CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212905Orig1s000

OTHER REVIEW(S)

MEMORANDUM

RESPONSE TO HUMAN FACTORS ADVICE MEMO

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

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:	May 17, 2023
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 212905
Product Name and Strength:	Ycanth[a] (cantharidin) topical solution, 0.7%
Applicant/Sponsor Name:	Verrica Pharmaceuticals, Inc.
TTT ID #	2023-3474
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Deputy Director:	Jason Flint, MBA, PMP

1 PURPOSE OF MEMORANDUM

On August 25, 2021, the Applicant submitted proposed in-service training kit labels and labeling for Ycanth (see Appendix A). The labels and labeling are in response to human factors validation study protocol recommendations in which we asked the Applicant to submit the proposed in-service training kit labels and labeling to ensure that the training kits are clearly labeled and well differentiated from the proposed product labels and labeling.[b]

2 DISCUSSION AND CONCLUSION

The Applicant submitted the proposed in-service training kit labels and labeling and we confirmed that they are clearly labeled and well differentiated from the proposed product labels and labeling. We have no additional recommendations at this time.

[a] The proprietary name for this NDA, Ycanth, was found conditionally acceptable on February 7, 2022. Ycanth is used throughout this review.

[b] Oguntimein M. Human Factors Study Protocol Review for cantharidin (IND 131163). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 23. RCM No.: 2020-1795.

APPENDIX A. IN-SERVICE TRAING KIT LABELS AND LABELING RECEIVED ON AUGUST 25, 2021

- In-Service Training Kit (images not shown) available from: \\CDSESUB1\EVSPROD\nda212905\0058\m1\us\111-information-amendment\quality-information-amendment-25-august-2021.pdf

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/s/

OLUWAMUREWA OGUNTIMEIN
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JASON A FLINT
05/17/2023 04:59:55 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 8, 2023
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 212905
Product Name, Dosage Form, and Strength:	Ycanth (cantharidin) topical solution, 0.7 %
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Verrica Pharmaceuticals Inc. (Verrica)
FDA Received Date:	December 23, 2020, and January 23, 2023, and April 27, 2023
TTT ID #:	2023-3475
DMEPA 1 Safety Evaluator:	Corwin D. Howard, PharmD
Acting DMEPA 1 Team Leader:	Madhuri R. Patel, PharmD

1 REASON FOR REVIEW

Verrica Pharmaceuticals Inc. submitted a Class 2 Resubmission for Ycanth (cantharidin) topical solution (NDA 212905).
As part of the approval process for Ycanth (cantharidin) topical solution, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Ycanth Prescribing Information (PI), Patient Package Insert (PPI), container labels and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

The application received a complete response (CR) on July 13, 2020 that included deficiencies in their HF validation study[a]. Verrica responded to the CR on December 23, 2020. However, NDA 212905 received another CR on September 16, 2021 for facility deficiencies. Verrica responded to the CR on November 24, 2021. We had previously reviewed the labels and labeling on March 4, 2022 and found them acceptable[b].

However, NDA 212905 received a CR on May 23, 2022 for facility deficiencies.

Verrica responded to the CR on January 23, 2023. We note Verrica did not resubmit labels and labeling with CR response, however they referenced the labels and labeling submitted on December 23, 2020, and November 24, 2021. Verrica submitted revised container labels and carton labeling on April 27, 2023.

2 MATERIALS 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
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

[a] Schlick, J. Label and Labeling and Human Factors Results Review for Ycanth (NDA 212905). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 27. OSE RCM No.: 2019-1920 and 2019-1922.

[b] Bhalodia, A. Memorandum Review of Revised Label and Labeling for Ycanth (NDA 212905). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 MAR 4. OSE RCM No.: 2019-1920-1.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)

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

3 CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed Ycanth Prescribing Information (PI), patient packet insert (PPI), container labels and carton labeling did not identify areas of vulnerability that may lead to medication errors. We note the Applicant did not submit prescribing information, container labels and carton labeling with this resubmission and referred to the labels and labeling submitted on December 23, 2020, and November 24, 2021. Verrica submitted revised container labels and carton labeling on April 27, 2023 to include the lot and expiration date format. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ycanth that Verrica Pharmaceuticals Inc. submitted on April 27, 2023.

Table 2. Relevant Product Information for Ycanth	
Initial Approval Date	N/A
Active Ingredient	cantharidin
Indication	Treatment of molluscum contagiosum.
Route of Administration	Topical
Dosage Form	Topical solution
Strength	0.7%
Dose and Frequency	To be administered by a healthcare professional. Should be applied directly to the affected molluscum skin lesion. Apply one time to each molluscum contagiousm lesion at each office visit. Cantharidin may be administered approximately 3 weeks apart as needed.
How Supplied	Cantharidin solution is supplied in a sealed glass ampule contained within a single-use applicator and enclosed in a protective paperboard sleeve. Each ampule contains approximately 0.45 mL of 0.7% (b) (4) cantharidin solution. A Break Tool is co-packaged as (b) (4) per each carton of applicators.
Storage	Store at controlled room temperature of 20°C to 25°C (68°F to 77°F) (b) (4).

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 13, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, "cantharidin". Our search identified four previous reviews[c,d,e,f], and we considered our previous recommendations to see if they are applicable for this current review.

[c] Bhalodia, A. Memorandum Review of Revised Label and Labeling for Ycanth (NDA 212905). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 MAR 4. OSE RCM No.: 2019-1920-1.

[d] Bhalodia, A. Human Factors Study Report and Labels and Labeling Review for Ycanth (NDA 212905). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 SEP 15. OSE RCM No.: 2019-1919; 2019-1920; 2020-2756.

[e] Bhalodia, A. Human Factors Results Review MEMO for Cantharidin (NDA 212905). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAY 05. OSE RCM 2020-2756 2019-1919 2019-1920.

[f] Schlick, J. Label and Labeling and Human Factors Results Review for Ycanth (NDA 212905). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 27. OSE RCM No.: 2019-1920 and 2019-1922.

APPENDIX F. LABELS AND LABELING

F.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 Ycanth labels and labeling submitted by Verrica Pharmaceuticals Inc..

- Container label(s) and Carton labeling received on April 27, 2023
- Prescribing Information and Patient Packet Insert (Image not shown) received on December 23, 2020, available from \\CDSESUB1\EVSPROD\nda212905\0044\m1\us\114-labeling\draft\labeling\11413-draft-labeling-text-tracked-changes-word.docx

F.2 Label and Labeling Images

Container label(s)

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

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/s/

CORWIN D HOWARD
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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: April 11, 2022

To: Mary Kim M.D
Clinical Reviewer
Division of Dermatology and Dentistry (DDD)

Matthew White
Senior Regulatory Project Manager
Division of Dermatology and Dentistry

From: Nazia Fatima, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for VP-102 (cantharidin) topical solution

NDA: 212905

In response to DDD consult request dated March 25, 2022, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI) and carton and container labeling for original NDA submission for VP-102 (cantharidin) topical solution (VP-102).

OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DDD on March 21, 2022 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI and were sent under separate cover on April 7, 2022.

OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DDD on March 21, 2022, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Nazia Fatima at 240-402-5041 or Nazia.Fatima@fda.hhs.gov.

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/s/

NAZIA FATIMA
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HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 30, 2022
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 212905
Product Type:	Combination Product
Drug Constituent Name and Strength	Ycanth[1] (cantharidin) topical solution, 0.7%
Device Constituent:	Pre-filled topical applicator
Rx or OTC:	Rx
Applicant/Sponsor Name:	Verrica Pharmaceuticals, Inc.
Submission Date:	December 14, 2021, January 07, 2022, January 28, 2022, March 8, 2022
OSE RCM #:	2019-1919-1
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director for Human Factors:	Jason Flint, MBA, PMP

[1] The proprietary name for this NDA, Ycanth, was found conditionally acceptable on February 7, 2022. Ycanth is used throughout this review.

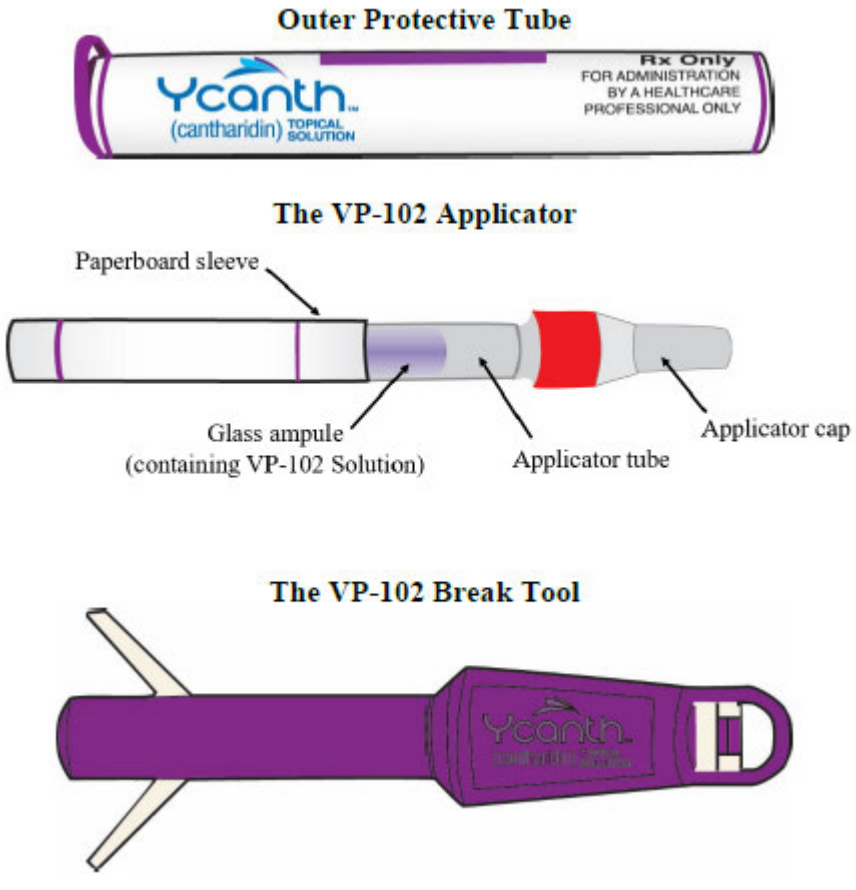
1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report submitted under NDA 212905 for Ycanth (cantharidin).

1.1 PRODUCT DESCRIPTION

This is a combination product with a proposed pre-filled topical applicator device constituent part that is intended for the treatment of molluscum contagiosum. Ycanth Solution is supplied in a sealed glass ampule contained within a single-use applicator and enclosed in a protective paperboard sleeve. The Ycanth Break Tool (break tool) is an accessory to the Ycanth applicator. The break tool was designed to assist with breaking of the ampule. Ycanth applicators will be commercialized in cartons of either 6 or 12 applicators co-packaged with (b) (4) (b) (4) break tools, respectively. Each carton will contain applicators packaged in an Outer Protective Tube, (b) (4) Ycanth break tools packaged in a bubble bag, a bundle of package inserts containing the device use instructions, (b) (4) See Figure 1 below and Appendix A for additional details.

Figure 1: Outer protective tube, applicator, and break tool



1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

- On September 19, 2019, Verrica Pharmaceuticals, Inc. (Applicant) submitted their New Drug Application (NDA) that included a human factors validation study report. The Applicant conducted their HF validation study without seeking Agency feedback on the study methodology prior to conducting the study.[2]
- On February 26, 2020, we provided our preliminary comments to the Applicant in a mid-cycle discipline review letter that additional mitigation strategies may be needed to optimize applicator use along with other revisions to the product user interface taking into consideration our identified concerns.[3] On March 4, 2020, the Applicant responded to our concerns.[4]
- On March 23, 2020, the Agency responded to the Applicant's March 4, 2020, submission indicating that that we still had concerns with the break force of the ampule and paperboard sleeve that could lead to accidental exposure to the users mouth or eye, and we provided additional comments outlining our continued concern.[5]
- On April 3, 2020, the Applicant provided a response including their justification for the break force of the ampule and paperboard sleeve.[6] The Applicant subsequently submitted an updated HF validation study protocol along with a comparative analyses and heuristic analysis on April 10, 2020. The Agency acknowledged the submission of the threshold and heuristic analysis was unsolicited. Furthermore, the Agency was still reviewing the information provided in previous submissions; therefore, we sent a withdrawal letter on April 24, 2020.[7]

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[2]Neall P. NDA 212905 Ycanth (Cantharidin) Human Factors Validation Study Report. \\CDSESUB1\evsprod\nda212905\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\molluscum-contagiosum\5354-other-stud-rep\verrica-vp102-0008\verrica-vp102-0008-report-body.pdf

[3] Song, Q. Mid-Cycle Discipline Review Letter. Submitted to DARRTS on February 26, 2020. https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af80543ddc&_afrRedirect=627132957944040984

[4] Response to February 26, 2020 Mid-Cycle Discipline Review Letter. \\cdsesub1\evsprod\nda212905\0017\m1\us\111-information-amendment\quality-information-amendment-04-march-2020.pdf

[5] Song, Q. Discipline Review Letter. Submitted to DARRTS on March 23, 2020. https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8054e00d&_afrRedirect=627152132744248234

[6] Response to March 23, 2020, Discipline Review Letter. \\cdsesub1\evsprod\nda212905\0021\m1\us\111-information-amendment\quality-information-amendment-03-april-2020.pdf

[7] Killen, M. Human Factors Validation Study Protocol Withdrawal. Submitted to DARRTS on April 24, 2020. https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8055b828&_afrRedirect=7747798822403184 Chan, Irene Z. Human Factors (HF) Validation Study Protocol Incomplete Letter for IND 131163. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019-JAN 02. RCM No.: 2018-2769.

- On July 13, 2020, the Agency sent the Applicant a Complete Response (CR) letter that included deficiencies in their HF validation study with noted use errors and difficulties with the critical task- 'Break the Ampule' and their heuristic analysis submitted on April 10, 2020 that indicated the average palmar pinch force (grip used to break an ampule) for adult females is 16 lbs. and that the average force to break the ampule with paperboard sleeve on is 19 lbs. From this information, the Applicant also concluded that the force to break the ampule could increase the potential for use errors. Based on these deficiencies, we indicated that we remained concerned that the Applicant's proposed combination product is not safe for use by HCPs. We also stated our concern that the risk of accidental exposure will outweigh the benefit of the treatment with this combination product. Inherent design issues exist with this product that may contribute to serious harm if accidental exposure occurs during use. Thus, we indicated that additional mitigation strategies were needed and could include the need for device design changes to optimize applicator use along with other revisions to the product user interface taking into consideration our previously identified concerns and the data collected from their HF validation study. After they implement additional risk mitigation strategies/modifications, we recommended they conduct an additional HF validation study to ensure that these modifications address the observed use errors and use difficulties and do not introduce any new risks. We recommended the Applicant submit their revised HF validation study protocol for feedback from the Agency before commencing the study. Based on our comments, the Applicant created a break tool to be used to crush the ampule, revised the instructions for use (IFU) to include information about the break tool, included information about when to remove the cap, what to look for when inspecting the ampule, and revised their URRA accordingly.
- On August 28, 2020, the Applicant submitted their revised HF validation study protocol, URRA and IFU under their IND 131163 for feedback from the Agency. We evaluated the proposed protocol and provided recommendations to the Applicant. We recommended that the Applicant implement all recommendations before commencing the HF validation study.[8]
- On December 23, 2020, the Applicant submitted a HF validation study results report as part of the class 2 resubmission of NDA 212905, which is the subject of this review.
- On February 16, 2021, we sent an Information Request to the Applicant which requested justification for including all trained participants. The HF validation study protocol submitted on August 28, 2020 under IND 131163 stated, "Formal training will not be provided to users" in Section 2.4 Training.[9]

[8] Oguntimein, M. Human Factors Protocol Review for cantharidin (IND 131163). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 23. RCM No.: 2020-1795.

