CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211363Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	July 26, 2022
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 211363
Product Name and Strength:	Epinephrine Injection, USP, 1 mg/10 mL (0.1 mg/mL)
Applicant/Sponsor Name:	International Medication Systems Limited (IMS)
OSE RCM #:	2018-495-3
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on June 17, 2022 and July 15, 2022 for Epinephrine Injection, USP. We reviewed the revised container label and carton labeling for Epinephrine Injection, USP (Appendix A) to determine if it is 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 Applicant implemented all of our recommendations and we have no additional recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Mehta, H. Label and Labeling Review for Epinephrine Injection (NDA 211363). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 May 27. RCM No.: 2018-495-2.

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/s/

HINA S MEHTA
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	May 27, 2022
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 211363
Product Name, Dosage Form, and Strength:	Epinephrine Injection, 1 mg/10 mL (0.1 mg/mL)
Product Type:	Combination Product (Drug + Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	International Medication Systems, Limited
FDA Received Date:	February 16, 2022, March 15, 2022, March 31, 2022, and April 8, 2022
OSE RCM #:	2018-495-2
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

As part of the approval process of the 505(b)(2) NDA class 2 resubmission for Epinephrine Injection, USP, we reviewed the proposed container label, carton labeling, and Prescribing Information (PI) for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND INFORMATION

International Medication Systems (IMS) has marketed Epinephrine Injection, USP as an unapproved product since 1976. IMS submitted Epinephrine Injection (NDA 211363) on February 14, 2018, as a 505(b)(2) application which relies upon the listed drug Epinephrine Injection, USP under NDA 205029 that is currently approved as 2 mg/2 mL (1 mg/mL) single-dose ampules. The proposed product will be available as a 1 mg/10 mL (0.1 mg/mL) single-dose prefilled syringe.

We previously reviewed the use related risk analysis, label and labeling.[ab] We agreed that a human factors validation was not needed at that time but provided label and labeling recommendations for the division and IMS. However, the application received a complete response (CR) on December 12, 2018 for product quality issues. Thus, IMS submitted a response to the CR letter on February 16, 2022.

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 Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

[a] Straka, M. URRA, Label and Labeling Review for Epinephrine Injection (NDA 211363). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 12. RCM No.: 2018-495.
[b] Straka, M. Label and Labeling Review Memo for Epinephrine Injection (NDA 211363). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 31. RCM No.: 2018-495-1.

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We note that Epinephrine Injection has the same active ingredient and dosage form (injection), as the reference listed drug. As stated above the proposed product will be available in a single-dose pre-filled syringe presentation whereas the listed drug is available in single-dose ampules. In addition, NDA 211363 is only being proposed for the hypotension associated with septic shock indication and intravenous route of administration.

We performed a risk assessment of the prescribing information (PI), container label, and carton labeling to identify deficiencies that may lead to medication errors and areas for improvement. We note the PI states the product should be diluted in (b) (4) mL of solution (b) (4) (b) (4) After discussion with the Division it was determined that the volume of the diluent can be 1,000 mL.

We identified areas of the proposed PI, container label, and carton labeling that could be revised to improve clarity and readability of important information. For the Division, we note the PI needs clarity with respect to use of USP nomenclature for dilution solutions and revisions to the dosage form to remove unnecessary information. For the Applicant we recommend removal of abbreviations, clarity on format of expiration date, and clarity on the strength statement. We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 below and advise they be implemented prior to approval of NDA 211363.

4 CONCLUSION & RECOMMENDATIONS

Our review concludes the proposed PI, container labels, and carton labeling may be improved to promote the safe use of the product. We provide specific recommendations for the Division in Section 4.1 and recommendations for International Medication Systems, Limited (IMS) in Section 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. Highlights of Prescribing Information
   a. Dosage and Administration
      i. In the third bullet, there are numeric values that are not immediately followed by their respective units and there is the ambiguous symbol '-' to represent the word 'to'. We recommend revising this bullet to read "Titrate 0.05 mcg/kg/min to 2 mcg/kg/min to achieve desired blood pressure.".

