Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesiology, Addiction Medicine and Pain Medicine
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Cross-Discipline Team Leader and Division Director Summary Review

Date	Refer to signature date at the end.
From	Izabella Khachikyan, MD; Primary Clinical Reviewer Sepideh Haghpanah, MD; Team Leader (Acting) Joette Meyer, PharmD; Associate Director for Therapeutic Review, Analgesics (Acting) Rigoberto Roca, MD; Division Director
NDA	212045
Applicant	Hikma Pharmaceuticals, S.A.
Date of Original Submission	April 30, 2019 Complete Response letter issued on February 28, 2020
Date of Complete Response Submission	October 29, 2020
PDUFA Goal Date	April 29, 2021
Proprietary Name	Kloxxado
Established or Proper Name	Naloxone Hydrochloride
Dosage Form	Nasal Spray; 8 mg of naloxone hydrochloride in 0.1 mL
Applicant Proposed Indication/Populations	Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/ or central nervous system depression for adult and pediatric patients
Applicant Proposed Dosing Regimen	Initial Dosing One spray delivered by intranasal administration into one nostril. Repeat Dosing Seek emergency medical assistance as soon as possible, after administering the first dose. If the desired response is not obtained after 2 or 3 minutes, administer an additional dose using alternate nostril. If there is still no response and additional doses are available, administer additional doses every 2 to 3 minutes, alternating nostrils until emergency medical assistance arrives. The requirement for repeat doses depends upon the amount, type, and route of administration of the opioid being antagonized.
Regulatory Action	Approval

Review Team

Discipline	Primary/Secondary/Tertiary Assessment
Office of Pharmaceutical Quality	
ATL	Valerie Amspacher
Drug Substance	Sam Bain/Donna Christner
Drug Product	Jizhou Wang/Julia Pinto
Process/Facilities	Yeung Chan/ Yaodong (Tony) Huang
Microbiology	Julia Marre/Neal Sweeney
Environmental	Jizhou Wang/Julia Pinto
RBPM	Anika Lalmansingh
Pharmacology/Toxicology	Carlic Huynh/Newton Woo/Richard Mellon
Clinical Pharmacology	Wei Qiu/Yun Xu
Clinical	Izabella Khachikyan/Sepideh Haghpanah/Joette Meyer
ADL	Lisa Basham
PM	Joyce Chin/Matthew Sullivan
Consults	
CDRH-Facility	Michaela Schulman/ Rumi Young
DMEPA	Ebony Whaley/ Mille Shah/Valerie Vaughan *Proprietary Name Review*: Zahra Farshneshani, Sofanit Getahum/Valerie Vaughan *Carton/Container Labeling*: Neha Kumar/Ebony Whaley/Lolita White
OPDP	Nima Ossareh/Sam Skariah
DMPP	Susan Redwood/Sharon Mills/LaShawn Griffiths

1. Benefit-Risk Assessment

The Applicant (Hikma) has developed naloxone hydrochloride nasal spray (NS) 8 mg, referred as "Naloxone NS 8 mg" in this review, under the new drug application (NDA) 212045, as a 505(b)(2) application to Narcan (naloxone hydrochloride injection, USP; NDA 16636).

There are currently two FDA approved naloxone products for use in adults and pediatric patients in the community. Evzio (naloxone hydrochloride injection; NDA 205787) was approved on 4/3/2014 and is a prefilled auto-injector for intramuscular and subcutaneous use that delivers a single 0.4 mg dose of naloxone hydrochloride per injection. Narcan nasal spray (naloxone hydrochloride; NDA 208411) was approved on 11/18/2015 and is approved in a single-dose 4 mg strength.

This is the second review cycle for this application. During the first review cycle in 2019 – 2020, the clinical team recommended approval for reversing a life-threatening opioid overdose based on available evidence of efficacy and safety. However, the submission received a complete response (CR) on 2/28/2020 due to multiple deficiencies related to product quality, nonclinical data, device constituent, and human factors studies (see Appendix 1).

On 10/29/2020, the Applicant submitted a class 2 response to the CR letter. The submission does not contain any new clinical data. The review team concluded that the submitted data adequately addresses the deficiencies in the complete response letter related to product quality, nonclinical data, device constituent, and human factors studies.

From a clinical perspective, the benefit-risk assessment of the product is unchanged and remains favorable for approval.