[9] Bui Nguyen, T. Information Request for NDA 212905. Silver Spring (MD): FDA, CDER, OSE (US); 2021 FEB 16. Available from:

- On February 19, 2021, the Applicant provided a response including their justification for including all trained participants. The Applicant stated that they intend to deploy the training program that was implemented in the HF validation study to train real-world users prior to product use. However, it is unclear how the Applicant will ensure that every user will consistently and routinely receive training and whether such a training program will continue to exist throughout the product's lifecycle on the market. We are concerned with understanding how users who do not receive training may perform when relying on the proposed user interface of the proposed product. Therefore, we found that the data obtained from their HF validation study with trained participants is not representative of real-world use. As such, we recommended that the Applicant conduct a supplemental HF validation study with 15 untrained healthcare professionals (HCPs) as a distinct user group.[10]
- On May 4, 2021, the Agency sent the Applicant a discipline review (DR) letter that included deficiencies in their HF validation study methodology- the use of all trained participants, and considerations as the Applicant conducts their supplemental study with 15 untrained HCPs.[11] We also asked the Division of Division of Dermatology and Dentistry (DDD) if they have other considerations (such as public health need) that we should take into consideration. There is no public heath need from DDD's perspective.
- On May 11, 2021, a teleconference meeting was held between the Agency and the Applicant to discuss the contents of the DR letter sent on May 4, 2021. During the teleconference meeting, FDA requested the Applicant to submit detailed training materials, information concerning (b) (4) and a detailed plan for a new HF study.[12]

https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805d27f1&_afrRedirect=493649575601784.

[10] Verrica Pharmaceuticals, Inc. Response to Information Request for cantharidin (NDA 212905). West Chester (PA): 2021, FEB 19.

[11] Van Horn III, H. Discipline Review Letter for cantharidin (NDA 212905). Silver Spring (MD): FDA, CDER, OND, DDD (US); 2021 MAY 4. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805ed530&_afrRedirect=492147532898471.

[12] Van Horn III, H. Information Request for cantharidin (NDA 212905). Silver Spring (MD): FDA, CDER, OND, DDD (US); 2021 MAY 14. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805f0870&_afrRedirect=218632711726479.

- On May 14, 2021 and May 18, 2021, the Applicant provided a response to the DR letter and the information requested during the teleconference meeting on May 11, 2021.[13,14]
- On June 21, 2021, the Applicant submitted a supplemental HF validation study results for untrained HCPs. We reviewed the results and provided several label and labeling recommendations to mitigate the use error observed in the HF validation study.[15]
- On September 16, 2021, the Agency sent the Applicant a Complete Response (CR) letter that included deficiencies regarding facilities inspections and safety updates. We informed the Applicant that Labeling, Human Factor comments and recommendations will be conveyed in a separate correspondence.[16]
- On September 22,2021, the Agency sent a general advice letter that noted the HF validation study identified use errors with critical tasks, that indicated the proposed user interface should be improved to further mitigate the residual risk in order to ensure safe and effective use of the product. We provided several label and labeling recommendations and informed the Applicant to demonstrate that the implemented improvements in the user interface address the Agency's identified concerns.[17] The Applicant implemented all our label and labeling recommendations.
- On November 24, 2021, the Applicant resubmitted their new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for cantharidin topical solution.[18]
- On December 14, 2021, the Applicant submitted a response to the Agency's general advice letter dated September 22, 2021.[19] The submission included the implemented label and labeling changes and a supplemental HF validation study, which is the subject of this review.

2 MATERIALS REVIEWED

[13] Verrica Pharmaceuticals, Inc. Response to Information Request for cantharidin (NDA 212905). West Chester (PA): 2021, MAY 14.

[14] Verrica Pharmaceuticals, Inc. Response to Information Request for cantharidin (NDA 212905). West Chester (PA): 2021, MAY 18.

[15] Bhalodia, A. Human Factors Results and Label and Labeling Review for Ycanth (cantharidin) (NDA 212905). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 SEP 15. RCM No.: 2019-1919, 2019-1920.

[16] Song,Q. Complete Response Letter for Ycanth (cantharidin) (NDA 212905). Silver Spring (MD): FDA, CDER, OND, DDD (US); 2021 SEP 16.

[17] Song,Q. General Advice Letter for Ycanth (cantharidin) (NDA 212905). Silver Spring (MD): FDA, CDER, OND, DDD (US); 2021 SEP 22.

[18] Verrica Pharmaceuticals, Inc. Resubmission for cantharidin (NDA 212905). West Chester (PA): 2021, NOV 24.

[19] Verrica Pharmaceuticals, Inc. Response to General Advice Letter for cantharidin (NDA 212905). West Chester (PA): 2021, DEC 14.

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, the use error observed, and our analysis to determine if the results indicate that the user interface is designed to support the safe and effective use of the proposed product.

3.1 SUMMARY OF STUDY DESIGN

Table 2 presents a summary of the HF validation study design. See Appendix C and D for more details on the study design.

<table>
<tr><th colspan="2">Table 2. Study Methodology for Human Factors (HF) Validation Studies</th></tr>
<tr><td>Study Design Elements</td><td>Details</td></tr>
<tr><td></td><td>Supplemental HF Validation Study</td></tr>
<tr><td>Participants</td><td>
<table>
<tr><th>Attribute</th><th>Category</th><th>Count (n=16)</th></tr>
<tr><td rowspan="4">Role</td><td>Physician</td><td>6</td></tr>
<tr><td>Physician Assistant</td><td>5</td></tr>
<tr><td>Registered Nurse</td><td>1</td></tr>
<tr><td>Nurse Practitioner</td><td>4</td></tr>
<tr><td rowspan="3">Specialty</td><td>Dermatology</td><td>7</td></tr>
<tr><td>Pediatrics</td><td>5</td></tr>
<tr><td>Family Medicine</td><td>4</td></tr>
<tr><td rowspan="3">Years' Experience</td><td>2-10 years</td><td>6</td></tr>
<tr><td>11-20 years</td><td>4</td></tr>
<tr><td>20+ years</td><td>6</td></tr>
</table>
</td></tr>
<tr><td>Training</td><td>No training was provided to the Healthcare Professionals (HCPs)</td></tr>
</table>

Study Environment	The study was conducted in a simulated patient exam room. Lighting Level: Overhead fluorescent lights illuminated the test room, which simulated the lighting level in a clinical setting. Sound Level: The test room was relatively quiet, comparable to a doctor's office. However, there was occasional acoustic distractions, such as telephones ringing, doors opening and closing, as well as other individuals passing by to simulate a true clinical setting. To minimize variability in the test environment, a recorded soundtrack of these occasional acoustic distractions was played during all test sessions.
Sequence of Study	• Simulated Use Scenario • Knowledge Task Questions • RCA

3.2 RESULTS AND ANALYSES

Table 3 describes the study results, Applicant's analyses of the results, and DMEPA's analysis.

Table 3. Identified Issues and DMEPA's Findings		
	Identified Issue, Subjective Feedback, Root Cause Analysis and Mitigations	DMEPA's Analysis and Findings
1.	For the task to inspect the applicator, there was 1 use error during the simulated use scenario. The participant did not remove the paperboard sleeve prior to placing the applicator in the break tool and therefore could not inspect the applicator. The subjective data and the Applicant's root cause analysis (RCA) indicated: This participant did not remove the paperboard sleeve prior to placing the applicator in the break tool, and, therefore, could not inspect the applicator. Once the study moderator directed the participant to "Step 3: Remove the Paperboard Sleeve," the participant removed the paperboard sleeve and was able to recognize damaged applicators and correctly answered that they would not use the damaged applicators. This participant was wearing personal protective equipment (PPE), so their hands and eyes would be protected in the event of any leaks due to a damaged applicator. Based on Applicant's URRA, if this task is omitted or not performed correctly there is risk of delayed treatment, or user or patient exposed to solution in location other than intended resulting in unintended blistering.	Our review of the study results indicated that the root cause analysis was incomplete because the Applicant did not identify why the participant did not remove the paperboard sleeve prior to placing the applicator in the break tool. We note that when the study moderator directed the participant to "Step 3: Remove the Paperboard Sleeve," the participant removed the paperboard sleeve, was able to recognize damaged applicators and correctly answered that they would not use the damaged applicators. Our review of the labels and labeling indicate that the IFU contains text and images to support this task and the paperboard sleeve on the ampule includes instruction to remove the paperboard sleeve and inspect the ampule.  (b) (4) We have not identified additional changes to the user interface to further reduce the risks associated with this use error. We find that the residual risk in this case is acceptable.

	The Applicant did not propose any mitigation strategies in response to the use error observed in this task.	

3.3 ANALYSIS OF OTHER TASK ERRORS

We note that the HF validation study showed no use errors, (e.g., failures, difficulties, or close calls) with non-critical tasks.

4 CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study demonstrate that representative users can use the product, as designed, safely and effectively. Our evaluation of the proposed packaging, label and labeling did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time.

4.1 RECOMMENDATIONS FOR VERRICA PHARMACEUTICALS, INC.

We found the proposed packaging, labels and labeling, and the results of your human factors (HF) validation study acceptable.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for cantharidin that Verrica Pharmaceuticals, Inc. submitted on December 14, 2021.

Table 5. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	a lipophilic compound from a naturally derived source
Active Ingredient (Drug or Biologic)	cantharidin
Indication	Treatment of molluscum contagiosum
Route of Administration	Topical
Dosage Form	Topical solution
Strength	0.7%
Dose and Frequency	This product is to be administered by a healthcare professional and is applied directly to the affected molluscum skin lesion. Cantharidin is applied one time to each molluscum contagiousm lesion at each office visit and may be administered approximately 3 weeks apart as needed.
How Supplied	Cantharidin solution is supplied in a sealed and crushable glass ampule contained within a single-use applicator and enclosed in a protective paperboard sleeve. Each ampule of cantharidin contains approximately 0.45 mL of 0.7% (b) (4) cantharidin solution. The applicators and two break tools are packaged in cartons containing 6 or 12 applicators per carton.
Storage	Room temperature of 20°C to 25°C (68°F to 77°F)
Container Closure/Device Constituent	Pre-filled topical applicator
Intended Users	Healthcare professionals (HCPs)
Intended Use Environment	Professional healthcare environment

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On February 21, 2022, we searched the L: drive and AIMS using the terms, cantharidin, Ycanth 212905 to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified four previous reviews[20,21,22,23], and one interaction[24] and we confirmed that our previous recommendations were implemented.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

Human Factors Engineering Report can be accessible in EDR via:
\\CDSESUB1\evsprod\nda212905\0056\m5\53-clin-stud-rep\535-rep-effic-safety-stud\molluscum-contagiosum\5354-other-stud-rep\verrica-vp-102-0020\verrica-vp-102-0020-report-body.pdf

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results reports can be accessible in EDR via:
Supplemental Human Factors Validation Report

\\CDSESUB1\evsprod\nda212905\0061\m5\53-clin-stud-rep\535-rep-effic-safety-stud\molluscum-contagiosum\5354-other-stud-rep\verrica-ycanth\verrica-ycanth-protocol.pdf

[20] Schlick, J. Human Factors Results and Labeling Review for cantharidin (NDA 212905). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020-MAY 27. RCM:2019-1920 and 2019-1922.

[21] Oguntimein, M. Human Factors Protocol Review for cantharidin (IND 131163). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 23. RCM No.: 2020-1795.

[22] Bhalodia, A. Human Factors Results Review Memorandum for cantharidin (NDA 212905). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAY 5. RCM No.: 2020-2756; 2019-1919; and 2019-1920.

[23] Bhalodia, A. Human Factors Results and Label and Labeling Review for Ycanth (cantharidin) (NDA 212905). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 SEP 15. RCM No.: 2019-1919, 2019-1920.

[24] Song, Q. Type A Post Complete Response Action Meeting Minutes for cantharidin topical solution. Silver Spring (MD): FDA, CDER, OND, DDD (US); 2020 NOV 6. NDA 212905.

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

- On January 05, 2022, we issued an Information Request (IR) stating the following:
  "We note you state that one participant did not remove the paperboard sleeve prior to placing the applicator in the break tool and therefore could not inspect the applicator in the December 2021 supplemental human factors validation study. It is unclear why the participant did not remove the paperboard sleeve. Please provide the root cause analysis based on the subjective feedback you gathered during the interview session as to why that participant did not remove the paperboard sleeve prior to placing the applicator in the break tool."

The Applicant provided a response on January 08, 2022 and can be accessible in EDR via:\\CDSESUB1\evsprod\nda212905\0062\m5\53-clin-stud-rep\535-rep-effic-safety-stud\molluscum-contagiosum\5354-other-stud-rep\verrica-ycanth\verrica-ycanth-study-report.pdf

- On January 26, 2022, we issued an IR stating the following:
  "It is unclear if you used the same HF validation study protocol that was used for the untrained HCP supplemental HF validation study conducted in May 2021. Please clarify whether the HF validation study protocol used for supplemental HF validation study conducted in December 2021 is the same HF validation study protocol that was used for the untrained HCP supplemental HF validation study conducted in May 2021."

The Applicant provided an acceptable response on January 28, 2022 and can be accessible in EDR via: \\CDSESUB1\evsprod\nda212905\0063\m5\53-clin-stud-rep\535-rep-effic-safety-stud\molluscum-contagiosum\5354-other-stud-rep\verrica-ycanth\verrica-ycanth-study-report.pdf

- On March 4, 2022, we issued an IR stating the following:
  "In the cover letter, you state that you conducted a supplemental human factors (HF) validation study on December 13, 2021. However, we note that you submitted the study results report to the Agency on December 14, 2021. Please confirm that you conducted and completed your supplemental HF validation study on December 13, 2021."

The Applicant provided an acceptable response on March 8, 2022, and can be accessible in DARRTS via:
https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8064c0bc

APPENDIX F. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[25] along with postmarket medication error data, we reviewed the following cantharidin labels and labeling submitted by Verrica Pharmaceuticals, Inc.

- Single Tube Applicator label received on November 24, 2021
- Paperboard Sleeve label received on November 24, 2021
- 6 Count Applicator Configuration Carton labeling received on November 24, 2021
- 12 Count Applicator Configuration Carton labeling received on November 24, 2021
- Break Tool Carton label received on November 24, 2021

E.2 Label and Labeling Images

(b) (4)

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

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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:	April 7, 2022
To:	Matthew White Senior Regulatory Project Manager **Division of Dermatology and Dentistry (DDD)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nazia Fatima, PharmD, MBA, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	[VP-102] YCANTH (cantharidin)
Dosage Form and Route:	topical solution
Application Type/Number:	NDA 212905
Applicant:	Verrica Pharmaceuticals Inc.

1 INTRODUCTION

On November 24, 2021, Verrica Pharmaceuticals Inc. resubmitted for the Agency's review an original New Drug Application (NDA) 212905 [VP-102] YCANTH (cantharidin) topical solution, in response to the Agency's Complete Response (CR) Letter dated September 16, 2021. The Applicant proposes the following indication for [VP-102] YCANTH (cantharidin) topical solution: for the treatment of molluscum cantagiosum.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dentistry (DDD) on March 28, 2022 and March 25, 2022, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for YCANTH (cantharidin) topical solution.

2 MATERIAL REVIEWED

- Draft [VP-102] YCANTH (cantharidin) topical solution PPI received on November 24, 2021, and received by DMPP and OPDP on March 21, 2022.
- Draft [VP-102] YCANTH (cantharidin) topical solution Prescribing Information (PI) received on November 24, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 21, 2022.

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 PPI 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 PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	March 4, 2022
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 212905
Product Name and Strength:	Ycanth (Cantharidin) topical solution, 0.7%
Applicant/Sponsor Name:	Verrica Pharmaceuticals, Inc.
OSE RCM #:	2019-1920-1
DMEPA 1 Safety Evaluator:	Avani Bhalodia, PharmD, BCPS
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on November 24, 2021 for Ycanth. The Division of Dermatology and Dentistry (DDD) requested that we review the revised container labels and carton labeling for Ycanth (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

Although not specifically reflected in the label and labeling submitted to the NDA at that time, based on the information request (IR) response received on December 14, 2021, the Applicant commits to distributing (b) (4) Thus, based on the foregoing and review of the revised label and labeling, the Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Bhalodia, A. Human Factors Results and Label and Labeling Review for Ycanth (NDA 212905). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 SEP 15. RCM No.: 2019-1919; 2019-1920; 2020-2756.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

MEMORANDUM

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

TO: Qianyiren Song, Regulatory Health Project Manager
Dermatology and Dentistry (DDD)

FROM: Tinya Sensie, MHA, Senior Regulatory Project Manager
Pediatric and Maternal Health (DPMH)

SUBJECT: Type 2 Resubmission following Complete Response (CR)

NDA: 212905

DRUG: cantharidin topical solution

On February 17, 2021, DPMH received a New NDA- class 2 resubmission consult for NDA 212905/cantharidin in response to the July 13, 2020 CR. Please refer to our previous review dated April 3, 2020.

Following the planning meeting on February 22, 2021, CMC and Human Factors/DMEPA identified deficiencies in the resubmission. A Discipline Review letter was sent to the applicant on May 4, 2021 noting these deficiencies. A major amendment for a review extension was received on May 13, 2021, extending the goal date by three months to September 23, 2021.

