risk of this error would be minimal as the steps in the IFU are clear.	We do not have any recommendations to mitigate the risk for these errors and we find the residual risk acceptable.
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3. Labeling Comprehension Evaluation

Overall, the participants were able to locate the information and comprehend the labeling to respond to the comprehension questions. However, two participants had difficulty determining that the autoinjector should be stored horizontally after failing to refer to the IFU, carton labeling, or device label. A third participant responded to the storage question correctly after referring to the IFU; however, we noted that this participant indicated that she would store the device vertically to save space, particularly if it remained in the carton. In addition, two participants failed to determine that the autoinjector should be allowed to warm up before preparing the injection after having difficulty finding the information in the IFU.

AstraZeneca indicated that storing vertically could have a minor impact on the ease of mixing Bydureon; thus, the recommendation to store horizontally is to facilitate mixing for the user. AstraZeneca determined that the risk for errors associated with these aspects has been mitigated and that the labeling has been optimized. However, we determined that the instructions regarding the mixing technique could be improved to include warnings that more effort may be required to mix the product if the autoinjector is stored vertically. Please see our recommendation for the IFU in Section 4.1 (sub-bullet 2b).

In addition, while AstraZeneca indicated that the IFU did not adequately communicate that the medication should be allowed to warm to room temperature, the sponsor determined that the minor discomfort associated with this error would not adversely affect the safety or efficacy of the product. Thus, AstraZeneca determined that the risk associated with this error has been mitigated and that the labeling has been optimized. We agree with this assessment.

3.2 LABELS AND LABELING

In addition to the human factors study evaluation, DMEPA reviewed the proposed labels and labeling to determine whether there are any significant concerns in terms of safety related to preventable medication errors. We noted several areas that could be clarified within the proposed container labels, carton labeling, patient instructions for use (IFU), and the prescribing information (PI) labeling. We provide recommendations in section 4.1 for the Prescribing Information and Instructions for Use and in Section 4.2 for container label and carton labeling.

In summary, we expect patients, caregivers, and health care professionals will be able to use Bydureon Bcise (exenatide extended-release suspension) safely and effectively.

4 CONCLUSION & RECOMMENDATIONS

The HF validation study results showed failures on critical tasks. The root cause analysis and subjective feedback indicated that additional changes to the proposed labeling are necessary to

improve clarity of the product labeling. We do not believe that the changes require additional HF validation study.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information (PI)

1. Revise the title as follows: “Bydureon Bcise (exenatide extended-release), injectable suspension for subcutaneous use”.
2. Highlights of Prescribing Information-Dosage Forms and Strengths
 - a. We recommend revising the statement “BYDUREON BCISE single-dose autoinjector” to read “BYDUREON BCISE single-dose autoinjector containing 2 mg”.
3. Full Prescribing Information: Section 16 (b) (4) How Supplied
 - a. Replace the NDC placeholder with the NDC number.
 - b. Remove (b) (4) statements to read as follows:

“Bydureon Bcise (exenatide extended-release) injectable suspension is supplied:

 - as an autoinjector that contains a sterile suspension of 2 mg of exenatide extended-release microspheres...
 - in cartons that contain four single-dose autoinjectors (NDC xxxx-xxxx-xx)”
 - c. Revise the statement (b) (4) (b) (4) to include information identifying characteristics like color (e.g., white suspension).
4. Full Prescribing Information: Section 16 (b) (4) Storage and Handling
 - a. Remove the following statements as they do not belong in this section of the PI and this information is available in the IFU:

(b) (4)

B. Instructions For Use (IFU)

1. Revise the presentation of the product name to correspond with the name approved for use on the final labeling for consistency across all product labeling as follows: “Bydureon Bcise (exenatide extended-release), injectable suspension”.
2. Based on the results of the human factors study, we identified the following areas for improvement:

- a. Under “Before Use”, we recommend revising the current image to also include an image of the autoinjector after use.
- b. Under Step 2B: “Shake the autoinjector hard,” we recommend adding the following statement after the sentence “Shake for at least 15 seconds.”: “The autoinjector may need to be shaken longer if the autoinjector has not been stored flat.”.
- c. We recommend revising the image for Figure F to include the entire arm to indicate that use of the entire arm is recommended for proper shaking and mixing of the autoinjector contents.
- d. Under Step 3B: “While still holding the autoinjector straight up, firmly unscrew the orange cap.”, we recommend revising the bolded statement to read, “While still holding the autoinjector straight up, firmly unscrew the orange cap in a counterclockwise direction.”

C. Medication Guide

1. Revise the presentation of the product name to correspond with the name approved for use on the final labeling for consistency across all product labeling as follows: “Bydureon Bcise (exenatide extended-release), injectable suspension”.

4.2 RECOMMENDATIONS FOR ASTRAZENECA

We recommend the following be implemented prior to approval of this NDA:

A. Carton Labeling

1. Revise the presentation of the product name to correspond with the name approved for use on the final labeling for consistency across all product labeling as follows: “Bydureon Bcise (exenatide extended-release) injectable suspension”.
2. Add the usual dosage information on the side panel to include the recommended dose per 21 CFR 201.55, as follows: “Usual Dosage: Inject 2 mg once per week”.

B. Container Label

1. Revise the presentation of the product name to correspond with the name approved for use on the final labeling for consistency across all product labeling as follows: “Bydureon Bcise (exenatide extended-release) injectable suspension”.