The deficiencies in the 2/28/2020 letter have been resolved and the review team recommends approval.

2. Background

The Applicant (Hikma Pharmaceuticals, S.A.), developed naloxone hydrochloride nasal spray (NS) 8 mg for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression for adult and pediatric patients. The Applicant conducted their clinical development program under INDs 126173 and 134954. The product is a single-use, drug-device combination product intended to be used in the community by laypersons to rescue patients experiencing life-threatening effects of an accidental or intentional opioid overdose while awaiting emergency medical attention.

On 04/30/2019, the Applicant submitted a 505(b)(2) NDA (212045), for Naloxone NS 8 mg. In support of their 505(b)(2) application, the Applicant submitted bioavailability data to reference Narcan injection (naloxone HCl; NDA 16636), an injectable formulation of naloxone hydrochloride as the listed drug. Although Narcan injection has been discontinued from marketing, the Agency determined that it was not withdrawn for reasons of safety or effectiveness (74 FR 22751). Therefore, the Applicant was able to use Narcan injection as the listed drug for their application. The Applicant used a generic naloxone hydrochloride injection product to perform two comparative bioavailability studies to create a scientific bridge to establish the safety and efficacy of Naloxone NS 8 mg for the proposed indication. Additionally, the Applicant relied on the published literature to support the safety of the product in adults as well as the safety and efficacy in the pediatric population.

The following are some of the notable differences between Naloxone NS 8 mg, Narcan (naloxone hydrochloride) injection (listed drug), which were addressed during the development program. A comparison to the other approved naloxone hydrochloride nasal spray formulation (Narcan nasal spray 4 mg) is also described.

- Naloxone nasal spray represents a change in the route of administration from intravenous (IV), intramuscular (IM), or subcutaneous (SC) injection to intranasal (IN). The intranasal route of administration differs in its pharmacokinetic profile compared to the approved parenteral routes. Therefore, it is important to confirm that Naloxone NS 8 mg achieves comparable or greater systemic exposures to naloxone compared to Narcan injection (listed drug), particularly in the period immediately after drug administration, to avoid irreversible injury or death. No comparison to Narcan nasal spray was performed or required.

- Naloxone NS 8 mg is a new formulation containing 20% ethanol that is intended to come in contact with the nasal mucosa. Therefore, the Applicant evaluated the potential for local toxicity in the relative bioavailability studies. Narcan nasal spray does not contain alcohol in the formulation.
- Narcan injection is generally used in healthcare settings by healthcare professionals, whereas Naloxone NS 8 mg is intended to be used in a community setting by laypersons. As noted above, Envizo and Narcan nasal spray 4 mg are also intended for community use. The Applicant was advised during development that a human factors evaluation to support the community use setting is required for product approval.
- The proposed dosing for Naloxone NS 8 mg is a fixed dose while Narcan injection (listed drug) labeling recommends weight-based dosing in pediatric patients. The proposed dosing regimen is the same as Narcan nasal spray 4 mg. In addition, the presence of alcohol in the formulation of Naloxone NS 8 mg necessitated a nonclinical juvenile toxicity assessment.

During the first review cycle, the Division concluded that approval of Naloxone NS 8 mg is supported by the available evidence of efficacy and safety from a clinical perspective. As noted in the CDTL review dated February 2, 2020.

> The Applicant's rationale for developing this 8 mg naloxone nasal spray is to make a product available for community use that delivers higher exposures than other products approved for community use. The Applicant has not provided comparative efficacy, safety or pharmacokinetic data to the aforementioned products approved for community use to inform the potential role of this product in the existing armamentarium for treating opioid overdose.
>
> The efficacy of the proposed product is supported by a scientific bridge between the proposed product and the reference product (listed drug), Narcan injection, through two pharmacokinetic (PK) studies. The Applicant submitted pharmacokinetic data that demonstrated that the PK profile of 8 mg naloxone NS delivered naloxone at greater than the lowest approved dose of the reference product, particularly in the early critical time period after drug administration. The C_{max} was lower than the C_{max} for the highest labeled dose in the reference product but the AUC exceeded the highest labeled dose of the reference product. Doses far exceeding those in the reference product are reported to have been well-tolerated in the literature and provide support for the safety of the product. The product is formulated with 20% alcohol. No major safety issues related to the drug with were identified in the review.
>
> As with other approved naloxone products, the risk of acute opioid withdrawal is outweighed by the benefit of reversing a life-threatening overdose. Approval of 8 mg naloxone nasal spray containing 20% of alcohol in the treatment of known or suspected opioid overdose in the adult and pediatric population is supported by the available evidence of efficacy and safety from a clinical perspective.