Another CR was issued on September 16, 2021 due to facility inspections, labeling and human factor issues.

This memorandum will close out the consult request.

DPMH RPM- Tinya Sensie
DPMH RPM Team Leader- George Greeley
DPMH Maternal Health Reviewer- Christos Mastroyannis
DPMH Maternal Health Team Leader- Tamara Johnson
DPMH Division Director- Lynne P. Yao

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HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	September 15, 2021
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 212905
Product Type:	Combination Product
Drug Constituent Name and Strength	Ycanth (cantharidin) topical solution, 0.7%
Device Constituent:	Pre-filled topical applicator
Rx or OTC:	Rx
Applicant/Sponsor Name:	Verrica Pharmaceuticals, Inc.
Submission Date:	December 23, 2020; February 19, 2021; May 14, 2021; May 18, 2021; June 21, 2021
OSE RCM #:	2019-1919; 2019-1920; 2020-2756
DMEPA 1 Safety Evaluator:	Avani Bhalodia, PharmD, BCPS
DMEPA 1 Team Leader (Acting):	Murewa Oguntimein, PhD, MHS, CPH, CHES
DMEPA 1 Associate Director for Human Factors:	Jason Flint, MBA, PMP
DMEPA 1 Deputy Director/Director (Acting):	Irene Z. Chan, PharmD, BCPS

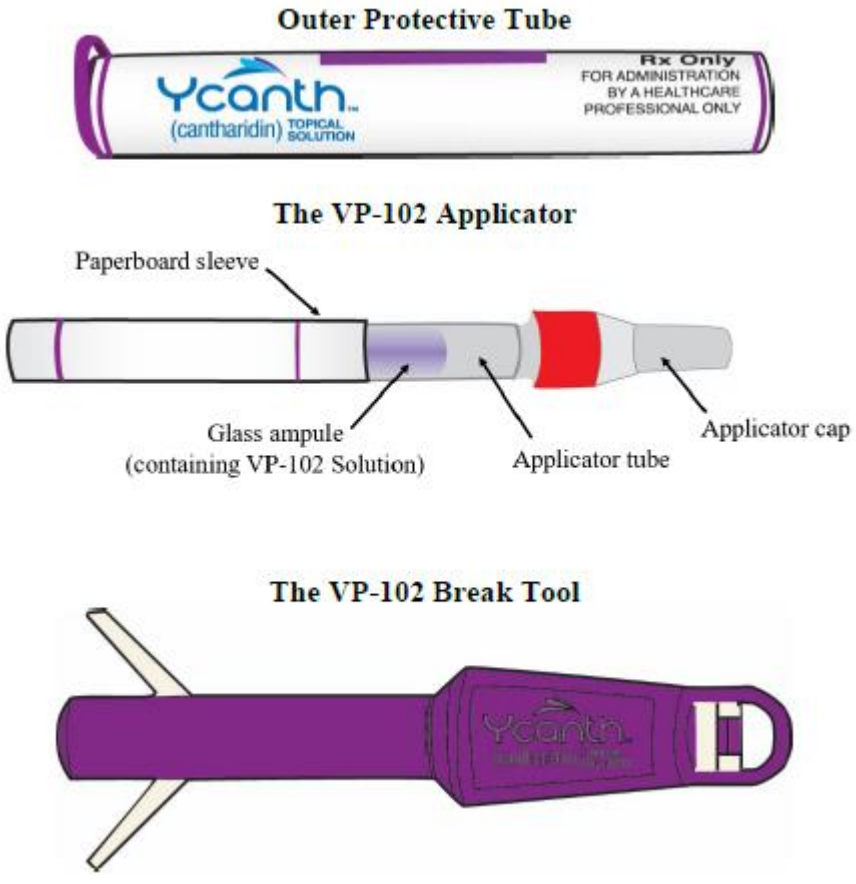
1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study reports and labels and labeling submitted under NDA 212905 for Ycanth (cantharidin).

1.1 PRODUCT DESCRIPTION

This is a combination product with a proposed pre-filled topical applicator device constituent part that is intended for the treatment of molluscum contagiosum. Ycanth Solution is supplied in a sealed glass ampule contained within a single-use applicator and enclosed in a protective paperboard sleeve. The Ycanth Break Tool (break tool) is an accessory to the Ycanth applicator. The break tool was designed to assist with breaking of the ampule. Ycanth applicators will be commercialized in cartons of either 6 or 12 applicators co-packaged with 2 break tools. Each carton will contain applicators packaged in an Outer Protective Tube, 2 Ycanth Break Tools packaged in a bubble bag, a bundle of package inserts containing the device use instructions, (b) (4) See Figure 1 below and Appendix A for additional details.

Figure 1: Outer protective tube, applicator, and break tool



1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

- On September 19, 2019, Verrica Pharmaceuticals, Inc. (Applicant) submitted their New Drug Application (NDA) that included a human factors validation study report. The Applicant conducted their HF validation study without seeking Agency feedback on the study methodology prior to conducting the study.[1]
- On February 26, 2020, we provided our preliminary comments to the Applicant in a mid-cycle discipline review letter that additional mitigation strategies may be needed to optimize applicator use along with other revisions to the product user interface taking into consideration our identified concerns.[2] On March 4, 2020, the Applicant responded to our concerns.[3]
- On March 23, 2020, the Agency responded to the Applicant's March 4, 2020 submission indicating that that we still had concerns with the break force of the ampule and paperboard sleeve that could lead to accidental exposure to the users mouth or eye, and we provided additional comments outlining our continued concern.[4]
- On April 3, 2020, the Applicant provided a response including their justification for the break force of the ampule and paperboard sleeve.[5] The Applicant subsequently submitted an updated HF validation study protocol along with a comparative analyses and heuristic analysis on April 10, 2020. The Agency acknowledged the submission of the threshold and heuristic analysis was unsolicited. Furthermore, the Agency was still reviewing the information provided in previous submissions; therefore, we sent a withdrawal letter on April 24, 2020.[6]

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[1]Neall P. NDA 212905 Ycanth (Cantharidin) Human Factors Validation Study Report. \\CDSESUB1\evsprod\nda212905\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\molluscum-contagiosum\5354-other-stud-rep\verrica-vp102-0008\verrica-vp102-0008-report-body.pdf

[2] Song, Q. Mid-Cycle Discipline Review Letter. Submitted to DARRTS on February 26, 2020. https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af80543ddc&_afrRedirect=627132957944 0984

[3] Response to February 26, 2020 Mid-Cycle Discipline Review Letter. \\cdsesub1\evsprod\nda212905\0017\m1\us\111-information-amendment\quality-information-amendment-04-march-2020.pdf

[4] Song, Q. Discipline Review Letter. Submitted to DARRTS on March 23, 2020. https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8054e00d&_afrRedirect=627152132744 8234

[5] Response to March 23, 2020 Discipline Review Letter. \\cdsesub1\evsprod\nda212905\0021\m1\us\111-information-amendment\quality-information-amendment-03-april-2020.pdf

[6] Killen, M. Human Factors Validation Study Protocol Withdrawal. Submitted to DARRTS on April 24, 2020. https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8055b828&_afrRedirect=774779882240 3184 Chan, Irene Z. Human Factors (HF) Validation Study Protocol Incomplete Letter for IND 131163. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019-JAN 02. RCM No.: 2018-2769.

- On July 13, 2020, the Agency sent the Applicant a Complete Response (CR) letter that included deficiencies in their HF validation study with noted use errors and difficulties with the critical task- 'Break the Ampule' and their heuristic analysis submitted on April 10, 2020 that indicated the average palmar pinch force (grip used to break an ampule) for adult females is 16 lbs. and that the average force to break the ampule with paperboard sleeve on is 19 lbs. From this information, the Applicant also concluded that the force to break the ampule could increase the potential for use errors. Based on these deficiencies, we indicated that we remained concerned that the Applicant's proposed combination product is not safe for use by HCPs. We also stated our concern that the risk of accidental exposure will outweigh the benefit of the treatment with this combination product. Inherent design issues exist with this product that may contribute to serious harm if accidental exposure occurs during use. Thus, we indicated that additional mitigation strategies were needed and could include the need for device design changes to optimize applicator use along with other revisions to the product user interface taking into consideration our previously identified concerns and the data collected from their HF validation study. After they implement additional risk mitigation strategies/modifications, we recommended they conduct an additional HF validation study to ensure that these modifications address the observed use errors and use difficulties and do not introduce any new risks. We recommended the Applicant submit their revised HF validation study protocol for feedback from the Agency before commencing the study. Based on our comments, the Applicant created a break tool to be used to crush the ampule, revised the instructions for use (IFU) to include information about the break tool, included information about when to remove the cap, what to look for when inspecting the ampule, and revised their URRA accordingly.
- On August 28, 2020, the Applicant submitted their revised HF validation study protocol, URRA and IFU under their IND 131163 for feedback from the Agency. We evaluated the proposed protocol and provided recommendations to the Applicant. We recommended that the Applicant implement all recommendations before commencing the HF validation study.[7]
- On December 23, 2020, the Applicant submitted a HF validation study results report as part of the class 2 resubmission of NDA 212905, which is the subject of this review.
- On February 16, 2021, we sent an Information Request to the Applicant which requested justification for including all trained participants. The HF validation study protocol submitted on August 28, 2020 under IND 131163 stated, "Formal training will not be provided to users" in Section 2.4 Training.[8]

[7] Oguntimein, M. Human Factors Protocol Review for cantharidin (IND 131163). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 23. RCM No.: 2020-1795.

[8] Bui Nguyen, T. Information Request for NDA 212905. Silver Spring (MD): FDA, CDER, OSE (US); 2021 FEB 16. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805d27f1&_afrRedirect=493649575601784.

- On February 19, 2021, the Applicant provided a response including their justification for including all trained participants. The Applicant stated that they intend to deploy the training program that was implemented in the HF validation study to train real-world users prior to product use. However, it is unclear how the Applicant will ensure that every user will consistently and routinely receive training and whether such a training program will continue to exist throughout the product's lifecycle on the market. We are concerned with understanding how users who do not receive training may perform when relying on the proposed user interface of the proposed product. Therefore, we found that the data obtained from their HF validation study with trained participants is not representative of real-world use. As such, we recommended that the Applicant conduct a supplemental HF validation study with 15 untrained healthcare professionals (HCPs) as a distinct user group.[9]
- On May 4, 2021, the Agency sent the Applicant a discipline review (DR) letter that included deficiencies in their HF validation study methodology- the use of all trained participants, and considerations as the Applicant conducts their supplemental study with 15 untrained HCPs.[10] We also asked the Division of Division of Dermatology and Dentistry (DDD) if they have other considerations (such as public health need) that we should take into consideration. There is no public heath need from DDD's perspective.
- On May 11, 2021, a teleconference meeting was held between the Agency and the Applicant to discuss the contents of the DR letter sent on May 4, 2021. During the teleconference meeting, FDA requested the Applicant to submit detailed training materials, information concerning (b) (4) , and a detailed plan for a new HF study.[11]
- On May 14, 2021 and May 18, 2021, the Applicant provided a response to the DR letter and the information requested during the teleconference meeting on May 11, 2021.[12,13]

[9] Verrica Pharmaceuticals, Inc. Response to Information Request for cantharidin (NDA 212905). West Chester (PA): 2021, FEB 19.

[10] Van Horn III, H. Discipline Review Letter for cantharidin (NDA 212905). Silver Spring (MD): FDA, CDER, OND, DDD (US); 2021 MAY 4. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805ed530&_afrRedirect=492147532898471.

[11] Van Horn III, H. Information Request for cantharidin (NDA 212905). Silver Spring (MD): FDA, CDER, OND, DDD (US); 2021 MAY 14. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805f0870&_afrRedirect=218632711726479.

[12] Verrica Pharmaceuticals, Inc. Response to Information Request for cantharidin (NDA 212905). West Chester (PA): 2021, MAY 14.

[13] Verrica Pharmaceuticals, Inc. Response to Information Request for cantharidin (NDA 212905). West Chester (PA): 2021, MAY 18.

- On June 21, 2021, the Applicant submitted a supplemental HF validation study results for untrained HCPs, which is also the subject of this review.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed, and our analysis to determine if the results indicate that the user interface is designed to support the safe and effective use of the proposed product.

3.1 SUMMARY OF STUDY DESIGN

Table 2 presents a summary of the HF validation study design. See Appendix C and D for more details on the study design.

Table 2. Study Methodology for Human Factors (HF) Validation Studies

Study Design Elements	**Details**	
	HF Validation Study	**Supplemental HF Validation Study**
Participants	16 trained healthcare professionals (HCPs) • Medical Doctors (Family Medicine, Pediatrics, Dermatology), n=11 • Physician's assistant, n=1 • Nurse Practitioner (NP), n=2 • Registered Nurse (RN), n=2	15 untrained healthcare professionals (HCPs) • Dermatologist, n=9 • Physician Assistant, n=6
Training	Training was provided to the HCPs	No training was provided to the HCPs
Study Environment	The study was conducted in a simulated patient exam room.	
Sequence of Study	Simulated Use Scenario → Knowledge Task Questions → RCA	

3.2 RESULTS AND ANALYSES

Table 3 describes eight critical task use error identified in the HF validation study, Applicant's analyses of the results, and DMEPA's analyses and recommendations.

Table 3. Identified Issues and DMEPA's Findings		
	Identified Issue, Subjective Feedback, Root Cause Analysis and Mitigations	**DMEPA's Analysis and Findings**
1.	For the task to put on personal protective equipment (PPE) (gloves and eye protection), there were 2 use errors (Participants U9 and U13) in the supplemental HF validation study with untrained participants in the simulated use scenario portion of the study. • Untrained 9 (U9) did not put on eye protection or gloves before breaking the ampule. • Untrained 13 (U13) did not put on eye protection. The subjective data and the Applicant's root cause analysis (RCA) indicated: • Test artifact – simulated use led participants to skip this step. The Applicant states that the Instructions for Use (IFU) include clear instruction for users to wear protective eyewear and gloves when handling Ycanth. The Applicant notes that they intend to train all users on how to use the Ycanth applicator, which will include the proper PPE to wear when handling Ycanth. As such, the Applicant did not implement additional mitigations to further address these use errors.	Based on Applicant's use-related risk analysis (URRA) if the user does not put on gloves there is a risk of the user or patient being exposed to solution in location other than intended resulting in unintended blistering and if the user does not put on eye protection there is risk of toxic solution getting in patient's or user's eye resulting in potential eye injury. Based on our discussion with the Medical Officer in the Division of Dermatology and Dentistry, ocular toxicity may occur if Ycanth comes in contact with the eyes. Adverse reactions from contact of Ycanth with the eyes can include corneal necrosis, ocular perforation, and deep ocular injuries. Furthermore, the medical officer noted that although dermatologists would typically have such PPE available in their office, if approved, it's likely that primary care physicians, such as internists, family medicine providers, pediatricians, or other providers may also use this medication. It is unclear whether other providers may customarily have such PPE available in their offices. Thus, we are concerned with the residual risk for this error. Our review of the study results identified subjective feedback that indicated that user may not have read the IFU or did not see the eye protection. For example, U9 stated, "In retrospect I should've just read the instructions" and U13 stated "Didn't see them over there". Our review of the labels and labeling notes that container label and carton labeling do not include the instruction to put on PPE before use.