B. Full Prescribing Information
   a. Dosage and Administration
      i. We recommend describing the diluent solution using proper USP terminology. We recommend revising all instances of "5 percent dextrose solution" to "5% Dextrose Injection, USP".
      ii. We note the amount of dilution solution is (b) (4) mL. Other epinephrine products describe the dilution solution volume of 1,000 mL. (b) (4)

[redacted] we recommend revising the dilution solution volume to 1,000 mL if allowable.

b. Dosage Forms and Strengths
    i. As currently presented, the physical description of the solution is not included. We recommend including the physical description (i.e. clear, colorless) of the solution.

c. How Supplied/Storage and Handling
    i. As currently presented, the physical description of the solution is not included. We recommend including the physical description (i.e. clear, colorless) of the solution.

[redacted]

4.2 RECOMMENDATIONS FOR INTERNATIONAL MEDICATION SYSTEMS

A. Container Label
    a. As currently presented, the route of administration is presented as an abbreviation "I.V.". Presenting the route of administration with an abbreviation may cause confusion. We recommend revising to "For Intravenous Use".
    b. As currently presented, the format of the expiration date is defined as "MM-YY". FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a forward slash or a hyphen be used to separate the portions of the expiration date.

B. Carton Labeling
    a. As currently presented on the principal display panel, the strength is expressed as [redacted] We recommend revising the strength statement so both statements appear together as follows:

        1 mg/10 mL
        (0.1 mg/mL)

    b. To improve readability, place adequate space between the numerical dose and unit of measure (i.e. 1 mg/10 mL instead of 1mg/10mL) on all panels where the strength is described.
    c. The back panel presents [redacted] We recommend removing this from the back panel as it is repetitive [redacted]

d. As currently presented, the format of the expiration date is defined as “MM-YY”. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a forward slash or a hyphen be used to separate the portions of the expiration date.

e. As currently presented, the proposed carton labeling contains the statement [redacted] (b) (4) We recommend revising this statement to read “Recommended Dosage: See Prescribing Information”.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Epinephrine received on February 16, 2022 from International Medication Systems, Limited, and the listed drug (LD).

Table 2. Relevant Product Information for Epinephrine and the Listed Drug

Product Name	**Epinephrine**	**Epinephrine (Belcher)**[c]
Initial Approval Date	N/A	**NDA 205029:** July 29, 2014
Active Ingredient	epinephrine	epinephrine
Indication	Non-selective alpha- and beta-adrenergic agonist indicated to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.	Non-selective alpha- and beta-adrenergic agonist indicated to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock. Emergency treatment of allergic reactions, including anaphylaxis. For induction and maintenance of mydriasis during intraocular surgery.
Route of Administration	Intravenous	Intravenous, intramuscular, subcutaneous, intraocular
Dosage Form	Injection	Injection
Strength	1 mg/10 mL (0.1 mg/mL)	1 mg/mL (1:1000)
Dose and Frequency	Intravenous infusion rate of 0.05 mcg/kg/min to 2 mcg/kg/min, titrated to achieve desired mean arterial pressure. The dosage may be adjusted periodically, such as every 10 - 15 minutes, in increments of 0.05 mcg/kg/min to 0.2 mcg/kg/min, to achieve the desired blood pressure goal. After hemodynamic stabilization, wean incrementally over time, such as by decreasing doses of	Suggested infusion rate of intravenously administered epinephrine is 0.05 mcg/kg/min to 2 mcg/kg/min, and is titrated to achieve a desired mean arterial pressure (MAP). The dosage may be adjusted periodically, such as every 10 - 15 minutes, in increments of 0.05 mcg/kg/min to 0.2 mcg/kg/min, to achieve the desired blood pressure goal.

[c] Epinephrine [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2016 MAY 18. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/205029s004lbl.pdf.

	epinephrine every 30 minutes over a 12- to 24-hour period.	0.3 mg-0.5 mg intramuscular or subcutaneous in adults and children over 30 kg and 0.01 mg/kg in children under 30 mg 1 mg in 100 mL to 1,000 mL ophthalmic irrigation fluid
How Supplied	Epinephrine Injection, USP, 1 mg/10 mL (0.1 mg/mL) is a clear and colorless solution available in a 10 mL single-dose Prefilled Syringe.	Epinephrine Injection USP, 1 mg/mL (1:1000) sterile solution containing 1 mg/1 mL epinephrine in a 2 mL clear glass ampule. Supplied in a box of 10 single-use ampules
Storage	Protect from light until ready to use. Do not refrigerate. Protect from freezing. Store at 20° to 25°C (68° to 77°F) (b) (4) (b) (4) [see Temperature].	Protect from light until ready to use. Do not refrigerate. Protect from freezing. Store at room temperature, between 20° to 25°C (68° to 77°F).
Container Closure	Luer Jet Luer Lock Prefilled syringe.	Clear glass ampule.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 17, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, Epinephrine. Our search identified 2 previous reviews[d,e] , and we considered our previous recommendations to see if they are applicable for this current review.