Despite adequate clinical data, the submission received a CR on 02/28/2020 due to 20 deficiencies related to other disciplines, including 15 deficiencies related to product quality and manufacturing, three deficiencies related to the device constituent, one deficiency related

to human factor validation study, and one deficiency related to nonclinical pharmacology. Deficiencies noted in the CR letter dated 02/28/2020 are included as Appendix 1.

On 10/29/2020, the Applicant submitted a class 2 resubmission to address the CR deficiencies.

3. Product Quality

During the first review cycle, the Chemistry, Manufacturing, and Controls (CMC) team recommended approval from the drug substance perspective, but they noted fifteen deficiencies related to the drug product quality and manufacturing. The Applicant has addressed all of those deficiencies in their current resubmission. As Dr. Valerie Amspacher stated in her review dated 03/29/2021, the CMC recommendation for this resubmission is approval. Drug product recommends approval with Postmarketing Commitments (PMC). Process/manufacturing recommend approval in this review cycle. Drug substance and microbiology recommended approval in the previous review cycle and their recommendation remains approval.

of the following is a brief summary of the Integrated Quality Assessment. Refer to complete CMC review dated 03/29/2021 for details.

Drug Product
In the resubmission, the Applicant has adequately tightened the acceptance criteria for specified impurity, assay of edetate disodium dihydrate (EDTA), total impurities, pH, spray pattern, droplet size distribution, and spray content uniformity based on stability data trends.

A new analytical method for EDTA has been developed and validated to achieve reproducible results.

The Applicant performed new extractables studies that address the issues of inappropriate sample preparation and narrow pH range of the buffer solution. CMC noted that the extractables studies did not use conditions that were sufficiently rigorous to be exhaustive. In addition, the two extractables studies were not congruent in their results. The Applicant also provided data to show leachables from the stopper are of minimal risk in the commercial product; however, there are leachables under the Applicant's analytical evaluation threshold which remain unidentified and may increase over time. It was determined that more information is needed to better understand the leachables profile; however, this issue did not cause a safety concern for CMC. Therefore, CMC is requesting more information in the form of postmarketing commitments (PMCs) (See Section 13).

The Applicant has fully validated the leachables methods for representative volatile, semi-volatile and non-volatile compounds. The Applicant has also adequately developed and validated leachables methods for special-case compounds (b) (4) (b) (4) that may be present in the rubber stoppers.

Stability data up to 9 months under accelerated and long-term studies fall into the revised specification.

Based on the 6 months of accelerated and 24 months of real-time stability data, a 24 months of shelf life proposed in the original submission is justified when stored at 20-25°C (68-77°F) with excursions permitted from (b) (4)°C to 40°C ((b) (4)°F to 104°F). Since the out of specifications (OOSs) happened for unspecified impurities and pH at accelerated storage conditions (40°C/75%RH) for at least 3 batches at optional 18 and/or 24 month time points, CMC recommends including the following statement in the label: "Avoid long storage at temperature higher than 40˚C."

Process/Manufacturing
First cycle review deficiencies associated with (b) (4), and extractable and leachable risks (b) (4) have been sufficiently addressed.

The drug substance manufacturing facility has experience manufacturing the API and is currently cGMP compliant and is deemed approvable at this time. The drug product facility has experience manufacturing nasal sprays and has successfully completed site transfer and qualification of entire manufacturing line and is currently cGMP compliant and also deemed approvable at this time.

Facility Status Assessment
During the first review cycle, the Applicant changed their commercial drug product manufacturing site to a West-Ward Columbus Inc. manufacturing facility in Columbus, Ohio and because new registration batches of the drug product were made at the new site, an inspection was requested by CDRH. However, the inspection could not be conducted during the review cycle because the facility was not ready for inspection and this was included as one of the CMC deficiencies.

In this second cycle, after evaluating the latest Establishment Inspection Report at the West-Ward Columbus facility, CDRH deemed the inspection not necessary as a site inspection conducted in April 2018 was considered adequate. The Office of Regulatory Affairs also recommends approval of this facility and the Office of Pharmaceutical Manufacturing Assessment concurs.