		Based on our overall assessment, we disagree with the Applicant that no additional mitigations are required to further mitigate this risk. As such, we find that the container label and carton labeling can be improved to further mitigate risk of failure to put on PPE. **We provide a recommendation in Table A to address this concern**.
2.	For the task to inspect the applicator, there were 4 use errors (Participants U2, U6, U9 and U13) in the supplemental HF validation study with untrained participants and 3 use errors (Participants P06, P12 and P14) in the HF validation study with trained participants in the simulated use scenario portion of the study. The subjective data and the Applicant's root cause analysis (RCA) indicated: • Lapse – didn't recall what an intact ampule/applicator should look like (U2). • Negative knowledge transfer – assumed sleeve was not removable based on Levulan Kerastick product (U6). • Lack of product familiarization–participant did not know what a damaged applicator would look like (U9). • Mismatch to users' expectations – participant thought to only inspect the ampule for leaks or breaks (U13). • Lapse – Users (P06, P12, P14) did not recall from training to identify a broken ampule as damaged during inspection. During device use, the users did not reference example images in the IFU or Quick Reference Guide (QRG) during the training or evaluation sessions.	Based on Applicant's URRA, if this task is omitted or not performed correctly there is risk of delayed treatment, or user or patient exposed to solution in location other than intended resulting in unintended blistering. The subjective feedback indicated that the participants did not fully read the IFU or only read the text and did not look at the images, but participants were able to locate the IFU images of types of damage to inspect the applicator for and understood the images. We note that even with training, use errors occurred, yet the Applicant did not propose further risk mitigation measures. We also note that while the Applicant identified that users who are wearing PPE would be protected for unintended exposure to the solution, that does not address patient exposure to solution in locations other than intended resulting in unintended blistering. Our review of the labels and labeling indicate that the IFU contains text and images to support this task and the paperboard sleeve includes instruction to inspect the ampule. Based on our overall assessment, we disagree with the Applicant that no additional mitigations are required to further mitigate this risk. As such, we find that the paperboard sleeve label and carton labeling can be improved to further mitigate risk of failure to inspect the applicator. **We provide recommendations in Table A to address this concern.**

	In the supplemental HF study with untrained participants, the Applicant states that the participants were able to locate the IFU images of types of damage to inspect the applicator for and understood the images. The Applicant intends to train all users on how to use the Ycanth applicator, which will include how to properly inspect the applicator for damage. The Applicant also states that the users are instructed to wear gloves and eye protection which will protect their hands and eyes from potential exposure if the drug solution would leak as the result of damage to the applicator. In the HF study with trained participants, the Applicant states that in the event that these users had attempted to use a broken ampule, the users had gloves and eye protection in place that would protect them from potential exposure if the drug solution would leak into the tip/cap prior to cap removal. As such, the Applicant did not implement additional mitigations to further address these use errors.	
3.	For the task to ensure applicator cap is in place, there was 1 use error (Participant P06) in the HF validation study with trained participants in the simulated use scenario portion of the study. The subjective data and the Applicant's root cause analysis (RCA) indicated: • Lapse - P06 did not recall from training to keep the applicator cap on when placing the applicator into the break tool. P06 was explicitly instructed in	Based on Applicant's URRA, if this task is omitted or not performed correctly there is risk of delayed treatment, or user or patient exposed to solution in location other than intended resulting in unintended blistering. The subjective feedback indicated that the participant did not recall from training to keep applicator cap on when placing the applicator into break tool. Our review of the study results identified that the Applicant did not collect subjective feedback related to elements of the user interface that may have contributed to the use error.

	training to not remove the applicator cap until after ampule break is completed. The Applicant states that the user executed all other mitigation steps to prevent the potential for exposure to solution in a location other than intended, resulting in unintended blistering. The user wore gloves and eye protection; break tool was used to break ampule and positioned with tip facing upward and away from user/patient; break tool has spill reservoir to contain any forward spray. The Applicant stated that these mitigations were effective, as there was no visible solution ejected from applicator during the breaking of the ampule. As such, the Applicant did not implement additional mitigations to further address this use error.	Our review of the labels and labeling (user interface, etc.) finds that step 5 contains the text "Ensure the applicator cap is in place", which supports this task. We determined at this time that the residual risk associated with this use error is acceptable without further mitigation.
4.	For the task, tap to move solution toward tip, there were 2 use errors (Participants P06 and P15) in the HF validation study with trained participants in the simulated use scenario portion of the study. The subjective data and the Applicant's root cause analysis (RCA) indicated: • Lapse - User (P06) had previously removed the applicator cap prior to breaking the ampule; did not reference IFU or QRG. Relied solely on memory. • Lapse - User (P15) did not recall from training to tap with cap on to advance solution. Did not use IFU or QRG. Relied solely on memory.	Based on Applicant's URRA, if this task is omitted or not performed correctly there is risk of user or patient exposed to solution in location other than intended resulting in unintended blistering. Our review of the study results identified that the Applicant did not collect subjective feedback related to elements of the user interface that may have contributed to the use error. We agree with the Applicant's proposal to remove Step 6 from the IFU based on the assessment that the Applicant provided, that the risk of potential critical use errors associated with Step 6 outweighs the benefit of the intended purpose of the step. The Applicant assessed an updated IFU with step 6 removed in the supplemental HF validation study with untrained users to demonstrate that

	The Applicant states that the IFU utilized in the HF validation study submitted in NDA 212905 included Step 6. “Tap YCANTH Applicator to move YCANTH Solution.” This additional step was introduced in this version of the IFU as a mitigation to comments related to difficulty generating enough force to dispense the drug solution. In addition to tapping, Step 7, “Test the YCANTH Applicator” was updated in this version to include applying a droplet to a paper towel or gauze to confirm the Ycanth Applicator is working properly. In the URRA, there are two potential critical use errors associated with Step 6. • Step 6.a “User removes the cap prior to tapping” • Step 6.d “User squeezes while tapping” The potential outcome and associated harm of not tapping the applicator (i.e., skipping Step 6) is the same as the potential outcome and associated harm for the potential use error stated in Step 6.b “User taps with the capped end pointing upward.” The harm associated with the potential use error in Step 6.b is delayed treatment, which has a severity score of 1 (negligible). In addition, if the user skips Step 6, but performs Step 7 correctly, the user will confirm that the applicator is working properly in Step 7 prior to applying the drug solution in Step 8 “Apply the YCANTH Solution.”	this mitigation strategy was successful. We find the residual risk acceptable and do not have any other recommendations for this issue at this time.

	As such, the Applicant concluded that the use-related risk is greater if the user performs Step 6 incorrectly than if the user does not perform the task at all; skipping Step 6 does not cause harm to the patient or user. Based on this assessment, the risk of potential critical use errors associated with Step 6 outweighs the benefit of the intended purpose of the step (a mitigation to address difficulty generating enough force to dispense); therefore, the Applicant proposed to remove Step 6 in its entirety from the IFU. The applicant intends to update the IFU, Quick Reference Guide, and URRA. In addition, Step 6 was removed from the supplemental HF validation study with 15 untrained users.	
5.	For the knowledge task question to request additional break tools, there were 2 use errors (Participants U6 and U9) in the supplemental HF validation study with untrained participants and 1 use error (Participant P07) in the HF validation study with trained participants. • Untrained 6 (U6) stated that they could use their hand to break the ampule if they didn't have access to a break tool, wait until a break tool was available, or contact the manufacturer. • Untrained 9 (U9) stated to get additional tool from another package, use fingers to break, or call manufacturer. • Trained (P07) stated if there wasn't another break tool in facility inventory, worst-case scenario they could break the glass ampule manually.	Based on Applicant's use-related risk analysis (URRA), if this task is omitted or not performed correctly there is risk of toxic solution getting in the patient's or user's open wound resulting in pain, burning, and there is an increased risk of systemic exposure. Thus, we are concerned with the residual risk for this error. The Applicant states that Ycanth break tool maintenance section of the IFU and QRG instructs the user to contact the Applicant to request additional break tools. However, this may not always be feasible if patient is already present for their appointment to get the treatment when prescriber discovers they need an additional break tool. Based on the subjective feedback collected, it appears that participants would proceed to manually breaking the ampule in some cases.

	The subjective data and Applicant's root cause analysis (RCA) indicated: • Negative Knowledge Transfer – participants aware of analogous products that are able to use hands to crack internal ampule (U6, U9). • Mismatch to user's expectation – User knew each carton of applicators was supplied with a break tool. Didn't realize could order independently. Didn't reference IFU/QRG during session. User had experience using similar products that do not require/offer a break tool to prepare applicator for use (P07). The Applicant states that Ycanth break tool maintenance section of IFU and QRG instruct the user to contact the Applicant to request additional break tools. Participants were able to locate and understand this information in the IFU. Each carton contains an extra break tool (2 total). Users are instructed to wear gloves and eye protection when handling the applicator. The Applicant stated they intend to train all users on how to use the Ycanth applicator, which will include how to order new break tools and to not use their hands to break the glass ampule. As such, the Applicant did not implement additional mitigations to further address these use errors.	Our review of the packaging notes that only 2 break tools are included in a carton of 6 and 12 applicators. Based on our overall assessment, we disagree with the Applicant that no additional mitigations are required to further mitigate this risk. As such, we find that the packaging can be improved to further mitigate risk of failure to break the ampule with the break tool. **We provide a recommendation in Table A to address this concern**.
6.	For the knowledge task question to assess following information on label, "WARNING: Flammable liquid, even	Based on the URRA, if this task is omitted or not performed correctly there is risk of exposure to open flame resulting in user or patient burn.

	after drying. Avoid fire, flame or smoking during treatment", there was 1 use error (Participant P13) in the HF validation study with trained participants. The subjective data and Applicant's root cause analysis (RCA) indicated: • Font size of Outer Protective tube warnings - the font size of the warning was too small for user (P13) without using their reading glasses to see easily. The Applicant states that the Identical warning statement is found in the IFU and was an appropriate text size for this user to see without having their reading glasses. As such, the Applicant did not implement additional mitigations to further address this use error.	The subjective feedback indicated that participant forgot their reading glasses so had a hard time reading the warning note on the outer protective tube label and missed where it said, 'even after drying'. Our review of the labels and labeling (user interface, etc.) finds that warning note font size on the outer protective tube label cannot be increased without taking away the prominence from other important information on the label and we have not identified additional labeling changes in the outer protective tube label that are likely to further reduce the residual risk associated with this use error. At this time, we find the residual risk acceptable and do not recommend any other changes to the user interface.
7.	For the knowledge task question to flush eyes with water for at least 15 minutes and seek medical attention if Ycanth Solution gets in the eyes, there were 3 use errors (Participants U3, U7 and U11) in the supplemental HF validation study with untrained participants and 3 use errors (Participants P04, P06 and P14) in the HF validation study with trained participants. The subjective data and Applicant's root cause analysis (RCA) indicated: • Mismatch to user's expectations – general practice for eye flushing is 5-10 minutes or until symptoms have subsided (U3, U7, U11).	Based on the URRA, if this task is omitted or not performed correctly there is risk of toxic solution getting in patient's or user's eye resulting in potential eye injury. We agree with the Applicant that mismatch to user's expectations may have played a role in these use errors. However, we are concerned that this use error occurred in trained and untrained participants. According to the Applicant's VP-102 Applicator Benefit Versus Residual Use-Related Risk Assessment, it is improbable that the use error will lead to the hazardous situation because the HCP would use their clinical judgement to determine sufficient flushing time and may determine that less than 15 minutes is necessary.

	• Mismatch to user's expectation - Users' (P04, P06) standard practice is to flush eyes for less than 15 mins. • Lapse - User (P14) did not recall from training to flush eyes for at least 15 minutes. User did not reference IFU/QRG. The Applicant states all participants knew to flush the eyes immediately and thoroughly. In practice, the healthcare provider would continue to assess the status of the affected eye(s) throughout the eye flushing process and use their clinical judgement to determine if the eyes had been sufficiently flushed. All participants were able to find that the IFU instructs to flush for 15 minutes in the supplemental HF validation study with untrained participants. As such, the Applicant did not implement additional mitigations to further address these use errors.	Our review of the labels and labeling (user interface, etc.) finds that IFU and carton labeling instructs to flush eyes with water for at least 15 minutes if VP-102 Solution gets in the eyes to support completion of this knowledge task and we have not identified additional labeling changes in the IFU or carton labeling that are likely to further reduce the residual risk associated with these use errors.
8.	For the knowledge task question to assess following information on label, "DO NOT cover any treated lesions with bandages", there was 1 use error (Participant U6) in supplemental HF validation study with untrained participants. The subjective data and Applicant's root cause analysis (RCA) indicated: • Negative knowledge transfer –other cantharidin products allow covering of the treated lesions, which differs from Ycanth (U6).	Based on the URRA, if this task is omitted or not performed correctly there is risk of improper treatment (increased penetration of drug) resulting in more blistering than intended. Our review of the study results identified that the Applicant did not collect subjective feedback related to elements of the user interface that may have contributed to the use error. Our review of the labels and labeling (user interface, etc.) finds that step 8 contains the text "DO NOT cover any treated lesions with bandages", which supports this knowledge task. We determined at this time that the residual risk associated with this use error is acceptable without further mitigation.

	The Applicant states that the participant was able identify that the IFU was the source for this information and correctly interpret based on the information in the IFU to not cover treated lesions with bandages. The IFU instructs users to not cover treated lesions with bandages. The Applicant stated they intend to train all users on how to use the Ycanth applicator, which will include instructions to leave treated lesions uncovered. As such, the Applicant did not implement additional mitigations to further address this use error.	

3.3 DISCUSSION REGARDING USER INTERFACE

The Applicant states that they plan to train all users of the product, however, it is not clear how the Applicant will ensure training is provided to every user without appropriate administrative controls. We also note that in the study results, despite training, use errors still occurred with the potential for serious adverse events. While we support provision of training for users, we determined that additional changes to the user interface are needed to support the safe and effective use of this product.

We discussed our concerns regarding the design of the user interface, including our conclusion that the Applicant had not optimized the design to support safe and effective use, with the Division of Dermatology and Dentistry on May 25, 2021. The Division of Dermatology and Dentistry indicated that they did not have the same level of clinical concern as DMEPA because they felt the occurrence rates for the use errors were likely to be low, and as such, this would lower the residual risk. While we recognize that risk is a function of severity of harm and rate of occurrence, we note that it is difficult to estimate occurrence rates for use errors. This is especially true in a premarket environment when the product has not yet been marketed in the United States. Furthermore, we note that the severity of harm associated with these use errors can be high. For example, if a physician were to have exposure of this toxic product to the eye and does not seek additional medical care, this can lead to ocular toxicity, which includes irreversible damage. As such, we determined that the Applicant should make further changes to their user interface in order to support the safe and effective use of this product. For example, at a minimum, we recommend the product is redesigned to ensure break tools are always available. The HF study results indicated that some users, if they did not have a tool present, would choose to manually break the ampule. We provide this recommendation in Table A below.

3.4 ANALYSIS OF OTHER TASK ERRORS

We note that the HF validation study showed no use errors, (e.g., failures, difficulties, and close calls) with the non-critical tasks.

3.5 LABELS AND LABELING

Tables 4 and A below include the identified medication error issues with the submitted label and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 4: Identified Issues and Recommendations for Division of Dermatology and Dentistry (DDD)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
Highlights of Prescribing Information			
1.	Dosage and Administration section does not include the statement, "See Full Prescribing Information (FPI) for instructions on the preparation and administration."	Healthcare professionals may overlook important preparation and administration instructions if they refer to the Highlights of Prescribing Information only, which may lead to incorrect/incomplete preparation and administration of the pre-filled topical applicator.	Add a statement under Dosage and Administration section to alert the health care provider that additional important information is in the FPI (e.g., see Full Prescribing Information for instructions on the preparation and administration.)

Table A: Identified Issues and Recommendations for Verrica Pharmaceuticals, Inc. (entire table to be conveyed to the Applicant)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
Single Tube Applicator Label, Paperboard Sleeve Label and Carton Labeling			
1.	Instructions for use (IFU) includes the instruction to put on personal protective equipment (PPE) but single tube applicator label, paperboard sleeve label and carton labeling do not include the instruction to put on PPE. Subjective feedback indicated that user may not have read the IFU.	We are concerned that the user interface is not optimized and there is a risk of users or patients being exposed to solution in a location other than intended resulting in unintended blistering if user does not put on gloves and toxic solution gets in a patient's or user's eye resulting in potential eye injury if a user does not put on eye protection.	Include information to instruct Healthcare Professionals (HCPs) to put on PPE while handling this product on the single tube applicator label, paperboard sleeve label and carton labeling.
Single Tube Applicator Label			
1.	IFU includes the instruction to break the ampule using the break tool but single tube applicator label does not include the instruction to break the ampule using the break tool.	We are concerned that the user interface is not optimized and there is a risk of toxic solution getting in patient's or user's open wound resulting in pain, burning, and increased risk of systemic exposure if the user breaks the ampule by hand or with another tool.	Add "Must break the ampule using the enclosed break tool" statement on the single tube applicator label to ensure break tool is used to break the ampule.