[d] Straka, M. URRA, Label and Labeling Review for Epinephrine Injection (NDA 211363). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 12. RCM No.: 2018-495.
[e] Straka, M. Label and Labeling Review Memo for Epinephrine Injection (NDA 211363). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 31. RCM No.: 2018-495-1.

APPENDIX G. LABELS AND LABELING

G.1. List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effect Analysis, along with postmarket medication error data, we reviewed the following epinephrine labels and labeling submitted by International Medication Systems.

- Container label received on February 16, 2022
- Carton labeling received on February 16, 2022
- Prescribing Information (Image not shown) received on April 8, 2022
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G.2 Label and Labeling Images

Container Label

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

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

Memorandum

Date: May 24, 2022

To: Maryann Gordon, M.D., Medical Officer
Division of Cardiology and Nephrology (DCN)

Quynh M. Nguyen, Regulatory Project Manager (DCN)

From: Charuni Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for EPINEPHRINE INJECTION USP, 1 mg/10 mL (0.1 mg/mL), for intravenous use

NDA: 211363

In response to DCN's consult request dated April 5, 2022, OPDP has reviewed the proposed product labeling (PI) for EPINEPHRINE INJECTION USP, 1 mg/10 mL (0.1 mg/mL), for intravenous use. This supplement provides an application indicated for the treatment of adults with hypotension associated with septic shock.

PI: OPDP's comments on the proposed labeling are based on the draft version received by electronic mail from DCN on May 18, 2022, and are provided below.

Thank you for your consult. If you have any questions, please contact Charuni Shah at (240) 402-4997 or charuni.shah@fda.hhs.gov.

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/s/

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

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

Memorandum

Date: December 21, 2018

To: Quynh M. Nguyen, Pharm.D., RAC, Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCaRP)

Michael Monteleone, MS, Associate Director for Labeling, (DCaRP)

From: Puja Shah, Pharm.D., RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Pharm.D., RAC, CPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for Epinephrine Injection USP, 1 mg/10 mL (0.1 mg/mL) Luer-Jet™ Luer-Lock Prefilled Syringe

NDA: 211363

This memo is in response to DCaRP's labeling consult request dated April 20, 2018. Reference is made to a Complete Response letter that was issued on December 12, 2018. Therefore, OPDP defers comment on the proposed labeling at this time, and request that DCaRP submit a new consult request during the subsequent review cycle.

If you have any questions, please contact Puja Shah at (240) 402-5040 or puja.shah@fda.hhs.gov.

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/s/

PUJA J SHAH
12/21/2018

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 31, 2018
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 211363
Product Name and Strength:	Epinephrine Injection USP, 1 mg/10 mL (0.1 mg/mL) Luer-Jet Luer-Lock prefilled syringe
Applicant/Sponsor Name:	International Medication Systems LTD (IMS) wholly owned subsidiary of Amphastar Pharmaceuticals, Inc. (Amphastar)
FDA Received Date:	October 30, 2018
OSE RCM #:	2018-495-1
DMEPA Safety Evaluator:	Maximilian Straka, PharmD, FISMP
DMEPA Acting Team Leader:	Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM

Division of Cardiovascular and Renal Products (DCRP) requested that we review the revised syringe container label and the carton labeling for the Epinephrine Injection USP, Luer-Jet Luer-Lock prefilled syringe (Appendix A) to determine if it is 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

We note that in response to our recommendations regarding the addition of the lot number and expiration date, IMS indicated that the non-varnish areas on the container label and the carton labeling represent the area where the lot number and expiration date (in the format: EXP MM-YY) are stamped.

The revised syringe container label and the carton labeling for Epinephrine Injection USP, Luer-Jet Luer-Lock prefilled syringe are acceptable from a medication error perspective.

We have no further recommendations (b) (4)

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[a] Straka M. Label and Labeling Review for Epinephrine (NDA 211363). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Oct 12. RCM No.: 20181-495.