4. Nonclinical Pharmacology/Toxicology

There were no new nonclinical toxicology studies submitted in this second cycle submission. During the first review cycle, the outstanding nonclinical deficiency was an inadequate extractable leachable assessment. Several extractable compounds were identified (b) (4) (b) (4). A determination that the methodology of the extractable studies was inadequate was made in consultation with the CMC review team.

In this cycle, the nonclinical review focused on updated information extractable leachable data. The proposed drug product is recommended for approval with proposed labeling changes. See brief summary below. The complete Pharmacology/Toxicology review by Carlic Huynh is dated 4/15/2021.

The Applicant has revised the drug product specifications. The specification for (b) (4) (b) (4) (Impurity (b) (4) is unchanged and still acceptable. There was a specification for (b) (4) (Impurity in the original drug product specification (NMT (b) (4) %); however, in this submission, the specification for "Impurity (b) (4)" has been changed to "Specified Unknown (RRT = (b) (4)) NMT (b) (4) %" due to lack of confidence in the structural assignment and this specification is adequately qualified by the 14-day toxicity study in rats.

In silico analysis predicts that two proposed naloxone degradation structures (b) (4) (b) (4) are negative for mutagenic potential.

The container closure has been used in other FDA-approved intranasal products. However, the original extraction studies were considered inadequate. The Applicant updated their extraction studies in this submission. In addition to analytical methods to detect semi-volatile, non-volatile/polar, and inorganic compounds, the updated extraction studies used CG/MS/MS, UPLC/MS/MS, CG/MSSIM to detect (b) (4) (b) (4)). A determination that the methodology of the extraction studies (original and updated combined) represents the worst-case scenario of potential leachables was made in consultation with the CMC review team.

Leachable data were reviewed for this resubmission in support of the safety of the container closure system. The newly submitted leachable evaluation included data monitoring for (b) (4) (b) (4) in addition to semi-volatiles, non-volatile/polar, and inorganic compounds. The limit of detection (LOD) of all compounds appeared sensitive enough to detect at least 5 mcg/day and the LOD for the (b) (4) was sensitive enough to detect at least (b) (4) ng/day as described in the (b) (4) guidance. (b) (4) were not detected and the LOD is considered adequate for these probable human carcinogens.

An unknown compound (RRT (b) (4)) was detected in the updated leachable study below the 5 mcg/day threshold. The Applicant also committed to identifying this unknown compound. The compound (b) (4) was not detected with a limit of detection (LOD) of (b) (4) ng/mL or a limit of quantitation (LOQ) of (b) (4) ng/mL and at the maximum daily volume, the maximum daily exposure is theoretically (b) (4) ng/day, respectively. Moreover, an acceptable intake (AI) per ICH M7 was calculated to be (b) (4) mcg/day based on a TD50 of (b) (4) mg/kg/day from the Carcinogenic Potency Database (CPDB). The updated leachable studies did not detect (b) (4).

As noted above in Section 3, there were some differences in the available data from various leachable studies. The Applicant has committed to further explore the differences in the leachable studies as PMCs (see Section 13). The pharmacology/toxicology review team concurs that these extractable/leachable issues are not safety concerns and do not rise to the level of postmarketing requirements (PMR).

The Applicant submitted a toxicological risk assessment for (b) (4) a product of the oxidation of alcohol, which is in the formulation, and as such, there is a concern for (b) (4) formation in the proposed drug product stored over time and an acceptable intake (AI) for (b) (4) was proposed by the Applicant and found to be acceptable.

The nonclinical review team recommended the inclusion of data from a juvenile rat study in Section 8.4 of labeling due to concerns with pediatric exposure to ethanol and propylene glycol via the proposed naloxone nasal spray (See Section 12).

5. Clinical Pharmacology

There was no new clinical pharmacology information in this submission. The clinical pharmacology team recommended approval during the first review cycle.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

No new clinical efficacy studies were submitted in this submission. The clinical team recommended approval during the first review cycle. See the clinical review dated 1/19/2020.

8. Safety

No new clinical studies were included in this submission. The Applicant stated that there were no new safety information and no significant changes in the safety profile of their product since the last submitted information in the original NDA (submission dated 04/30/2019).

9. Advisory Committee Meeting

No advisory committee meeting was held because there were no issues identified that required input from an advisory committee.