2.	The “Rx Only” statement appears more prominent than the established name on the principal display panel.	The Rx-only statement should not compete in size and prominence with critical information on the principal display panel[14].	Decrease the prominence of the statement “Rx Only”.
3.	As currently presented, the “Usual Dose” statement is not in the correct format.	Per 21 CFR 201.55, “…labels for prescription drugs bear a statement of the recommended or usual dosage.”	To ensure consistency with the Prescribing Information, revise the statement, [redacted] (b) (4) to read “Recommended Dosage: See prescribing information.”
4.	A linear barcode is missing from the immediate container label.	The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible.	Therefore, we request you add the product’s linear barcode to each individual container label as required per 21CFR 201.25(c)(2). The barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i). Consider orienting the linear barcode to a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to single tube applicator curvature.[15]
5.	We note that your single tube applicator label includes a “MM/YYYY” format	There is a risk for deteriorated drug medication errors if the expiration date is misinterpreted.	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

[14] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

[15] Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

	for the expiration date.		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.
Paperboard Sleeve Label			
1.	Your paperboard sleeve container label is not consistent with your IFU with regards to the instruction to inspect the applicator. The IFU states, "Inspect the VP-102 Applicator for the following types of damage" while the paperboard sleeve container label states, (b) (4)	Inconsistencies between container label and IFU with regards to the instruction to inspect the applicator may lead to misinterpretation.	To be consistent with IFU, revise statement (b) (4) to "Remove paperboard sleeve and inspect the applicator before using break tool." Additionally, add more emphasis to the instruction to inspect the applicator on paperboard sleeve label.
2.	The "Rx Only" statement appears more prominent than the established	The Rx-only statement should not compete in size and prominence with critical information on the principal display panel[16].	Decrease the prominence of the statement "Rx Only".

[16] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

	name on the principal display panel.		
3.	The intended location for the lot number and expiration date is not provided on proposed paperboard sleeve label.	The lot number statement is required on the carton labeling per 21 CFR 201.10(i)(1) and the product expiration date is also required on the carton labeling per 21 CFR 201.17.	Add the lot number and expiration date on paperboard sleeve label. When determining this placement, please ensure that there are no other numbers located in close proximity to the lot number/expiration date that can be mistaken as the lot number/expiration date. 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.
4.	Storage information is inconsistent with the Prescribing Information.	Inconsistency in storage information could lead to medication errors due to improper storage.	To ensure consistency with the Prescribing Information, revise the statement [redacted] (b) (4) to read "Protect from light".
Carton Labeling for the 6 Count Applicators and 12 Count Applicators Configuration			
1.	The carton labeling does not include a usual dose statement.	A usual dose statement is required per 21 CFR 201.55.	Revise the carton labeling to include the statement "Recommended Dosage: See prescribing information."

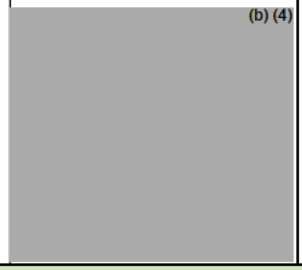
2.	Manufacturer information is competing in size and prominence with important information such as proprietary and proper names and strength.	The manufacturer name should not compete in size and prominence with critical information on the principal display panel[17].	Relocate the manufacturer information to the side panel as it clutters the principal display panel and takes readers' attention away from important information such as proprietary and proper names and strength.
3.	The carton labeling does not include a 2D data matrix barcode.	In June 2021, FDA finalized guidance on product identifiers required under the Drug Supply Chain Security Act.[18] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively.	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling.
4.	We note your principal display panel does not reflect the number of	Carton labeling should state the net quantity of contents.	Please ensure carton labeling is updated to reflect the number of break tools per carton.

[17] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

[18] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. Food and Drug Administration. 2021. Available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

	break tools in the carton.		
5.	IFU includes the instruction to inspect the applicator but carton labeling does not include the instruction to inspect the applicator. Subjective feedback indicated that user may not have read the IFU.	We are concerned that the user interface is not optimized and there is risk of delayed treatment, or user or patient exposed to solution in location other than intended resulting in unintended blistering if user does not inspect the applicator.	We recommend adding instruction to inspect the applicator on carton labeling.
6.	We note warning statements on the carton labeling are currently on the side panel and lacks emphasis.	Warning statements may need more emphasis.	Include additional warnings on the principal display panel. Consider moving RX Only statement, the manufacturer and storage information to the back panel to create more space for the warnings on the principal display panel.
Carton Labeling for the 6 Count Applicators Configuration			
1.	We note that your proposed 6 count applicators (b) (4) carton labeling includes a "MMMYYYY" format for the expiration date.	There is a risk for deteriorated drug medication errors if the expiration date is misinterpreted.	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.

Carton Labeling for the 12 Count Applicators Configuration			
1.	The intended location for the lot number and expiration date is not provided on proposed 12 count applicators and [redacted] carton labeling.	The lot number statement is required on the carton labeling per 21 CFR 201.10(i)(1) and the product expiration date is also required on the carton labeling per 21 CFR 201.17.	Add the lot number and expiration date on 12 count applicators and [redacted] carton labeling. When determining this placement, please ensure that there are no other numbers located in close proximity to the lot number/expiration date that can be mistaken as the lot number/expiration date. 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 hyphen or a space be used to separate the portions of the expiration date.
Break Tool Carton Labeling			
1.	Your break tool labeling is misleading because it includes the YCanth proprietary name.	We are concerned users may misinterpret the labeling to mean that the break tool carton contains drug product.	To decrease the risk of medication error, we recommend you remove the proprietary name from the break tool carton labeling or emphasize that this is the Break Tool for use with Ycanth.
2.	There are inconsistencies between the supplemental HF validation study	This lack of clarity with regards to the break tool packaging my lead to confusion as the users may not recognize and use the break tool if	Ensure your break tool is packaged in a carton.

	report and the carton labeling with regards to the break tool packaging. For example, the HF validation study report states, "the break tools is packaged in a bubble bag" and the break tool in Figure 9 (see below) is not in a carton. However, you include a break tool carton label in your labeling submission. Figure 9: (b) (4) 	it is not packaged in a carton with additional information.	
Packaging			
1.	Each carton of 6 and 12 applicators only includes 2 break tools.	We are concerned that if a user is missing a break tool and does not know how to order additional break tools, the user may break the ampule by hand, which may lead to the risk of toxic solution getting in patient's or user's open	Utilize a method to ensure break tool is always available.

		wound resulting in pain, burning, and increased risk of systemic exposure.	

4 CONCLUSION AND RECOMMENDATIONS

The results of the human factors (HF) validation study identified use errors with critical tasks. After, taking into consideration the review of the subjective feedback and root cause analysis, we are concerned that there is residual risk associated with exposure to the toxic solution on the skin or in the patient's or user's eye(s), which could result in irreversible eye injury. We determined that the proposed user interface should be improved to further mitigate the residual risk in order to ensure safe and effective use of the product, and the risk mitigation strategies should be evaluated in another HF validation study.

Our evaluation of the proposed label and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 4 for the Division and Table A for the Applicant. We ask that the Division convey Table A in its entirety to the Applicant.

4.1 RECOMMENDATIONS FOR THE VERRICA PHARMACEUTICALS, INC.

Our evaluation of the results of your human factors (HF) validation study identified use errors with critical tasks. After, taking into consideration the review of the subjective feedback and root cause analysis, we are concerned with the residual risk associated with exposure to the toxic solution on the skin or in the patient's or user's eye. We determined that the proposed user interface should be improved to further mitigate the residual risk in order to ensure safe and effective use of the product, and the risk mitigation strategies should be evaluated in another HF validation study. Furthermore, our review of the labels and labeling identified areas of vulnerability that may lead to medication errors. We provide these recommendations in Table A and we recommend that you implement these recommendations prior to conducting another HF validation study.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for cantharidin that Verrica Pharmaceuticals, Inc. submitted on December 23, 2020.

Table 5. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	a lipophilic compound from a naturally derived source
Active Ingredient (Drug or Biologic)	cantharidin
Indication	Treatment of molluscum contagiosum
Route of Administration	Topical
Dosage Form	Topical solution
Strength	0.7%
Dose and Frequency	This product is to be administered by a healthcare professional and is applied directly to the affected molluscum skin lesion. Cantharidin is applied one time to each molluscum contagiousm lesion at each office visit and may be administered approximately 3 weeks apart as needed.
How Supplied	Cantharidin solution is supplied in a sealed and crushable glass ampule contained within a single-use applicator and enclosed in a protective paperboard sleeve. Each ampule of cantharidin contains approximately 0.45 mL of 0.7% (b) (4) cantharidin solution. The applicators and two break tools are packaged in cartons containing 6 or 12 applicators per carton.
Storage	Room temperature of 20°C to 25°C (68°F to 77°F)
Container Closure/Device Constituent	Pre-filled topical applicator
Intended Users	Healthcare professionals (HCPs)
Intended Use Environment	Professional healthcare environment

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On July 20, 2021, we searched the L: drive and AIMS using the terms, cantharidin, Ycanth 212905 to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified three previous reviews[19,20,21], and one interaction[22] and we confirmed that our previous recommendations were implemented.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

Human Factors Engineering Report can be accessible in EDR via:
\\CDSESUB1\evsprod\nda212905\0056\m5\53-clin-stud-rep\535-rep-effic-safety-stud\molluscum-contagiosum\5354-other-stud-rep\verrica-vp-102-0020\verrica-vp-102-0020-report-body.pdf

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results reports can be accessible in EDR via:

Supplemental Human Factors Validation Report for Untrained Users
\\CDSESUB1\evsprod\nda212905\0056\m5\53-clin-stud-rep\535-rep-effic-safety-stud\molluscum-contagiosum\5354-other-stud-rep\verrica-vp-102-0019\verrica-vp-102-0019-report-body-1.pdf

Use-Related Risk Analysis and Critical Information Analysis for Supplemental HF Validation Study
\\CDSESUB1\evsprod\nda212905\0056\m5\53-clin-stud-rep\535-rep-effic-safety-stud\molluscum-contagiosum\5354-other-stud-rep\verrica-vp-102-0019\verrica-vp-102-0019-report-body-2.pdf

VP-102 Applicator Benefit Versus Residual Use-Related Risk Assessment: Supplemental HF Validation Study
\\CDSESUB1\evsprod\nda212905\0056\m5\53-clin-stud-rep\535-rep-effic-safety-stud\molluscum-contagiosum\5354-other-stud-rep\verrica-vp-102-0019\verrica-vp-102-0019-report-body-3.pdf

Human Factors Validation Report for Trained Users
\\CDSESUB1\evsprod\nda212905\0044\m5\53-clin-stud-rep\535-rep-effic-safety-stud\molluscum-contagiosum\5354-other-stud-rep\vp102-0017\vp102-0017-study-report.pdf

[19] Schlick, J. Human Factors Results and Labeling Review for cantharidin (NDA 212905). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020-MAY 27. RCM:2019-1920 and 2019-1922.

[20] Oguntimein, M. Human Factors Protocol Review for cantharidin (IND 131163). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 23. RCM No.: 2020-1795.

[21] Bhalodia, A. Human Factors Results Review Memorandum for cantharidin (NDA 212905). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAY 5. RCM No.: 2020-2756; 2019-1919; and 2019-1920.

[22] Song, Q. Type A Post Complete Response Action Meeting Minutes for cantharidin topical solution. Silver Spring (MD): FDA, CDER, OND, DDD (US); 2020 NOV 6. NDA 212905.

Human Factors Report for Trained Users
\\CDSESUB1\evsprod\nda212905\0044\m5\53-clin-stud-rep\535-rep-effic-safety-stud\molluscum-contagiosum\5354-other-stud-rep\verrica-vp102-0005\verrica-vp102-0005-report-body.pdf

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

- On February 16, 2021, we issued an Information Request (IR) to request the Applicant's justification for including all trained participants in their HF validation study. The Applicant responded on February 19, 2021. See response in link below:
    - \\CDSESUB1\evsprod\nda212905\0046\m1\us\111-information-amendment\quality-information-amendment-18-february-2021.pdf

APPENDIX F. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[23] along with postmarket medication error data, we reviewed the following cantharidin labels and labeling submitted by Verrica Pharmaceuticals, Inc.

- Single Tube Applicator label received on December 23, 2020
- Paperboard Sleeve label received on December 23, 2020
- 6 Count Applicator Configuration Carton labeling received on December 23, 2020
- 12 Count Applicator Configuration Carton labeling received on December 23, 2020
- Break Tool Carton label received on December 23, 2020
- Instructions for Use (Image not shown) received on December 23, 2020
    - EDR link: \\CDSESUB1\evsprod\nda212905\0044\m1\us\114-labeling\draft\labeling\11413-draft-labeling-text.pdf
- Prescribing Information (Image not shown) received on December 23, 2020
    - EDR link: \\CDSESUB1\evsprod\nda212905\0044\m1\us\114-labeling\draft\labeling\11413-draft-labeling-text.pdf

E.2 Label and Labeling Images

4 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

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/s/

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JASON A FLINT
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IRENE Z CHAN
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	September 9, 2021
To:	Qianyiren Song, PharmD Regulatory Project Manager **Division of Dermatology and Dentistry (DDD)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Patient Package Insert (PPI)
Drug Name (established name):	[VP-102] TRADENAME (cantharidin)
Dosage Form and Route:	topical solution
Application Type/Number:	NDA 212905
Applicant:	Verrica Pharmaceuticals Inc.

1 INTRODUCTION

On December 23, 2020, Verrica Pharmaceuticals Inc. re-submitted for the Agency's review an Original New Drug Application (NDA) 212905 for [VP-102] TRADENAME (cantharidin) topical solution, in response to the Agency's Complete Response (CR) Letter dated July 13, 2020. With this re-submission, the Applicant proposed the following indication for [VP-102] TRADENAME (cantharidin) topical solution: for the treatment of patients with molluscum contagiosum. On June 2, 2021, the Division of Dermatology and Dentistry (DDD) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for [VP-102] TRADENAME (cantharidin) topical solution.

This memorandum documents the DMPP review deferral of the Applicant's proposed PPI for [VP-102] TRADENAME (cantharidin) topical solution.

2 CONCLUSIONS

Due to outstanding deficiencies, DDD plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A comprehensive review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

SHARON R MILLS
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MEMORANDUM

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)

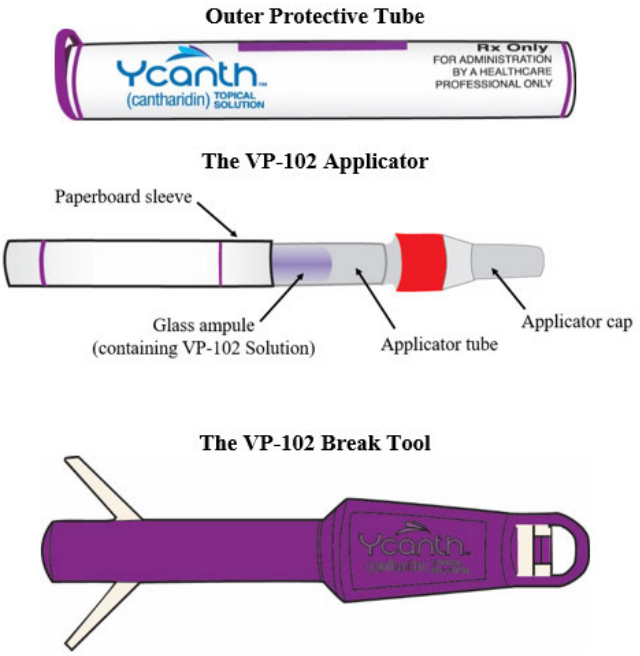
Date of This Memorandum:	May 5, 2021
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 212905
Product Name, Dosage Form, and Strength:	Cantharidin topical solution, 0.7%
FDA Received Date:	December 23, 2020
Applicant Name:	Verrica Pharmaceuticals
FDA Received Date:	December 23, 2020; February 19, 2021
OSE RCM #:	2020-2756; 2019-1919; 2019-1920
DMEPA Safety Evaluator:	Avani Bhalodia, PharmD, BCPS
DMEPA Team Leader (Acting):	Ebony Whaley, PharmD, BCPPS
DMEPA Associate Director for Human Factors (Acting):	Lolita White, PharmD
DMEPA Associate Director for Nomenclature and Labeling:	Mishale Mistry, PharmD, MPH

1 PURPOSE OF MEMORANDUM

This memorandum provides our preliminary evaluation of the human factors (HF) validation study results report for cantharidin, NDA 212905 submitted on December 23, 2020. This is a combination product with a proposed pre-filled topical applicator device constituent part that is intended for the treatment of molluscum contagiosum. This product is to be administered only by a healthcare professional via direct application to the skin lesion. Cantharidin may be administered to treatable lesions every 3 weeks (b) (4) Cantharidin topical solution is supplied in a sealed glass ampule contained within a single-use applicator and enclosed in a protective paperboard sleeve (see Figure 1 below). Each ampule of cantharidin contains approximately 0.45 mL of 0.7% (b) (4) solution. Cantharidin is supplied in a 6-count and