C. Professional Sample Container Label and Carton Labeling

1. Revise the presentation of the product name to correspond with the name approved for use on the final labeling for consistency across all product labeling as follows: “Bydureon Bcise (exenatide extended-release), injectable suspension”.

2. Add the usual dosage information on the side panel to include the recommended dose per 21 CFR 201.55, as follows: “Usual Dosage: Inject 2 mg once per week”.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Bydureon Bcise that AstraZeneca provided in the December 21, 2016 submission and Bydureon.

Table 2. Relevant Product Information for Bydureon and Bydureon Bcise		
	Bydureon (NDA 022200)	Bydureon Bcise (NDA 209210)
Approval Date	January 27, 2012	n/a
Active Ingredient	Exenatide extended-release	
Indication	an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	
Route of Administration	Subcutaneous	
Dosage Form	For injectable suspension	Injectable suspension
Strengths	2 mg	
Dose & Frequency	2 mg injected subcutaneously every 7 days (once weekly)	
How Supplied	Single dose tray containing 2 mg vial Single dose 2 mg pen	Pre-filled single-dose autoinjector
Storage	• Store in the refrigerator at 36°F to 46°F (2°C to 8°C), up to the expiration date or until preparing for use. • Do not freeze. • Protect from light. • Bydureon can be kept at room temperature not to exceed 77°F (25°C) for no more than a total of 4 weeks.	• Store in the refrigerator at 36°F to 46°F (2°C to 8°C), up to the expiration date or until preparing for use. • Bydureon Bcise can be kept at room temperature not to exceed 86°F (30°C) for no more than a total of 4 weeks, if needed. • Store in original packaging and protect from light. • Bydureon Bcise must be stored flat.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On March 22, 2017, we searched the L:drive using the term exenatide to identify reviews previously performed by DMEPA. In addition, on March 22, 2017, we searched DARRTS (IND 107815 and NDA 209210) to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified zero previous reviews on the L:drive and three previous human factor protocol reviews in DARRTS (under IND 107815),^f and we confirmed that the comments included in two of the three reviews (RCM #: 2015-1578 and RCM #: 2015-1578-1) were implemented. The comments provided in our final review of the protocol (RCM # 2015-1578-3) were not sent to AstraZeneca in error; therefore, the comments from that review were not implemented when the study was conducted.

^f Vee S. Human Factors Protocol Review for exenatide extended-release suspension (IND 107815). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 Aug 14. RCM #: 2015-1578.

Vee S. Review of Human Factors Protocol Memo for exenatide extended-release suspension (IND 107815). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 Nov 11. RCM #: 2015-1578-1.

Garrison N. Review of Human Factors Protocol Memo for exenatide extended-release suspension (IND 107815). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 Mar 9. RCM #: 2015-1578-3.

APPENDIX C. HUMAN FACTORS STUDY

On December 21, 2016, AstraZeneca submitted their Human Factors Validation Study. The complete submission is available via the following link.

<\\cdsesub1\evsprod\nda209210\0000\m3\32-body-data\32r-reg-info\medical-device-autoinjector.pdf>

APPENDIX D. INFORMATION REQUESTS

On April 11, 2017, we issued an information request to AstraZeneca. Relevant findings from AstraZeneca's responses, submitted April 25, 2017, are identified below.

- AstraZeneca provided information comparing the IFU used in the HF validation study to the IFU that was provided with their December 21, 2016 submission to FDA.
- AstraZeneca provided additional data for the study participants who were omitted from the analysis by the sponsor because the errors were determined to be study artifacts.
- AstraZeneca provided additional information to clarify the effect that storing the autoinjector would have on the medication.
- AstraZeneca provided additional information to clarify if patients that waited less than 15 seconds before pulling the needle out during an injection would receive a full dose of medication. In addition, AstraZeneca concluded that a complete dose is delivered (b) (4) versus the 15 seconds specified in the IFU. The intention for instructing users to wait 15 seconds is to allow for the repetition of 15 throughout the IFU (i.e., 15 minutes out of the fridge and 15 second minimum shake time).

The complete response is available via the following link.

<\\cdsesub1\evsprod\nda209210\0011\m1\us\responses-quality-2017-04-hfquestions.pdf>

On May 25, 2017, we issued another information request to AstraZeneca to clarify the proposed commercial packaging for the autoinjector presentation. AstraZeneca's response, submitted via email on May 26, 2017, is noted below.

- *"The Bydureon Bcise presentations includes a sample 1-pack and sales 4-pack. To clarify the presentations within the NDA, we propose to submit updated sample 1-pack carton and device labels to add the additional text "PROFESSIONAL SAMPLE – NOT FOR SALE" (to allow for this new text, the current trademark statement will be deleted as it is not needed). No changes to the US prescribing information are planned as sample packs are generally not listed. The anticipated submission of the updated artwork would be mid-June."*

APPENDIX E. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^g along with postmarket medication error data, we reviewed the following Bydureon Bcise labels and labeling submitted by AstraZeneca on December 21, 2016 and June 16, 2017.

- Container label
- Carton labeling
- Instructions for Use
- Medication Guide

E.2 Label and Labeling Images

Container label

(b) (4)



^g Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/

ARIANE O CONRAD
09/08/2017

HINA S MEHTA
09/08/2017

MISHALE P MISTRY on behalf of QUYNHNHU T NGUYEN
09/08/2017