10. Pediatrics

Narcan injection (listed drug) is approved for use in the entire pediatric age range. As noted in the first review cycle, the use of Naloxone NS 8 mg is supported in pediatric patients from

birth to 17 years. A human factors study conducted with adults and adolescents 12 years of age and older administering the product to an adult-sized mannequin was found to be adequate by the Division of Medication Error Prevention and Analysis (DMEPA). The review by the Division of Pediatrics and Maternal Health noted that including mannequins resembling infants and neonates and also include caregivers of younger children would more fully assess proper dosing delivery to the proposed population. DAAP presented the pediatric assessment to the Pediatric Review Committee (PeRC) on 1/28/2020. Although a human factors evaluation was not part of the agreed Pediatric Study Plan reviewed and agreed to by PeRC in 2018, PeRC recommended the Division request the Applicant conduct human factor studies to assess use in infants and include caregivers of infants. However, PeRC acknowledged that if these studies were not previously requested it may be difficult to request them at the current time. The Division Director review dated 2/28/2020 concluded that although a mannequin that resembled infants/neonates was not included in the human factors study, use of Naloxone NS 8 mg from birth to less than 12 years of age is supported for single-dose emergency use. The review also stated that the Division will discuss the review of the human factors study and future study plan design with the DMEPA.

Therefore, the lack of such a human factors study for infants/neonates was discussed again with DMEPA during the current review cycle. It was concluded that no additional human factors study is required for this product, as the proposed device and administration volume are the same as the approved Narcan nasal spray.

11. Other Relevant Regulatory Issues

Other deficiencies noted during the first review cycle were related to device constituent and user interface that are included under Center for Devices and Radiologic Health (CDRH) and Human Factors Validation Study, respectively.

Center for Devices and Radiologic Health (CDRH)
During the first review cycle, there were three deficiencies related to:

- Unanswered questions in response to an information request sent 10/11/19.
- The reliability study and spray characteristics of the to-be-marketed 20% alcohol formulation (e.g., spray actuation content/dose accuracy, spray pattern, spray content uniformity, droplet size distribution, plume geometry, and actuation force reliability verification testing)
- The procedure for the corrective and preventive actions (CAPA) system.

In this second review cycle, the Applicant responded adequately to all the deficiencies either in the CR submission or subsequently in response to information requests from CDRH, with the exception of actuation force. Multiple information requests were sent to the Applicant during the current review cycle to provide additional data related to actuation force.

The sponsor proposed an actuation force specification of (b) (4) kg based upon literature data. CDRH reviewed the data and concluded that males 10 to less 14 years of age and females 10 to less than 16 years, 65 to 69 years, and over 75 years of age do not have palmar pinch

strength to actuate a device with (b) (4) kg of force. Naloxone NS 8 mg is intended for community use. In this setting the patient is not administering the product to themselves and another person (e.g., layperson) will be administering the product to the patient. In order to ensure the patient receives sufficient exposure to naloxone to reverse the overdose, the product should be designed such that it can to be actuated easily in an emergency setting by a broad range of people. Therefore, it was recommended to the Applicant that the actuation force specification should be reduced to no greater than (b) (4)

The Applicant agreed to an acceptance criterion for actuation force of no greater than (b) (4) There was additional discussion with the Applicant on the validation of actuation force methods and how the actuation force is calculated. The Applicant clarified the methods (based upon point A on the actuation force curve which is the bridge breaking force or "triggering force") and that if any point between B and D, including C on the curve is over (b) (4), it will trigger an investigation. The proposal was found acceptable and the overall device component recommendation from CDRH is acceptable.

Human Factors Validation Study
During the first review cycle, the DMEPA noted that the Applicant did not provide sufficient data to support the design of the proposed user interface submitted in the marketing application. The applicant was requested to update the product's user interface and use-related risk analysis (URRA) and submit the results of the human factors (HF) validation study. DMEPA's review of the current submission concludes the methodology of the HF validation study is acceptable and the results demonstrate that representative users can use the product safely and effectively. See review by Zahra Farshneshani dated 4/5/2021.

DMEPA also provided other comments on the labeling, including carton/container labels, prescribing information, and instructions for use intended to reduce the risk of medication errors. These comments were conveyed and agreed upon by the Applicant.

12. Labeling

Proprietary Name
DMEPA rejected the Applicant's original proposed proprietary name (b) (4). On 2/8/2021, the Applicant proposed the proprietary name Kloxxado, which was found to be conditionally acceptable by DMEPA on 2/23/2021.