12-count carton containing 6 and 12 co-packaged applicators, respectively. Additionally, each carton of cantharidin contains (b) (4)

Figure 1. Cantharidin product components



2 REGULATORY HISTORY

- On September 19, 2019, Verrica Pharmaceuticals Inc. (Applicant) submitted their New Drug Application (NDA) that included a human factors validation study report. The Applicant conducted their HF validation study without seeking Agency feedback on the study methodology prior to conducting the study.[a]
- On February 26, 2020, we provided our preliminary comments to the Applicant in a mid-cycle discipline review letter that additional mitigation strategies may be needed to optimize applicator use along with other revisions to the product user interface taking into consideration our identified concerns.[b] On March 4, 2020, the Applicant responded to our concerns.[c]

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[a] Neall P. NDA 212905 Ycanth(Cantharidin) Human Factors Validation Study Report. \\CDSESUB1\evsprod\nda212905\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\molluscum-contagiosum\5354-other-stud-rep\verrica-vp102-0008\verrica-vp102-0008-report-body.pdf

[b] Song, Q. Mid-Cycle Discipline Review Letter. Submitted to DARRTS on February 26, 2020. https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af80543ddc&_afrRedirect=627132957944 0984

- On March 23, 2020, the Agency responded to the Applicant's March 4, 2020 submission indicating that that we still had concerns with the break force of the ampule and paperboard sleeve that could lead to accidental exposure to the users mouth or eye, and we provided additional comments outlining our continued concern.[d]
- On April 3, 2020, the Applicant provided a response including their justification for the break force of the ampule and paperboard sleeve.[e] The Applicant subsequently submitted an updated HF validation study protocol along with a comparative analyses and heuristic analysis on April 10, 2020. The Agency acknowledged the submission of the threshold and heuristic analysis was unsolicited. Furthermore, the Agency was still reviewing the information provided in previous submissions; therefore, we sent a withdrawal letter on April 24, 2020.[f]
- On July 13, 2020, the Agency sent the Applicant a Complete Response (CR) letter that included deficiencies in their HF validation study with noted use errors and difficulties with the critical task- 'Break the Ampule' and their heuristic analysis submitted on April 10, 2020 that indicated the average palmar pinch force (grip used to break an ampule) for adult females is 16 lbs. and that the average force to break the ampule with paperboard sleeve on is 19 lbs. From this information, the Applicant also concluded that the force to break the ampule could increase the potential for use errors. Based on these deficiencies, we indicated that we remained concerned that the Applicant's proposed combination product is not safe for use by HCPs. We also stated our concern that the risk of accidental exposure will outweigh the benefit of the treatment with this combination product. Inherent design issues exist with this product that may contribute to serious harm if accidental exposure occurs during use. Thus, we indicated that additional mitigation strategies were needed and could include the need for device design changes to optimize applicator use along with other revisions to the product user interface taking into consideration our previously identified concerns and the data collected from their HF validation study. After they implement additional risk mitigation strategies/modifications, we recommended they conduct an additional HF validation study to ensure that these modifications address the observed use errors and use difficulties and do not introduce any new risks. We recommended the Applicant submit

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[c] Response to February 26, 2020 Mid-Cycle Discipline Review Letter. \\cdsesub1\evsprod\nda212905\0017\m1\us\111-information-amendment\quality-information-amendment-04-march-2020.pdf

[d] Song, Q. Discipline Review Letter. Submitted to DARRTS on March 23, 2020. https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8054e00d&_afrRedirect=627152132744823 4

[e] Response to March 23, 2020 Discipline Review Letter. \\cdsesub1\evsprod\nda212905\0021\m1\us\111-information-amendment\quality-information-amendment-03-april-2020.pdf

[f] Killen, M. Human Factors Validation Study Protocol Withdrawal. Submitted to DARRTS on April 24, 2020. https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8055b828&_afrRedirect=7747798822403184 Chan, Irene Z. Human Factors (HF) Validation Study Protocol Incomplete Letter for IND 131163. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019-JAN 02. RCM No.: 2018-2769.

their revised HF validation study protocol for feedback from the Agency before commencing the study. Based on our comments, the Applicant created a break tool to be used to crush the ampule, revised the Instruction for use (IFU) to include information about the break tool, included information about when to remove the cap, what to look for when inspecting the ampule, and revised their URRA accordingly.

- On August 28, 2020, the Applicant submitted their revised HF validation study protocol, URRA and IFU under their IND 131163 for feedback from the Agency. We provided recommendations to the HF validation study protocol on October 23, 2020[g].
- On December 23, 2020, the Applicant submitted a HF validation study results report as part of the class 2 resubmission of NDA 212905 which is the subject of this review.

3 DISCUSSION AND CONCLUSION

We evaluated the HF validation study results report for cantharidin topical solution that the Applicant submitted as part of their response to the July 13, 2020 CR letter, and we identified concerns with the study methodology. Specifically, we note the HF validation study did not include untrained participants. We note that we reviewed the HF validation study protocol for the proposed product under IND 131163.[h] However, a revision was made to the study methodology, where all the study participants received individual, in-person training; this formal training was not originally included as part of our review of the previously submitted HF validation study protocol dated October 23, 2020.

It is unclear how the Applicant will ensure that every user of the proposed product will consistently and routinely receive training and whether such training program will continue to exist throughout the product's lifecycle on the market. Therefore, we find that the data obtained from the HF validation study is not representative of real-world use. This study methodology deficiency precludes our ability to assess whether the HF validation study demonstrates that the proposed combination product user interface supports safe and effective use by the intended users, for the product's intended uses and under the expected use conditions. Thus, based on the identified deficiency, we recommend that the Applicant submit a supplemental HF study with 15 untrained HCP participants. Additionally, we noted that despite all participants receiving training, use errors occurred with critical tasks. As such, we recommend Applicant consider whether additional modifications to the user interface are necessary to address the observed use errors in the HF validation study, prior to conducting the supplemental study with untrained participants. We have provided letter ready comments for the division to incorporate as part of their communication to the Applicant (*see Section 4*).

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[g] Oguntimein, M. Human Factors Protocol Review for cantharidin IND 131163. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 23. RCM No.: 2020-1795.

[h] Oguntimein, M. Human Factors Protocol Review for cantharidin IND 131163. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 23. RCM No.: 2020-1795.

4 RECOMMENDATIONS FOR VERRICA PHARMACEUTICALS

Our review of your human factors (HF) validation study results report for your NDA 212905 cantharidin topical solution identified a deficiency in your study methodology. Specifically, we note your HF validation study did not include a user group of 15 untrained healthcare provider (HCP) participants. This deficiency precludes the Agency's ability to assess whether the HF validation study demonstrated that the proposed combination product user interface supports safe and effective use by the intended users, for the product's intended uses and under the expected use conditions.

Therefore, we recommend you submit a supplemental HF validation study with 15 untrained HCP participants to address the deficiency listed below. We have also provided comments for your consideration as you conduct your supplemental study.

Additionally, we note that despite all participants receiving training, use errors occurred with critical tasks. As such, we recommend you consider whether additional modifications to your user interface are necessary to address the observed use errors in your HF validation study, prior to conducting your supplemental study with untrained participants.

HF validation study methodology deficiency

1) Your HF validation study included all trained participants. We note the participant training reviewed all sections of the instructions for use (IFU) and included an introduction to cantharidin, a demonstration by the trainer, and hand-on practice with coaching from the trainer. We note a revision was made to the study methodology in the previously submitted HF validation study protocol, where all the study participants received individual, in-person training; this formal training was not originally included as part of our review of the previously submitted HF validation study protocol dated October 23, 2020.

   In response to the Agency's February 16, 2021 Information Request which requested justification for including all trained participants, you indicated that you intend to deploy the training program that was implemented in the HF validation study to train real-world users prior to product use. However, it is unclear how you will ensure that every user will consistently and routinely receive training and whether such a training program will continue to exist throughout the product's lifecycle on the market. We are concerned with understanding how users who do not receive training may perform when relying on the proposed user interface of the proposed product. Therefore, we find that the data obtained from your HF validation study is not representative of real-world use. As such, we recommend you conduct a supplemental HF validation study with 15 untrained healthcare professionals (HCPs) as a distinct user group.

Consider the following as you conduct your supplemental study with 15 untrained HCPs.

2) Your instructions for use (IFU) state that users should "gently tap the capped end of the VP-102 Applicator on a horizontal surface for approximately 10 seconds or until the VP-102 Solution has collected at the bottom of the applicator tube." However, in your

results report, the success criterion for the task "tap to move solution" in Table 9 Critical Tasks does not state that the user should gently tap the capped end of the applicator on a horizontal surface for approximately 10 seconds or until the solution has collected at the bottom of the applicator tube. As such, we are concerned that you have not clearly stated the success criterion for the "tap to move solution" task. This lack of clarity may confuse the study personnel during the data collection process of the use scenario of your study. Revise the success criterion for the task "tap to move solution" in table 9 critical tasks of your results report to indicate that the user must gently tap the capped end of the applicator on a horizontal surface for approximately 10 seconds or until the solution has collected at the bottom of the applicator tube, as stated in your IFU.

3) You propose to (b) (4)

4) Your HF validation study included simulated-use and knowledge task questions. Your results report indicates that root cause analysis (RCA) was conducted after the knowledge task questions only. We are concerned that conducting an RCA only after the knowledge task questions may lead to recency bias. For example, the responses in the RCA for the simulated-use tasks may be biased by the recency of the knowledge task questions rather than conducting the RCA directly after the simulated-use tasks. Revise your study protocol to conduct an RCA after the simulated-use tasks and after the knowledge task questions.

5) You propose to supply your product in a 6-count and 12-count carton containing 6 and 12 co-packaged applicators, respectively. Additionally, each carton will contain (b) (4) We note in your risk mitigation effectiveness column in your results report for use error when "user does not know how to order additional break tools, so breaks the ampule by hand or with another tool", "*one participant stated they would obtain another break tool from a carton in their facility inventory. If another break tool was not available, the participant indicated that they could break the ampule manually.*" We also note that based on your URRA, if a user breaks the ampule by hand or with another tool, there is a risk that toxic solution gets in a patient's or user's open wound resulting in pain, burning, and increased risk of systemic exposure. We acknowledge that applicators were presented in a 6-count carton in the HF validation study. Given the subjective feedback from the study, consider co-packaging additional break tools in both 6-count and 12-count cartons.

6) Based on your URRA, if user does not inspect the applicator or attempts to use a damaged applicator with broken ampule, there is a risk that user or patient may be exposed to solution in location other than intended resulting in unintended blistering. We note in your risk mitigation effectiveness column for use error when "user does not

Inspect applicator and attempts to use a damaged applicator – broken ampule", you state, that gloves and eye protection are a mitigation to protect users from potential exposure resulting in unintended blistering in the event that the drug solution would leak into the tip/cap prior to cap removal. However, we find gloves and eye protection may not protect other parts of the face. Consider implementing additional mitigation strategies to protect other parts of healthy skin from accidental exposure.

APPENDIX A. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT AND LABELING

The HF study results can be accessible in EDR via:
\\CDSESUB1\evsprod\nda212905\0044\m5\53-clin-stud-rep\535-rep-effic-safety-stud\molluscum-contagiosum\5354-other-stud-rep\verrica-vp102-0005\verrica-vp102-0005-report-body.pdf

Draft labeling can be accessible in EDR via:

\\CDSESUB1\evsprod\nda212905\0044\m1\us\114-labeling\draft\labeling\11413-draft-labeling-text.pdf

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LOLITA G WHITE
05/05/2021 02:05:03 PM

MISHALE P MISTRY
05/06/2021 12:59:37 PM

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)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 27, 2020
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	NDA 212905
Product Name, Dosage Form, and Strength:	Ycanth (cantharidin) topical solution, 0.7%
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Verrica Pharmaceuticals
FDA Received Date:	September 13, 2019; March 4, 2020; April 3, 2020; April 10, 2020
OSE RCM #:	2019-1920 and 2019-1922
DMEPA Safety Evaluator:	James Schlick, MBA, RPh
DMEPA Team Leader:	Millie Shah, PharmD, BCPS
Associate Director for Human Factors:	Quynh Nhu Nguyen, MS
DMEPA Deputy Director:	Irene Chan, PharmD, BCPS

1 REASON FOR REVIEW

We reviewed the human factors (HF) validation study report and proposed labels and labeling submitted under NDA 212905 for Ycanth (cantharidin) topical solution. This is a combination product with a proposed pre-filled topical applicator device constituent part for the treatment of molluscum contagiosum.

2 PRODUCT DESCRIPTION

The Ycanth applicator is a hand-held mechanical device for drug delivery, and is a single use applicator system comprised of multiple components allowing the Ycanth solution to be administered to the skin. It contains an ampule inside plastic housing and a paperboard sleeve. The ampule must be broken before the applicator can be used to apply the solution to the skin. The Ycanth applicator is intended for use by a healthcare professional since the solution is flammable and can be toxic when ingested, especially in young children. See Appendix A.1 for more information on the applicator device.

3 REGULATORY HISTORY

The sponsor conducted their human factors (HF) validation study without seeking Agency feedback on the study methodology prior to conducting the study.

4 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
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Sponsor's Responses to Discipline Review Letters	F
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

5 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The sections below provide a summary of the use-related risk analysis (URRA), HF study design, errors/close calls/use difficulties observed with critical and non-critical tasks (Table 3, Section 5.3 and Section 5.4), and our analysis to determine if the proposed user interface supports the safe and effective use of the proposed product.

5.1 URRA REVIEW

After reviewing the URRA, we note that the sponsor did not evaluate the risk of incorrect timing of cap removal. If the user removes the cap before the appropriate time noted in the IFU, the user or patient could be at increased risk for accidental exposure to the solution during the task of breaking the ampule since the removal of the cap provides a pathway for the drug to be released from the tip of the applicator if excessive force is applied to break the ampule. We note that Participant 10 (See Table 3, Section 5.4) removed the cap before breaking the ampule and confusion with the timing of cap removal was noted by participants P3 and P4 during the post-test interview. Thus, the URRA should be updated to include the assessment of this risk .

5.2 SUMMARY OF STUDY DESIGN

The sponsor conducted their HF validation study without seeking Agency feedback on the study methodology prior to conducting the study.

We reviewed the HF validation study methodology and found that the sponsor did not test two important warning statements (flammable liquid and highly toxic) with knowledge task questions. Additionally, we disagree with the risk categorization of some non-critical tasks. See Table 3 and Section 5.3 for additional information on the non-critical tasks that should be categorized as critical. Table 2 provides a summary of the study design.

Table 2. Study Methodology for Human Factors (HF) Validation Study

Study Design Elements	Details
Participants	15 healthcare professionals consisting of medical doctors, nurse practitioners, registered nurses, and licensed practical nurses
Training	No training was provided to participants. The product and IFU were made available to participants to use as they normally would.
Test Environment	Simulated clinical office setting

5.3 ANALYSIS OF NON-CRITICAL TASKS

We acknowledge that there were use-related issues (e.g. use errors, close calls, or use difficulties) on non-critical tasks (e.g. did not inspect applicator, improper use of paperboard sleeve, testing applicator prior to use, applying drug, and allowing drug solution to dry), submitted in the HF study results report. Although the sponsor considered them non-critical tasks, we do not agree with the sponsor's categorization of some of the non-critical tasks. Given that the sponsor indicated in their use-related risk analysis (URRA) that serious harm could occur to the user as an outcome (e.g. glass cuts user and blistering of patient's skin), these tasks should be categorized as critical tasks.[a] See Table 3 in Section 5.4 for the non-critical tasks that should be categorized as critical tasks.

5.4 RESULTS AND ANALYSES

TABLE 3: SUMMARY AND ANALYSES OF ERRORS/CLOSE CALLS/USE DIFFICULTIES OBSERVED WITH CRITICAL TASKS

Tasks	Number of Failures/Use Errors, Close Calls and Use Difficulties	Description of Failures/Use Errors, Close Calls and Use Difficulties	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Break Ampule	**Use Error – 1** P10 **Difficulty – 3** P1,P4,P11	**Use Error** The participant (P10) attempted to apply the placebo drug solution to the target lesions without breaking the glass ampule. When the participant couldn't expel	**Use Error** P10- **Lack of training** - Participant P10 did not read the use step instructions	No Discussion. Per Section 1.5 *'Conclusion and Summary Test Findings'*- Applicator has been found to be reasonably safe	We acknowledge all participants were able to break the ampule despite several participants having difficulty breaking the ampule. We also note that no accidental exposure occurred in the study.