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/s/

MAXIMILIAN STRAKA
10/31/2018

SEVAN H KOLEJIAN
10/31/2018

LABEL AND LABELING AND HUMAN FACTORS 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:	October 12, 2018
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 211363
Product Name and Strength:	Epinephrine Injection USP, 1 mg/10 mL (0.1 mg/mL) Luer-Jet Luer-Lock prefilled syringe
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	International Medication Systems LTD (IMS) wholly owned subsidiary of Amphastar Pharmaceuticals, Inc. (Amphastar)
FDA Received Date:	February 14, 2018, May 8, 2018, May 15, 2018 and June 4, 2018
OSE RCM #:	2018-495
DMEPA Safety Evaluator:	Maximilian Straka, PharmD, FISMP
DMEPA Acting Team Leader:	Sevan Kolejian, PharmD, MBA
Senior Human Factors Specialist:	Shannon Hoste, MS
DMEPA Deputy Director:	Danielle Harris, PharmD, BCPS

1 REASON FOR REVIEW

As part of the New Drug Application (NDA) review, this review evaluates the proposed container label, carton labeling, and prescribing information (PI) for Epinephrine Injection, USP, 1 mg/10 mL (0.1 mg/mL) Luer-Jet Luer-Lock Prefilled Syringe for risk of medication error.

1.1 REGULATORY HISTORY

International Medication Systems (IMS) has marketed the Epinephrine Injection, USP pre-filled syringe, 1 mg/10 mL (0.1 mg/mL), as an unapproved product since 1976.

On February 14, 2018, IMS submitted a 505(b)(2) NDA for Epinephrine Injection USP, 1 mg/10 mL (0.1 mg/mL) Luer-Jet Luer-Lock Prefilled Syringe. The listed drug is the Epinephrine Injection, USP, 1 mg/1 mL, NDA 205029, packaged in ampules from Belcher Pharmaceuticals, LLC.

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: Use Related Risk Analysis (URRA)	C
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E- N/A
Other: Medication Error Report Complaints, Syringe Complaints	F
Labels and Labeling	G

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 noted that the Applicant is seeking approval for a product that has been marketed since 1976. To facilitate our review, we sent comments to the Applicant on April 23, 2018 in the NDA Filing Communication Letter[a] requesting an analysis of U.S. medication error reports and an analysis of U.S. complaints associated with Epinephrine Injection, USP, 1 mg/10 mL Luer-Jet Luer-Lock Prefilled Syringe. Also, we requested the description of any activities undertaken in the past 5 years to prevent medication errors or address complaints associated with Epinephrine Injection 1 mg/10 mL Luer-Jet Luer-Lock Prefilled Syringe. Additionally, we requested that the Applicant submit a comprehensive use related risk analysis (URRA), comparative analyses, and justification for not conducting a Human Factors (HF) validation study (See Appendix C and Appendix F).

On May 8, 2018 the Applicant provided an analysis[b] of the three U.S. medication error reports and four product complaints cases associated with Epinephrine Injection 1mg/10mL Luer-Jet Luer-Lock Prefilled Syringe in the last 5 years. We reviewed these reports to inform our label and labeling review. In the response, IMS also notes that since there were no recurring errors, or errors associated with a mitigatable cause, there have been no activities undertaken in the past 5 years to address medication errors or complaints.

On June 4, 2018 IMS provided [c] their URRA and justification of using the Luer-Jet prefilled syringe system and current labeling content. IMS determined that all residual risks identified in their use related risk analysis have been mitigated to an acceptable level and the benefits of the use of the product outweigh the residual risks. As such, IMS determined that the overall residual risk was acceptable, and a human factors validation study was not necessary. IMS further stated that Epinephrine Injection utilizes the well-established IMS's family of Luer-Jet prefilled syringe system which includes seven other approved and/or legacy marketed products. We acknowledge that Epinephrine Injection IMS Luer-Jet prefilled syringe has been marketed and used by health care providers for over 40 years; and, we are not aware of any post-market use-related issues based on our routine post-marketing surveillance that haven't already been addressed by IMS. Additionally, we anticipate that the intended user population (i.e., healthcare providers) is familiar with the use and manipulation of the IMS Luer-Jet prefilled syringe and other similar pre-filled syringe device designs.