Prescribing Information
Labeling recommendations were made during the first review cycle and sent to the Applicant with the CR letter on 2/28/2020. In the resubmission the Applicant updated the PI, addressing the Division's recommendations. The PI was aligned, as appropriate, with the approved PI for Narcan nasal spray. The following is a summary of the additional substantive labeling recommendations made during this review cycle:

- Adverse reactions reported with KLOXXADO in 47 adults in the two pharmacokinetic studies were added to the Adverse Reactions section of Highlights and Section 6.1

Clinical Trials Experience in the Full PI. In addition, observed signs of nasal irritation that were reported as part of assessment of nasal cavity are also described.

> In two pharmacokinetic studies a total of 47 healthy adult volunteers were exposed to a single dose of KLOXXADO, one spray in one nostril. The following adverse reactions were reported in two subjects each: abdominal pain, asthenia, dizziness, headache, nasal discomfort, and presyncope. On local tissue assessments for nasal irritation, signs of nasal inflammation and nasal congestion were observed.

- The Pharmacology Toxicology review team recommended the inclusion of data from a juvenile rat study in Section 8.4 of labeling due to concerns with pediatric exposure to ethanol and propylene glycol via the proposed naloxone nasal spray.

> Juvenile Animal Study
> In a juvenile animal study, male and female juvenile rats were administered a single intranasal dose of saline, vehicle consisting of 20% alcohol and 5% propylene glycol, or naloxone (123 mg/kg, 185 mg/kg, and 246 mg/kg) on postnatal day 7 (PND 7). There were no test article-related findings on sexual maturation, neuroapoptosis, or on a limited number of neurocognitive endpoints which included social interactions as well as learning and memory. The no-effect dose level for neurodevelopmental toxicity was the high dose tested, which is 6.8-times a neonate dose from two nasal sprays of KLOXXADO based on body surface area comparison and a neonate weight of 2.5 kg.

Other Labeling
The Office of Prescription Drug Promotion (OPDP) had no comments on the Prescribing Information. Comments on the Patient Package Insert (PPI) and Instructions for Use (IFU) were made in conjunction with the Division of Medical Policy Programs (DMPP) and were included along with other comments from DMEPA and the review team. The version of the PI, PPI and IFU submitted 4/27/21 is addressed all the comments and is considered final. Final carton/container labeling was submitted 4/12/2021.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

A REMS is not recommended at this time.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

No PMRs are recommended at this time. The following PMCs are recommended by the CMC team:

4051-1 Provide additional characterization of the extractables and leachables in this drug product.

- Perform additional extractables studies to show the extraction methods used are exhaustive and reanalyze the extractables detected to attempt to at least assign a compound class.

- Provide additional assurance of the suitability of the leachables methods with additional validation and by spiking drug product samples with stopper extracts as well as known compounds to ensure the leachables method can detect them.

For the milestone dates, see the approval letter.

14. Recommended Comments to the Applicant

Not Applicable.

Appendix 1
List of NDA 212045 Deficiencies from Complete Response Letter Dated February 28, 2020

Product Quality

- We have identified the following deficiencies regarding the extractables studies:

  a. Different maximum daily doses (MDD) have been used to calculate the analytical evaluation thresholds (AETs) for the extractables studies. Specifically, in the (b) (4) 2011 report, an MDD of 8 mg/day was used to calculate the AET for volatile, semi-volatile and non-volatile, while in (b) (4) report TTP-IOX-M0083, 32 mg/day (i.e., 4 doses per day) was used for the calculation of AETs for polar compounds and elemental impurities. Clarify the discrepancies and provide the revised AETs with the correct MDD.

  b. You stated that the profile (b) (4) contained (b) (4) (b) (4) (b) (4). However, we cannot locate the information. Provide this information in your resubmission.