[a] *Applying Human Factors and Usability Engineering to Medical Devices.* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

		the solution from the applicator, the paperboard sleeve was removed. When still unsuccessful dispensing the placebo drug, the participant went to test the applicator on the mayo stand and broke the glass ampule after squeezing the applicator tube with both hands. The participant had previously removed the paperboard sleeve and cap before breaking the ampule. The applicator tip was facing downward (incorrect orientation) above a paper towel on the mayo stand. Harm to the patient or user did not result from these actions and the potential for harm would be of minor severity **<u>Difficulty</u>** Participant P01 had difficulty generating	provided in the IFU. **<u>Difficulty</u>** P1 – **Applicator design** - the force required to break the glass ampule through the plastic of the applicator tube as well as the paperboard sleeve is higher than the participant can generate with one hand. P4- **Applicator design** - the force required to break the glass ampule through the plastic of the applicator tube as	and effective for the intended users, use and use environments. The methods and results described in the proceeding sections support this conclusion.	Yet, the use errors and difficulties related to breaking the ampule indicate that the design of the applicator is not fully optimized. We conferred with the Office of Pharmaceutical Quality (OPQ) about the force required to break the ampule with the paperboard sleeve in place. OPQ noted that the force required was 21 +/- 3lbs of force. The sponsor noted in their heuristic analysis of the device that the average force to break the ampule with paperboard sleeve on was 19 lbs. The sponsor's heuristic analysis also indicated that the average palmar pinch force (grip used to break an ampule) for adult females is 16 lbs. The sponsor concluded that *"there is a potential that users will struggle to break the glass ampule due to the amount of force*

		enough force to break the glass ampule and required two hands and several attempts to break the glass ampule. Participant P04 had difficulty generating enough force to break the glass ampule and required two hands to break the ampule. As such, the participant held the applicator horizontally instead of upright to accommodate the grip required to break the glass ampule. Participant P11 attempted to apply the placebo drug solution to the target lesions without breaking the glass ampule or removing the paperboard sleeve. When unsuccessful in dispensing the placebo drug solution the participant replaced	well as the paperboard sleeve is high enough to require Participant P04 to alter their grip on the applicator in order to produce the force required. P11- **Lack of training** - Participant P11 did not read the use step instructions provided in the IFU.		*required. There is risk that some users may remove the paperboard sleeve in order to try and break the glass ampule. There is also potential for users to utilize other means to break the ampule if they are unable to generate enough force with their hands."* (See Appendix F) We note that some users in the HF validation study altered the upright orientation of the device, which is inconsistent with the instructions in the IFU, due to difficulty with breaking the ampule and oriented the device with the cap removed downward (P1) or horizontally (P4). We are concerned that difficulty with breaking the ampule can lead to users changing the orientation of the applicator and applying excessive force to break the ampule. Coupled with premature cap removal,

		the cap, shook the applicator back and forth, slid the paperboard sleeve down halfway, broke the top of the glass ampule, slid the paperboard sleeve back on the applicator and continued with applying the placebo drug solution. Harm to the patient or user did not result from these actions and the potential for harm would be of minor severity.			this can lead to solution being released onto the HCP or patient resulting in accidental exposure. The severity of harm if cantharidin gets on the skin or mucosal surfaces (eyes and mouth) is blistering, which we consider serious harm. We also note postmarketing cases with a similar product, Eskata, that led to accidental exposure in HCPs and patients during use of the product due to the liquid unexpectedly squirting into the eyes or skin of the HCP or patient. Thus, we do not agree with the sponsor's conclusion that the product is reasonably safe and effective for use and find the residual risk unacceptable. We provide comments to the sponsor in Section 7 to address this issue.

Remove Paperboard Sleeve and Inspect Applicator* (Do not use a broken applicator as a broken ampule glass can cut user and/or lead to accidental exposure of a toxic drug that can blister the skin) *This task should be labeled as a critical task as it can cause harm to the user based on the URRA.	**Use Error – 2** P8 and P11	Users did not inspect the applicator or glass ampule by removing the paperboard sleeve.	Users did not read the IFU.	No Discussion. Per Section 1.5 '*Conclusion and Summary Test Findings'*- Applicator has been found to be reasonably safe and effective for the intended users, use and use environments. The methods and results described in the proceeding sections support this conclusion.	We note that Participant 8 provided subjective feedback that they didn't notice sub steps 1 of the IFU. There are multiple steps in Step 1 related to the paperboard sleeve. Having sub steps in Step 1 may have contributed to overlooking or not reading this step. Revisions to the IFU could improve the relevance and importance of these sub steps. Thus, we disagree that no mitigation strategies are needed for this task. Given potential for user harm as noted in the URRA, we find the residual risk unacceptable. See Section 7 for our recommendation to the sponsor.
					(b) (4)

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(b) (4)

the URRA.					
Apply Drug to Target Lesions* If excessive solution is dispensed, the solution can spread to healthy skin leading to blistering of skin adjacent to the lesion.	**Difficulties – 2** P2, P11	• P02 continued to crush the glass ampule along the length of the applicator tube and shook the applicator in order to encourage drug flow. • P11 experienced difficulty since the paperboard sleeve had not been removed from the applicator and increased the force	No information for P2, P11 use error	No Discussion. Per Section 1.5 '*Conclusion and Summary Test Findings'*- Applicator has been found to be reasonably safe and effective for the intended users, use and use environments. The methods and results described in the proceeding	P11 experienced difficulty applying the solution due to the extra force required with the paperboard sleeve on, which might have been unexpected from this user. Thus, we disagree that no mitigation strategies are needed for this task as users should be provided information about the force needed to squeeze the tube to expel the drug. Given the potential for user harm as noted in the URRA, we find

*This task should be labeled as a critical task as it can cause harm to the user or patient based on the URRA.		required to squeeze the tube to expel the drug solution.		sections support this conclusion.	the residual risk unacceptable. See Section 7 for our recommendation to the sponsor.
Allow Solution to Dry* If the HCP does not allow enough time for the solution dry after the application of the drug, accidental exposure to others if they touch affected area could lead to	**Use Error- 1** P14	• Participant P14 did not mention that the drug solution must be checked that it is dry prior to releasing the patient after treatment. The participant had not read that step in the IFU.	Participant did not read that part of the IFU.	No Discussion. Per Section 1.5 '*Conclusion and Summary Test Findings'*- Applicator has been found to be reasonably safe and effective for the intended users, use and use environments. The methods and results described in the proceeding sections support this conclusion.	We note that P14 did not read that part of the IFU (Step 6). Based on the root cause analysis, it is unclear why the participant did not read this step in the IFU. We reviewed Step 6 'Complete Treatment' and note it contains several pieces of important information that is arranged in paragraph format making the text dense, which may have contributed to P14 not reading the step. This step in the IFU could be revised to bring more prominence to this information. Given potential for user harm as noted in the URRA, we find

blistering of the skin. *This task should be labeled as a critical task as it can cause harm to the user based on the URRA.					the residual risk unacceptable. See Section 7 for our recommendation to the sponsor.

5.5 INTERACTIONS WITH THE SPONSOR DURING THE REVIEW CYCLE AND EVALUATION OF ADDITIONAL INFORMATION

We provided our preliminary analysis to the sponsor in a Mid-Cycle Discipline Review letter that additional mitigation strategies may be needed to optimize applicator use along with other revisions to the product user interface taking into consideration our identified concerns.[b] The sponsor responded to our concerns on March 4, 2020.[c] We still had concerns with the break force of the ampule and paperboard sleeve that could lead to accidental exposure to the users mouth or eye, and we provided additional comments outlining our continued concern.[d] The sponsor provided a response on April 3, 2020 including their justification for the break force of the ampule and paperboard sleeve.[e]

The sponsor subsequently submitted an updated HF validation study protocol along with a comparative analyses and heuristic analysis on April 10, 2020.[f] We acknowledge the submission of the threshold and heuristic analysis was unsolicited. Furthermore, we were still reviewing the information provided in previous submissions and that the acceptability of the justification may impact the final product user interface. Therefore, we sent a withdrawal letter on April 24, 2020.[g]

Our review of the heuristic analysis determined that the average palmar pinch force (grip used to break an ampule) for adult females is 16 lbs. and that the average force to break the ampule with paperboard sleeve on is 19 lbs. As such, the sponsor concluded that the force to break the ampule could increase the potential for use errors - *"there is a potential that users will struggle to break the glass ampule due to the amount of force required. There is risk that some users may remove the paperboard sleeve in order to try and break the glass ampule. There is also potential for users to utilize other means to break the ampule if they are unable to generate enough force with their hands."* We align with the sponsor's conclusion and therefore, we determined that additional considerations should be explored with regards to matching the

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[b] Song, Q. Mid-Cycle Discipline Review Letter. Submitted to DARRTS on February 26, 2020. https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af80543ddc&_afrRedirect=627132957944 0984

[c] Response to February 26, 2020 Mid-Cycle Discipline Review Letter. \\cdsesub1\evsprod\nda212905\0017\m1\us\111-information-amendment\quality-information-amendment-04-march-2020.pdf

[d] Song, Q. Discipline Review Letter. Submitted to DARRTS on March 23, 2020. https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8054e00d&_afrRedirect=627152132744 8234

[e] Response to March 23, 2020 Discipline Review Letter. \\cdsesub1\evsprod\nda212905\0021\m1\us\111-information-amendment\quality-information-amendment-03-april-2020.pdf

[f] See Appendix C.4 for link to April 10, 2020 submission

[g] Killen, M. Human Factors Validation Study Protocol Withdrawal. Submitted to DARRTS on April 24, 2020. https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8055b828&_afrRedirect=774779882240 3184[h] Chan, Irene Z. Human Factors (HF) Validation Study Protocol Incomplete Letter for IND 131163. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019-JAN 02. RCM No.: 2018-2769.

product design specification with the intended users' capability to generate the force to break the ampules. Additionally, if the sponsor proceeds with the modified design, additional data from a human factors validation study should be submitted to demonstrate that intended users can perform this critical task safely and effectively.

Furthermore, we reviewed the sponsor's threshold/comparative analyses with Eskata and Levualn Kerastick; products similar to the proposed product in this review. We determined that the Levulan Kerastick has a different user interface than the sponsor's proposed product because the Levulan Kerastick includes the Kerastick Krusher device as a means of breaking the ampule prior to administration. This difference may impact the performance of critical task of breaking the ampule.

With respect to the comparative analyses to the Eskata product, we note postmarketing medication error cases that report accidental exposure to patient and health care professionals when using the product. Given some similar design attributes with the proposed product, we are concerned that accidental exposure can occur with toxic cantharidin topical solution. As such, we plan to convey the above determation to the sponsor and encourage the sponsor to submit a revised protocol to the IND for review.

5.6 LABELS AND LABELING

We defer review of the labels and labeling until the next review cycle as portions of the product user interface (e.g. IFU, container label, carton labeling, prescribing information) need to be updated to promote the safe and effective use of the product.

6 CONCLUSION

We determined that the user interface of the proposed product does not support the safe and effective use of this product for intended users, uses and use environments. The HF validation study results identified several use errors and use difficulties with critical tasks. Based on the study participants' subjective feedback and the sponsor's root cause analyses, we recommend that the sponsor implement these revisions to the user interface, including device design and the IFU, along with any additional mitigations that the sponsor determines necessary to address these use-related issues, and then conduct and submit results of another human factors validation study to demonstrate that the mitigations are effective and do not introduce new risks.

7 RECOMMENDATIONS FOR THE SPONSOR

As we previously communicated, our review of the human factors (HF) validation study data noted use errors and difficulties observed with the critical task- 'Break the Ampule'. We note one use error and three difficulties with this critical task. The error occurred when the user removed the cap and paperboard sleeve, tipped the applicator upside down and broke the ampule with two hands. Additionally, three other users had difficulty breaking the ampule, which required two hands to break. Of these three use difficulties, one user also tilted the applicator horizontally. Based on your use-related risk analysis (URRA), this task is considered critical because premature cap removal and incorrect applicator orientation can lead to

accidental exposure to the patient or healthcare provider's (HCP's) mouth or eyes leading to serious harm. Despite the use error and difficulties, you did not propose any additional mitigation strategies to address the use issues (e.g., reducing the force required to break the ampule).

We note your heuristic analysis submitted on April 10, 2020 indicates that the average palmar pinch force (grip used to break an ampule) for adult females is 16 lbs. and that the average force to break the ampule with paperboard sleeve on is 19 lbs. From this information you concluded that the force to break the ampule could increase the potential for use errors - *"there is a potential that users will struggle to break the glass ampule due to the amount of force required. There is risk that some users may remove the paperboard sleeve in order to try and break the glass ampule. There is also potential for users to utilize other means to break the ampule if they are unable to generate enough force with their hands."*

We also reviewed your April 10, 2020 threshold/comparative analyses with Eskata and Levualn Kerastick; products with some similarities to the proposed product in this review. We determined that the Levulan Kerastick has a different user interface than your proposed product because the Levulan Kerastick includes the Kerastick Krusher device as a means of breaking the ampule prior to administration. This difference may impact performance of the critical task of breaking the ampule. Furthermore, with respect to the comparative analyses to the Eskata product, we note postmarketing medication error cases that report accidental exposure to patient and health care professionals when using the product. Given some of the similar design attributes with your proposed product, we are concerned that accidental exposure can occur with toxic cantharidin topical solution, which presents a different risk. As such, we have determined that a leveraging approach for your proposed product is not appropriate and the residual risk with your product is unacceptable.

In summary, we remain concerned that your proposed cantharidin combination product is not safe and effective for use by health care providers (HCPs). We are concerned the risk for accidental exposure will outweigh the benefit of the treatment with this combination product. Inherent design issues exist with this product that may contribute to serious harm if accidental exposure occurs during use. Thus, additional mitigation strategies are needed and could include the need for device design changes to optimize applicator use along with other revisions to the product user interface taking into consideration our previously identified concerns and the data collected from your HF validation study. After you implement additional risk mitigation strategies/modifications, we recommend you conduct an additional HF validation study to ensure that these modifications do, in fact, address the observed use errors and use difficulties and do not introduce any new risks.

We recommend you submit your revised HF validation study protocol for feedback from the Agency before commencing your study. Please note we will need 60 days to review and provide comments on the HF validation study protocol. Plan your development program timeline accordingly.

As you further develop your proposed product and prepare your next human factors study protocol to address the above concerns, we have the following additional recommendations:

a. You indicated in your comparative analysis submitted on April 10, 2020 that the Levulan Kerastick product is similar to your proposed product. We note the Kerastick Krusher device has a means of breaking the ampule prior to administration that differs from your product. The design of the Levulan Kerastick product may inform how you address the break force issues identified during your human factors product development.

b. We noted use errors, difficulties, and subjective feedback indicating concerns with the readability of the IFU, but you have not proposed additional risk mitigation strategies to address the use errors and difficulties. Thus, we recommend additional mitigation strategies to address these use errors and difficulties as part of the overall changes to the user interface.

c. We disagree with your characterization of some tasks as non-critical. Tasks that could cause harm to users, as noted in your URRA, should be noted as critical tasks (e.g. Inspect Applicator; (b) (4) Apply Solution; and Allow Solution to Dry). Additionally, we note that the task 'Remove Cap' in your URRA does not assess the risk of incorrect timing of cap removal, which can increase the risk of accidental exposure. Because of the potential for causing harm to the user or patient, these tasks should be re-categorized as critical tasks in your updated URRA.

8 APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for Ycanth received on September 13, 2019 from Verrica Pharmaceuticals.

Table 5. Relevant Product Information for Ycanth	
Initial Approval Date	N/A
Active Ingredient	cantharidin
Indication	Treatment of molluscum contagiosum
Route of Administration	topical
Dosage Form	topical solution
Strength	0.7%
Dose and Frequency	This product is to be administered only by a healthcare professional via direct application to the skin lesion. No more than two (2) applicators should be used during a single treatment session. Cantharidin may be administered to treatable lesions every 3 weeks (b) (4)
How Supplied/ Container Closure	Cantharidin topical solution is supplied in a sealed glass ampule contained within a single-use applicator and enclosed in a protective paperboard sleeve. Each ampule of cantharidin contains 450 µL of 0.7% (b) (4) solution. The applicators are packaged in cartons containing 6 or 12 applicators per carton.
Storage	Room temperature

A.1

Figure 1 - VP-102 Applicator

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 30, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, Cantharidin, VP-102, and IND 131163. Our search identified two previous interactions with the Applicant.[h,i]

APPENDIX C. HUMAN FACTORS STUDY RESULTS AND APRIL 10, 2020 THRESHOLD ANALYSIS, HEURISTIC ANALYSIS, AND HF PROTOCOL SUBMISSION

C.1

Table 6. Study Methodology for Human Factors (HF) Validation Study	
Study Design Elements	**Details**
Participants	15 healthcare professionals consisting of medical doctors, nurse practitioner, registered nurses, and licensed practical nurses
Training	No training was provided to participants. The product and IFU were made available to participants to use as they normally would.
Test Environment	Simulated clinical office setting
Methods	During each use evaluation, the participant engaged in one representative use scenario and a post-scenario interview. Use scenarios generated in the protocol were tailored to ensure a natural workflow representative of the end-user's environment. If a use error occurred during a scenario, HF personnel questioned the participant after the scenario was complete in order to gain insight on the root-cause of the error. There were no knowledge task assessments to test users understanding of the warnings in the user interface.