Based on the aforementioned reasons, over 40 years of marketing history, the healthcare provider's familiarity with the products, and IMS's ongoing monitoring of all customer complaints through the Management Review Program, we find the proposed Epinephrine

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[a] See DARRTS, Filing Communication Letter to IMS dated 4/23/2018 available at \\cdsesub1\evsprod\nda211363\0002\m1\us\fda-letter.pdf

[b] See DARRTS, Narrative Response to NDA Filing Communication Letter dated 5/8/18 available at \\cdsesub1\evsprod\nda211363\0002\m1\us\narrative-response.pdf

[c] See DARRTS, Quality/Response to information request dated 6/4/2018 available at \\cdsesub1\evsprod\nda211363\0005\m3\32-body-data\32r-reg-info\user-related-risk-assessment.pdf

Injection IMS Luer-Jet prefilled syringe acceptable and agree that a human factors validation study is not needed at this time.

Label and Labeling

Based on our review of the Prescribing Information (PI), container label and carton labeling, we identified areas where the labels and labeling may be improved to promote the safe use of the product. We provide recommendations in Section 4.1 and 4.2 below.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed label and labeling for Epinephrine injection may be improved to promote the safe use of the product as described in Section 4.1 and Section 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information
    1. How Supplied/Storage and Handling Section
        a. We recommend the applicant change the strength presentation to "Epinephrine Injection USP, 1 mg/10 mL (0.1 mg/mL)" in accordance with USP General Chapter <7>.
        b. We note that the term "Single Use" is used on carton labeling. We defer to OPQ to determine the appropriate package type term. We recommend that the OPQ determined package type term is used throughout the label and labeling.

4.2 RECOMMENDATIONS FOR INTERNATIONAL MEDICATION SYSTEMS LTD.

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

A. Carton Labeling

1. Revise the carton labeling to include the lot number per 21 CFR 201.10(i).
2. For consistency with the statement in the Prescribing Information, change the statement on the carton labeling from: (b) (4) to "Do not use if the solution is colored or cloudy or contains particulate matter."
3. Add the expiration date on carton labeling in accordance per 21 CFR 201.17 and USP General Chapter <7>. Ensure that it is clearly differentiated from the lot number to prevent confusion.[d] We recommend that the expiration date on the drug package label include a year, month, and non-zero day to minimize confusion. We recommend that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month.

B. Container Labels

1. For consistency with the statement in the Prescribing Information, change the statement on the container label from: (b) (4) to "Do not use if the solution is colored or cloudy or contains particulate matter."
2. Remove the line that reads (b) (4) on the container label. Replace with the total strength presentation "1 mg/10 mL (0.1 mg/mL)" in accordance with USP General Chapter <7>. USP General Chapter <7> states that the total strength per total volume should be the primary and most prominent expression of strength followed in close proximity by the strength per mL enclosed in parenthesis.[e]
3. Revise the container label to include the lot number per 21 CFR 201.10(i).

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[d] Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert Acute Care. 2014;19(23):1-4.

[e] United States Pharmacopoeia (USP) General Chapter <7> Labeling

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for epinephrine injection, USP received on May 15, 2018 from IMS.

Table 2. Relevant Product Information for Epinephrine Injection, USP	
Initial Approval Date	N/A
Active Ingredient	epinephrine
Indication	To increase mean arterial blood pressure in adult patients with hypotension associated with septic shock.
Route of Administration	Intravenous
Dosage Form	Injection
Strength	1 mg/10 mL (0.1 mg/mL)
Dose and Frequency	Intravenous infusion rate of 0.05 mcg/kg/min to 2 mcg/kg/min, titrated to achieve desired mean arterial pressure.
How Supplied	Epinephrine Injection USP, 0.1 mg/mL [redacted] (b) (4) containing a Luer-Jet Luer-Lock Prefilled Syringe. Ten cartons per package.
Storage	Epinephrine is light sensitive. Protect from light until ready to use. Do not refrigerate. Protect from freezing. Store at room temperature, between 20° to 25°C (68° to 77°F). (See USP Controlled Room Temperature.) Protect from alkalis and oxidizing agents.
Container Closure	[redacted] (b) (4) Luer-Jet Luer-Lock Prefilled Syringe.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 6, 2018, we searched for previous DMEPA reviews relevant to this current review using the terms, “epinephrine”, NDA # “211363", “sodium bicarbonate injection” and “atropine abboject”. Our search identified three previous relevant reviews[f,g,h], and we considered our previous recommendations to see if they are applicable for this current review.