- We have identified the following deficiencies regarding the leachable studies:

  a. We do not agree with your design for leachables testing following the concept of ICH Q1D "Bracketing and Matrixing designs for the stability testing of new drug substance and products." Potential leachables may decompose to generate secondary leachables over time. Therefore, the full stability protocol must be followed in order to determine the full leachable trend throughout the product life cycle.

  b. You stated that all the naloxone nasal spray samples were stored in horizontal orientation as a worst-case scenario during the stability studies. However, inverted position will maximize stopper/drug product solution contact. Re-run the leachables studies in the inverted position or justify why the horizontal position is the worst case scenario for leachable determination.

  c. In 3.2.P.2.4.10.4. Characterization of Leachables and the original report IOXM0085 report: Semi-Quantitation of Extractables from (b) (4) Stoppers, you have adopted an AET of (b) (4) µg/mL, which is 100-fold higher than the AET (b) (4) (b) (4) used for extractables studies. In addition, 3 of 4 reporting limits for the target leachables (b) (4) are much higher than the AET (b) (4) as shown in Table 9 and Table 11 below. Clarify these discrepancies and provide a revised AET based on a SCT of (b) (4) µg/day.

3. The acceptance criterion for "Total Impurities" (b) (4) is too wide in the release and stability specification. Tighten the acceptance criterion based on the data trend.

4. Include the acceptance criterion for the potential degradation impurity (b) (4) (b) (4) in both release and stability specification as per ICH Q3B. Alternatively provide sufficient batch data to show it is absent in the drug product with validated methods.

5. We acknowledge that (b) (4) has been controlled in the vendor's Certificate of Analysis (COA) for dehydrated ethyl alcohol. (b) (4) (b) (4) demonstrate that your analytical method can detect (b) (4) that (b) (4) is absent in the drug product.

6. We have identified the following deficiencies regarding the method validation:

   a. Provide the forced degradation studies for CH.0103: Assay and Identification of Naloxone in Naloxone Nasal Spray, 8 mg/Spray.

   b. Provide system suitability requirements for the following validation reports:

      i. Method CH.0151: Assay of Ethanol by GC-FID
      ii. Method CH.0109: Impurities (b) (4) by HPLC
      iii. Method CH.0117: Impurity (b) (4) by HPLC
      iv. Method CH.0110: Impurity (b) (4) by HPLC.

   c. Provide a complete method validation report for Impurity (b) (4)

   d. Provide the details for the referenced Report.CH.0046 for Method CH.0109: Method Validation Report for Impurities (b) (4) by HPLC method.

7. We have identified the following deficiencies regarding the structural assignment for Impurity (b) (4):

   a. You have assigned Impurity (b) (4) based on the presence of the signal (b) (4). Provide the sources (b) (4) on page 4 of Analysis Report: (b) (4) and clarify why (b) (4) is a diagnostic (b) (4).

   b. Since reference standard for (b) (4) is not available to verify the structure of Impurity (b) (4), provide direct spectroscopic evidences for (b) (4) (b) (4) Impurity (b) (4)

   c. If you cannot unambiguously assign the structure of Impurity (b) (4) list the impurity as a specified unknown impurity with RRT in the release and stability specification.

8. Provide the design and materials of construction of the labels used on the primary container for naloxone hydrochloride nasal spray.

9. Provide the vendor COA for (b) (4) vial.

10. In 3.2.P.2.2 the stability study results have demonstrated that formulations with EDTA at a concentration of (b) (4) % w/w at a pH of (b) (4) yielded the most stable formulations with an optimum impurity profile. However, you have adopted a much wider pH range (b) (4) for both release and stability specification. Justify the wider pH ranges by providing data to demonstrate the continued stability of the API and Edetate Disodium at higher or lower pH's or revise the pH specification (range) for release and stability, based on the observed values for drug product batches tested thus far.

Manufacturing

11. (b) (4)
(b) (4)
3.2.P.3.3 (b) (4).

12. Leachable and extractable studies are critical to assure no elements or chemical substances are extracted from the manufacturing components under stress conditions to compromise quality of the drug product. We acknowledge you have presented extractable and leachable study results for (b) (4) rubber stopper and leachable screen of aged naloxone nasal spray DP in 3.2.P.2 to profile potential extractable contaminants. However, you did not offer any leachable or extractable studies result for all product-contact materials used in manufacturing process to demonstrate that no elemental or chemical impurities were extracted from your manufacturing (b) (4) under the given process operation conditions. Provide leachable and extractable data for all the formulation contacting (b) (4) components used during the manufacturing process and confirm all formulation contacting (b) (4) components used in manufacturing of the drug product meet the ASTM standards (b) (4). In addition, provide a statement of compliance to pertinent CFR sections for indirect food additives for all formulation contacting components used in manufacturing of the drug product.