C.2 Non-Critical Tasks Categorized by Sponsor That Should be Categorized as a Critical Task Because the Tasks Can Cause Harm Based on the URRA if Done Incorrectly

1. Inspect Applicator
2. (b) (4)

[h] Chan, Irene Z. Human Factors (HF) Validation Study Protocol Incomplete Letter for IND 131163. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019-JAN 02. RCM No.: 2018-2769.

[i] Chan, Irene Z. Human Factors (HF) Validation Study Protocol Incomplete Letter for IND 131163. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019-JUN 07. RCM No.: 2019-1109.

3. Remove Cap
(b) (4)
5. Apply Solution
6. Allow Solution to Dry

C.3 Study Design and Results

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C.4 April 10, 2020 Submission Links

Threshold Analysis:

\\cdsesub1\evsprod\nda212905\0022\m5\53-clin-stud-rep\535-rep-effic-safety-stud\molluscum-contagiosum\5354-other-stud-rep\verrica-vp102-0002\verrica-vp102-0002-report-body.pdf

Heuristic Analysis:

\\cdsesub1\evsprod\nda212905\0022\m5\53-clin-stud-rep\535-rep-effic-safety-stud\molluscum-contagiosum\5354-other-stud-rep\verrica-vp102-0001\verrica-vp102-0001-report-body.pdf

HF Validation Study Protocol:

\\cdsesub1\evsprod\nda212905\0022\m5\53-clin-stud-rep\535-rep-effic-safety-stud\molluscum-contagiosum\5354-other-stud-rep\verrica-vp102-0005\verrica-vp102-0005-report-body.pdf

APPENDIX D. ISMP NEWSLETTERS – N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) – N/A

APPENDIX F. SPONSOR'S RESPONSES TO DISCIPLINE REVIEW LETTERS

Sponsor's Response to February 26, 2020 Mid-Cycle Discipline Review Letter; Submitted on March 4, 2020:
\\cdsesub1\evsprod\nda212905\0017\m1\us\111-information-amendment\quality-information-amendment-04-march-2020.pdf

Sponsor's Response to March 23, 2020 Discipline Review Letter; Submitted on April 3, 2020:
\\cdsesub1\evsprod\nda212905\0021\m1\us\111-information-amendment\quality-information-amendment-03-april-2020.pdf

APPENDIX G. LABELS AND LABELING

G.1 List of Submitted Labels and Labeling

- Container label received on September 13, 2019
- Carton labeling received on September 13, 2019
- Prescribing Information and Instructions for Use received on September 13, 2019
    - \\cdsesub1\evsprod\nda212905\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text-pdf.pdf

G.2 Label and Labeling Images

Container Label

(b) (4)

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/s/

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QUYNHNHU T NGUYEN
05/27/2020 05:39:25 PM

IRENE Z CHAN
05/28/2020 08:28:13 AM

Clinical Inspection Summary

Date	05/14/2020
From	Jenn Sellers, M.D., Ph.D., Medical Officer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Qianyiren Song, Pharm.D., Regulatory Project Manager Maryjoy Meija, M.D., Clinical Reviewer Snezana Trajkovic, M.D., Clinical Team Leader Division of Dermatology and Dentistry (DDD)
NDA #	212905
Applicant	Verrica Pharmaceuticals Inc.
Drug	Cantharidin
NME	No
Therapeutic Classification	Dermatological Agent: A Natural Toxin
Proposed Indication	Treatment of Molluscum Contagiosum
Consultation Request Date	12/20/2019
Summary Goal Date	05/25/2020
Action Goal Date	06/29/2020
PDUFA Date	07/13/2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMEBLATIONS

The clinical sites of Drs. Katz and Ashley were inspected in support of this NDA. Based on the results of these inspections, the study (Protocols VP-102-101) appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

The clinical sites of Drs. Elosegui (Site 031, Florida) and Howard (Site 027, Kentucky), both for Protocol VP-102-102, were also initially selected for inspection. However, at the current time, the COVID-19 global pandemic has significantly limited our ability to conduct on-site GCP inspections. As a result, and in an effort to protect the health, safety, and welfare of FDA employees and study staff, the need for these planned inspections in support of NDA 212905 was reevaluated. Following discussion between OSI and DDD, a decision was made that assessment of the application could proceed without inspections of Drs. Elosegui and Howard. Since the completed inspections only covered Protocol VP-102-101, at this time OSI will be unable to determine if Protocol VP-102-102 was conducted adequately and whether the study data are reliable in support of the proposed indication

II. BACKGROUND

Verrica Pharmaceuticals Inc submitted this NDA 212905 to support the use of cantharidin for the treatment of molluscum contagiosum.

Clinical inspections were conducted for Protocol VP-102-101. The following is the brief description of the protocol. It should be noted that Protocol VP-102-101 and the other pivotal study, Protocol VP-102-102, were identical.

Protocol VP-102-101

Title: "A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Pivotal Study to Evaluate the Safety and Efficacy of VP-102 Topical Film-Forming Solution [0.7% (w/v) Cantharidin] in Subjects (2 years and older) with Molluscum Contagiosum"

The primary study objective was to determine the efficacy of dermal application of VP-102 relative to placebo, when applied once every 21 days for up to 4 applications, to treat molluscum lesions in subjects ≥2 years of age by assessing the proportion of subjects achieving complete clearance of all treatable molluscum lesions (baseline and new) on the Day 84 visit.

The primary efficacy endpoint was the proportion of subjects exhibiting complete clearance of all treatable molluscum lesions (baseline and new) on the Day 84 visit (End of Study, EOS).

Rationale for Site Selection

The clinical investigator (CI) sites were selected for inspection due to large enrollment, treatment effect size, protocol deviations, and prior inspection histories.

III. RESULTS

1. **Scott L. Katz, M.D.**
   Site #009
   4001 W 15th St Ste 350
   Plano, TX 75093-5863
   Inspection dates: 02/18/2020 - 02/20/2020

At this site for Protocol VP-102-101, a total of 29 subjects were screened and enrolled, and 27 subjects completed the study. The two discontinuations consisted of one subject withdrawing consent due to parents not seeing treatment effect (Subject (b) (6) in placebo group), and the other subject withdrawing due to an adverse event (Subject (b) (6) in VP-102 treatment group, abscess caused by staphylococcus aureus in the area where molluscum lesions were present), which was reported.

The study records for all 29 enrolled subjects were reviewed. These records included, but were not limited to, informed consent; eligibility; molluscum history and previous treatment; study drug application; physical exams including vitals, lesion counts and dermatologic examinations; efficacy endpoint data; Safety Evaluation of Response to Treatment (SERT) for 24-hour, 7 day, and 14 day follow up; adverse events/serious adverse events; pregnancy test (where applicable); concomitant medications; subject disposition; and protocol deviations. The FDA investigator confirmed that the blinded assessors were trained for their roles and they did not perform any duties that would unblind the treatment.

The primary efficacy endpoint data were verified against the data line listings provided by the sponsor; no discrepancies were noted. There was no evidence of underreporting of adverse events.

2. **Claude T. Ashley, Jr., M.D., Ph.D.**
   Site #003
   364 Honeysuckle Rd
   Dothan AL 36305-1140
   Inspection dates: 03/16/2020 - 03/18/2020

At this site for Protocol VP-102-101, 46 subjects were screened and enrolled, and 43 subjects completed the study. Three subjects withdrew consent due to "personal reasons."

The inspection reviewed the informed consent forms (ICFs) for all 46 screened subjects, the primary efficacy endpoint and adverse events for 20 enrolled subjects, and all study records for 16 enrolled subjects. The study records included, but were not limited to, Independent Review Board (IRB) approvals, training records, delegation of authority logs, financial disclosures, drug accountability, randomization scheme, study eligibility criteria, medical histories, physical examinations, progress notes, concomitant medications, the primary efficacy endpoint data, adverse event reporting, monitoring reports, and protocol deviations.

The primary efficacy endpoint data were verified against the data line listings provided by the sponsor; no discrepancies were noted. There was no evidence of underreporting of adverse events.

{See appended electronic signature page}

Jenn W. Sellers, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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CONCURRENCE:

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Phillip Kronstein, M.D.
Team Leader
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Kassa Ayalew, M.D., M.P.H
Branch Chief
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cc:
Central Doc. Rm. NDA 212905
DDD /Project Manager/Qianyiren Song
DDD/Medical Officer/Maryjoy Meija
DDD/Clinical Team Leader/Snezana Trajkovic
OSI/Office Director/David Burrow
OSI/Deputy Office Director/Laurie Muldowney
OSI/DCCE/Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Jenn Sellers
OSI/GCP Program Analyst/Yolanda Patague

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/s/

JENN W SELLERS
05/14/2020 04:21:03 PM

PHILLIP D KRONSTEIN
05/14/2020 04:27:44 PM

KASSA AYALEW
05/14/2020 04:49:31 PM

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

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

Memorandum

Date: May 13, 2020

To: Maryjoy Mejia, MD, Clinical Reviewer
Division of Dermatology and Dentistry (DDD)

Qianyiren Song, Regulatory Project Manager, (DDD)

Barbara Gould, Regulatory Project Manager, (DDD)

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for cantharidin solution

NDA: 212905

This memo is in response to DDDP's labeling request dated December 5, 2019. Reference is made to an email from DDD (Qianyiren Song) to OPDP (Laurie Buonaccorsi) on May 13, 2020, indicating that DDD will be issuing a Complete Response letter for cantharidin solution. Therefore, OPDP defers comment on the proposed labeling at this time, and requests that DDD submit a new consult request during the subsequent review cycle for this NDA.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

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/s/

LAURIE J BUONACCORSI
05/13/2020 12:04:27 PM

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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PLLR Labeling Memorandum

Date: April 3, 2020 **Date consulted:** January 13, 2020

From: Tamar Lasky, PhD, FISPE, Clinical Analyst, Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health, Division of Pediatric and Maternal Health

To: Division of Dermatology and Dental Products (DDDP)

Drug: Ycanth (cantharidin) topical solution, 0.7% (b) (4)

NDA: 212905

Applicant: Verrica Pharmaceuticals

Subject: Pregnancy and Lactation Labeling

Indication(s) Treatment of Molluscum contagiosum in patients 2 years of age and older

Materials Reviewed:

- September 13, 2019 NDA submission
  - Applicant's proposed labeling
  - 2.7.4 Clinical Summary of Safety

Consult Question:
The Division requests assistance with the review of the PLLR labeling.

BACKGROUND

On September 13, 2019, Verrica Pharmaceuticals submitted this original NDA application (NDA 212905) for Ycanth (cantharidin) topical solution, 0.7%, for the treatment of molluscum contagiosum in patients 2 years of age and older. Cantharidin has been marketed unapproved for decades at a 0.7% concentration in a base of flexible collodion and is on the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act for the treatment of molluscum contagiosum. DDDP requested assistance with the review of the Ycanth labeling for compliance with the Pregnancy and Lactation Labeling Rule (PLLR).

Cantharidin is an inhibitor for protein phosphatases types 1 and 2A. The Applicant believes that the topical application of cantharidin weakens desmosomes in the epidermis through the release of neutral serine proteases. The Applicant has developed a film-forming VP-102 topical solution containing cantharidin, 0.7% to treat molluscum contagiosum, an infection caused by a poxvirus.

Molluscum contagiosum is a localized skin infection, consisting of flesh-colored, dome-shaped papules with central umbilication and is caused by the pox virus, Molluscum contagiosum virus (MCV) [1]. The virus affects the surface of the body and does not spread internally [2]. Common sites are the neck, armpits, sides of the chest, thighs, buttocks, genitals, and face. The number of bumps ranges from 1 to dozens, and they are often grouped together. Molluscum clears on its own over months to a few years, treatment is not needed if the bumps are not bothersome. It most often occurs in children, with the highest incidence in young children ages 1-4 and 5-9, followed by children 10-14 [3]. It can be spread to other people by direct skin-to-skin contact with the papules, and to other areas of the patients' own skin ("auto-inoculation") by scratching or rubbing. It can also be spread by contact with an object (e.g., towel, gym mat, razor) [2]. Molluscum that develops in teenagers and adults may be due to sexual activity [2]. Immunocompromised persons, especially those with HIV infection, may be at increased risk for molluscum contagiosum [4].

DATA REVIEW

Nonclinical Data

Animal toxicology studies (including in vivo genotoxicity studies, repeat-dose toxicity studies, and reproductive and developmental toxicity studies) are waived due to cantharidin's highly toxic nature. The applicant reported negative test results for genotoxicity. Micromedex TERIS reported that no animal teratology studies of cantharidin have been published [5].

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[1] Isaacs S. Molluscum contagiosum. In: Hirsch M, Levy M, Rosen T, Ofori A, editors. UpToDate2020.
[2] Schaffer JV, Berger EM. Molluscum Contagiosum. JAMA Dermatol. 2016;152(9):1072.
[3] Olsen JR, Piguet V, Gallacher J, Francis NA. Molluscum contagiosum and associations with atopic eczema in children: a retrospective longitudinal study in primary care. Br J Gen Pract. 2016;66(642):e53-8.
[4] Leung AKC, Barankin B, Hon KLE. Molluscum Contagiosum: An Update. Recent Pat Inflamm Allergy Drug Discov. 2017;11(1):22-31.
[5] Cantharidin. Micromedex TERIS, 2020

Clinical Data

The applicant did not submit any data regarding pregnant or lactating women exposed to cantharidin during clinical trials. No review of the published literature was provided in the submission.

DPMH search of the literature including PubMed, Embase, Micromedex Reprotox[6], Micromedex TERIS[7], and the Cochrane Database of Systematic Reviews[8] did not identify any reports of cantharidin use during pregnancy.

DPMH search of the literature including PubMed, Embase, LactMed[9] and Hale's Medications & Mother's Milk[10] did not identify any information regarding cantharidin use during lactation.

DPMH search of the literature including PubMed, Embase did not identify any information regarding cantharidin and human fertility.
In addition, (b) (4) omitted from Ycanth labeling.

Reviewer's Comment
This reviewer finds the applicant's submission adequate because the applicant responded appropriately to our request for more details to support their labeling subsection 8.1 statement (b) (4) *and confirmed that they have not conducted studies with cantharidin in pregnant or lactating women. There is no further information about cantharidin exposure in these populations in the scientific literature.*

DISCUSSION/CONCLUSIONS

There are no clinical data available with use of cantharidin in pregnant women or lactating women for review; and no data regarding cantharidin's effect on human fertility. Thus, no safety concerns have been identified with cantharidin use in these populations.

Pregnancy
DPMH does not recommend postmarketing studies in pregnant women because Ycanth is minimally absorbed systemically and is not expected to result in exposure of the fetus. The majority of the patients treated with the product are not of reproductive potential and few pregnant women would be available for enrollment in a study.

Lactation
DPMH does not recommend postmarketing studies in lactating women because Ycanth is minimally absorbed systemically by the mother and breastfeeding is not expected to result

[6] Micromedix Reprotox
[7] Micromedix Teris
[8] Cochrane Database of Systematic Reviews https://www.cochranelibrary.com/ Accessed on March 11, 2019
[9] Lactmed. https://www.ncbi.nlm.nih.gov/books/NBK501922/ Accessed on March 11, 2019.
[10] Hale, T. W. (2004). *Medications and mothers' milk*. Amarillo, TX: Pharmasoft Medical Pub.

in exposure of the infant. The majority of the patients treated for molluscum contagiosum are not of reproductive potential.

RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 in the Ycanth labeling for compliance with the PLLR (see below). DPMH presented the labeling recommendations at the April 3, 2020 labeling meeting. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

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/s/

TAMAR LASKY
04/03/2020 02:54:29 PM

TAMARA N JOHNSON
04/03/2020 03:02:48 PM