[f] White, L. Human Factors Consult for Sodium Bicarbonate Injection (ANDA 202494, ANDA 202495, ANDA 202679). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 Jul 13. RCM No.: 2015-1107

[g] Thomas, S. Label and Labeling Review for Atropine Injection (NDA 021146/S-018). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Aug 11. RCM No.: 2017-862

[h] Thomas, S. Label and Labeling Review for Epinephrine Injection (NDA 209359). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Sep 22. RCM No.: 2017-348

APPENDIX C. HUMAN FACTORS STUDY- Use Related Risk Analysis submitted on June 4, 2018

See EDR at \\cdsesub1\evsprod\nda211363\0005\m1\us\narrative-response.pdf

IMS's URRA Conclusion

In summary, with the current risk mitigation and controls in place, the risks related to the use of the Epinephrine Injection USP, 1 mg/10 mL (0.1 mg/mL) Luer-Jet Luer-Lock prefilled syringe all fall into the "Acceptable Risk" portions of the grid and ongoing monitoring of customer complaints are continually performed through the Management Review Program. Additional Human Factors studies to confirm acceptable user risks are not required since the users (caregivers and medical professionals) have used this product and the IMS Luer Jet family of products for years with a history of low customer complaints. The 10 mL Luer-Jet prefilled syringe system is appropriate and suitable for the administration of Epinephrine Injection. All risks in relation to the usage of Epinephrine Injection are identified and evaluated to be acceptable and sufficiently mitigated.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On September 6, 2018 and October 2, 2018, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters in the last five years that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care ISMP Medication Safety Alert Community/Ambulatory Care ISMP Medication Safety Alert Nurse Advise-ERR
Search Strategy and Terms	Match Exact Word or Phrase: — epinephrine (September 6, 2018) — luer-jet (October 2, 2018) — luer-lock (October 2, 2018)

D.2 Results

The search retrieved no relevant articles associated with label and labeling for epinephrine, luer-jet or luer-lock.

APPENDIX F. INFORMATION REQUEST and IMS RESPONSE

IR dated April 23, 2018 & IMS's response dated May 8, 2018

See EDR at: \\cdsesub1\evsprod\nda211363\0002\m1\us\narrative-response.pdf

Medication Error Report Complaints from 2013 to 2018

Attachment 1: Epinephrine Injection 1mg/10mL Luer-Jet™ Luer Lock Prefilled Syringe Medication Error Report Complaints (2013-2018)

Report Number	Report Date	Occurrence Date	Type of Error	Case Narrative	Intended Reason for Use	Route of Administration	Outcome
(b) (6)	4/7/2017						
Case A		(b) (6)	15-Day Reportable Adverse Drug Experience	For Case A, a 77-year-old male patient was brought into the hospital with 3rd degree burns to 70% of total body surface area after being pulled from a house fire. He was taken to the OR for debridement and escharotomy. During the procedure, the provider intended to administer a Calcium Chloride 1000mg/10ml injection, but instead gave an Epinephrine 1mg/10ml injection due to similar appearance of the prefilled syringes.	Provider intended to administer Calcium Chloride Injection but mistakenly administered an Epinephrine Injection.	Injection	The patient was transferred to ICU for further management. No additional details of the event's outcome were reported. Labeling of the IMS product is appropriate to allow correct identification of the medication. No further action taken.
Case B			15-Day Reportable Adverse Drug Experience	For Case B, a 34-year-old male patient was brought into the hospital post gun shot wound to abdomen and head. Glasgow Coma Scale 3 upon arrival to ED. The patient was intubated and sent to OR for Exploratory laparotomy. During the procedure, Calcium Chloride 1000mg/10ml injection and Epinephrine 1mg/10ml injection syringes were removed from their boxes, prepared, and placed side by side. A provider meant to give an entire syringe of Calcium Chloride Injection, but instead gave 0.7mg of Epinephrine Injection.	Provider intended to administer Calcium Chloride Injection but mistakenly administered an Epinephrine Injection.	Injection	The patient became hypersensitive, resulting in increased bleeding. He was hemodynamically unstable throughout the procedure requiring massive transfusion. The patient expired shortly after the procedure. Labeling of the IMS product is appropriate to allow correct identification of the medication. No further action taken.
Case C			15-Day Reportable Adverse Drug Experience	For Case C, the event occurred while a 39-year-old female patient was undergoing gravid hysterectomy. During the heavy blood loss part of the procedure, the patient became hypotensive and 100 mcg Epinephrine Injection (1 mL) from a Luer Jet (1 mg/10 ml) was administered. Many Luer Jets of Calcium Chloride Injection were given during the case. At one point, during resuscitation, a resident attempted to give Calcium Chloride Injection but picked up an Epinephrine Injection Luer Jet, 400 mcg of Epinephrine Injection was mistakenly given.	Provider intended to administer Calcium Chloride Injection but mistakenly administered an Epinephrine Injection.	Injection	The outcome of the patient's Adverse Event is unknown. No details were provided by reporter. Labeling of the IMS product is appropriate to allow correct identification of the medication. No further action taken.