13. You have not proposed any acceptance limits for pH, viscosity, and density for the (b) (4) solution. Include this information as part of the in-process controls per 21 CFR 211.110. Note that the acceptance limits must be justified with exhibit batch and/or development studies data. Further, provide a side-by- side comparison table listing all in-process tests and their acceptance limits for commercial and exhibit batches. For exhibit batches, summarize their in-process test results. In addition, revise contents in 3.2.P.3.4 and the commercial MBR in 3.2.P.3.3 accordingly.

14. Measurement of yield is an estimation of robustness of the process, since deviation investigations are typically performed if yield in the reconciliation section is outside of the specification limits. Your use of reconciliation yield limits for batch reconciliation in

commercial MBR are not acceptable (b) (4) and is not an accurate reflection of manufacturing process performance. Per CFR 211.103 and CFR211.186(b)(7), revise your proposed commercial MBR in 3.2.P.3.3 to include actual yield and actual yield target specification for each unit operation and total production, wherever is applicable.

15. Our field investigator could not complete inspection of the West-Ward Columbus Inc. (FEI: 1510690) manufacturing facility at Columbus, Ohio because the facility was not ready for inspection. Satisfactory inspection is required before this NDA may be approved. Notify us in writing when this facility is ready for inspection.

Center for Devices and Radiological Health

16. In your October 18, 2019, response to our October 11, 2019, information request, you provided several responses (Questions 12 to 25) with target timelines for completion of June 30, 2020. In your resubmission, provide full responses to the questions within this request that were left unanswered. These include the following questions that were left without a full response: 12, 14, and 16 through 23.

17. In your October 18, 2019, response to Question 21c, you provide a justification to support using one lot of the (b) (4) % alcohol formulation as a part of your reliability study. While we acknowledge that the to-be-marketed 20% alcohol formulation was used as well, you did not provide an adequate justification to support using the (b) (4) % alcohol formation to support the reliability of the to-be-marketed 20% alcohol formulation. In your justification you state: "Hikma acknowledges that the (b) (4) % alcohol formulation may have slightly different spray characteristics compared to that of the 20% alcohol formulation due to minor differences in (b) (4) properties including viscosity, specific gravity, and density". Given that the spray characteristics will likely be influenced by the alcohol content in the respective drug product, provide spray actuation content/dose accuracy, spray pattern, spray content uniformity, droplet size distribution, plume geometry, and actuation force reliability verification testing with the to-be-marketed 20% alcohol formulation of your product.

18. In your October 18, 2019, response to Question 24d, you provided a brief summary of your CAPA procedure and referenced your internal CAPA procedure; however, there is limited detail regarding your CAPA procedures and a determination of the adequacy of the procedure cannot be made. Provide your internal CAPA procedure for our review. Ensure that your procedure includes the following elements:

    a. Requirements to analyze processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems.

b. Review and disposition process of nonconforming product, including documentation of disposition. Documentation should include the justification for use of nonconforming product and the signature of the individual(s) authorizing the use.

c. Appropriate statistical analysis of these quality data to detect recurring quality problems.

d. Investigations into the cause of nonconformities relating to product, processes, and the quality system.

e. Requirements for identification and implementation of actions needed to correct and prevent recurrence of nonconformities and other quality problems.

f. Verification or validation of the corrective and preventive actions taken to ensure that such action is effective and does not adversely affect the finished device.

g. Procedures for rework, to include retesting and reevaluation of the nonconforming product after rework, and to ensure that the product meets its current approved specifications.

h. Requirements for implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems.

i. Ensure that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems.

j. Submission of relevant information on identified quality problems, as well as corrective and preventive actions, for management review.

k. Documentation of all CAPA activities.

Nonclinical

19. You have not provided adequate extractable leachable data to permit a toxicological risk assessment of leachable compounds. Update the extractable leachable assessment to address the Chemistry, Manufacturing, and Controls deficiencies in the resubmission. Submit a toxicological risk assessment for any compound detected in the leachable study present at 5 mcg/day or greater.

Human Factors

20. There is insufficient information to support the design of your proposed user interface. We refer you to our April 26, and August 9, 2019, Advice Letters regarding your Human Factors Validation Study under IND 134954. Update your product's user interface and use-related risk analysis, and submit the results of your HF validation study.

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

/s/

JOETTE M MEYER
04/29/2021 03:05:56 PM

RIGOBERTO A ROCA
04/29/2021 03:08:09 PM