Syringe Complaints from 2013 to 2018

Attachment 2: Epinephrine Injection 1mg/10mL Luer-Jet™ Luer Lock Prefilled Syringe Complaints (2013-2018)

Complaint Number	Complaint Date	Type of Complaint	Narrative Description	Outcome
CM13-0010	3/27/2013	Technical: Other	A pump alarmed for an upstream occlusion during an Epinephrine infusion (programmed amount and delivery rate unknown). The nurse reported that the keypad was frozen and that the infusion could not be restarted. In response, the medication was delivered manually in order to maintain the patient's blood pressure.	The lot number, stock number and name of the Epinephrine product are unknown. Per reporter, the issue was not with the Epinephrine, or any other drug product, but with the pump itself. No drug product lot number is involved and facility does not have any Adverse Event reported from this event. This is an isolated case and no further action was required.
CM13-0021	6/18/2013	Technical: Glass Breakage	A nurse opened the carton box and found a product unit in which the syringe was in proper condition, but the medication vial only contained 1mL of medication, rather than 10 mL. There was no report of any cracks or leakage on the vial, and no damage on the carton. The unit was not used on any patient and no injuries were reported. This is the first time of occurrence.	The returned unit included an empty medication vial with a crack visible at its base. Staining was observed inside the unit carton, indicating leakage had occurred when the vial was still within the carton. Review of the batch record for the complaint lot did not reveal any anomalies during manufacture, testing, and release of the product. Retain inspection of reserve units and other lots manufactured with the same glass lot did not highlight any discrepancies; no breakage was noted on any of the vials. The medication vial may have received rough handling after being removed from its protective case. No further action was required in response to the complaint.
CM14-0051	7/29/2014	Technical: Malfunction	During a code, a nurse obtained a product unit but reported that the medication vial slid off the back of the plastic injector, and a second unit had to be used. Per reporter, the unit was assembled properly but there is no knowledge of whether or not the medication was administered. It was noted that the nurse experienced the issue at least once before but the lot number involved is unknown. No injuries were reported for this event.	The customer returned unit was functionally tested and the stopper syringed smoothly to the bottom of the empty medication vial. Subsequently, the vial was disengaged from the injector. The threads on the inside of the injector where the rubber stopper connects and the threads on top of the stopper were examined; no anomalies were observed. The results for the dimensional testing of the vial met all specifications. The retain inspection and functional testing of reserve units for the subject lot and the inspection of other lots manufactured with the same glass vial lot met specifications. The in-process dimensional measurements of the stopper lots used to manufacture the product lot were within specification. The reported event could not be duplicated. No further action was required in response to the complaint.
CM15-0024	6/5/2015	Technical: Malfunction/User	A paramedic in training attempted to inject the unit when the medication came out the back. A different paramedic used another syringe and it worked properly.	Per customer, an error was made on their part while assembling the unit. The paramedic did not make enough turns during the assembly to engage the threads into the injector. The unit was erroneously forwarded to another manufacturer and not made available for return. The batch record for the product lot was reviewed and no discrepancies were found for the manufacturing, testing and release records at the time of release. Inspection of retain samples for the subject lot revealed no anomalies; functionality testing of sample units determined that the units met specifications. No further action was required in response to the complaint.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[i] along with postmarket medication error data, we reviewed the following epinephrine labels and labeling submitted by International Medication Systems LTD.

- Container label received on February 14, 2018
- Carton labeling received on February 14, 2018
- Prescribing Information (Image not shown) received on May 15, 2018

G.2 Label and Labeling Images

Figure 1: Epinephrine Luer-Jet Luer-Lock Prefilled Syringe Label

(b) (4)

[i] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MAXIMILIAN STRAKA
10/12/2018

SEVAN H KOLEJIAN
10/12/2018

DANIELLE M HARRIS on behalf of SHANNON M HOSTE
10/12/2018

DANIELLE M HARRIS
10/12/2018