CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217722Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 134611

MEETING REQUEST-
WRITTEN RESPONSES

Harm Reduction Therapeutics
Attention: Tom Huijbers
Regulatory Affairs
4800 Montgomery Lane, Suite 400
Bethesda, MD 20814

Dear Mr. Huijbers:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RiVive (naloxone hydrochloride) nasal spray, 3 mg/0.1 mL.

We also refer to your submission dated December 16, 2020 containing a meeting request. The purpose of the requested meeting was to discuss your planned new drug application (NDA) for RiVive (naloxone hydrochloride) nasal spray, 3 mg/0.1 mL.

Further reference is made to our Meeting Granted letter dated January 6, 2021, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your March 15, 2021 background package (we note that in a correspondence dated March 22, 2021, you withdrew Question 3 given the topline results of the bioavailability study were not available as you had anticipated).

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions, call Sherry Stewart, PharmD, Regulatory Project Manager, at (301) 796-9618.

Sincerely,

{See appended electronic signature page}

Nushin Todd, MD, PhD
Director
Division of Nonprescription Drugs I
Office of Nonprescription Drugs
Center for Drug Evaluation and Research

Enclosure:

- Final Written Response

WRITTEN RESPONSES

Meeting Type: Type B

Meeting Category: Pre-New Drug Application (Pre-NDA)

Application Number: IND 134611

Product Name: RiVive (naloxone hydrochloride) nasal spray, 3 mg/0.1 mL

Indication: Reversal of suspected opioid overdose

Sponsor: Harm Reduction Therapeutics, Inc.

Regulatory Pathway: 505(b)(2) of the Federal Food, Drug, and Cosmetic Act

1.0 BACKGROUND

Naloxone hydrochloride is an opioid antagonist, currently available only by prescription, for the reversal of suspected opioid overdose. Harm Reduction Therapeutics, Inc. (HRT) requested a meeting to discuss a future new drug application for the nonprescription marketing of naloxone.

The Division of Nonprescription Drugs I met with HRT on November 15, 2018 to discuss the firm's development plan for naloxone. Following this meeting, the Office of New Drug Products provided written responses to the Sponsor's questions about impurities, microbial limits, registration-stability batches, reliability testing and assessment, and development testing.

Previous regulatory interactions include:

- Investigational New Drug Application submitted on April 14, 2020
- Study May Proceed Letter issued May 19, 2020
- Proprietary Name "RiVive" conditionally granted May 5, 2020
- Type C Written Responses issued August 5, 2020
- Fast Track Designation Request denied on March 16, 2021
- Pediatric Study Plan initially agreed upon on March 26, 2021

The Sponsor's questions are in bold font. FDA's response is in italics.

2.0 QUESTIONS AND RESPONSES

Question 1:
Does the Agency agree with HRT's proposal to include data on device essential performance requirements collected in the registration stability and performance characterization studies in the NDA, while collecting reliability test data from the process validation batches post-approval?

FDA Response:
We do not agree with your proposal. As your product is intended for emergency use, reliability testing is essential for assuring the product is safe and effective. See Additional Comments below for information regarding your verification approach, reliability program and information to submit in a future marketing application. Additionally, see our response to Question 2.

Question 2:
a. Depending on assessment of the data that will be submitted in the NDA as described above, would the Agency be willing to approve a shelf-life for RiVive of 24-months?

b. If not, would the Agency be willing to accept submission of the 12 months stability data approximately 3 months after the NDA is submitted?

FDA Response:
It is unclear how you will demonstrate safe and effective device performance for a shelf-life of 24 months with either methods posed in parts a or b; thus, we do not agree with your approach.

You need to demonstrate that your device constituent functions safely and effectively at your labeled shelf-life at the time of submission of the NDA. Based on question 2, parts a and b, we expect data demonstrating device performance is maintained at least 24 months using real-time or accelerated aging testing. This includes assessments made within your fault tree analysis (FTA). If you intend to rely on accelerated aging data to support expiry, you need to justify how those temperature/humidity conditions correlate to the proposed shelf-life and ensure real-time aging testing is conducted post-approval to confirm device constituent performance up to the proposed shelf-life.

Question 3 [WITHDRAWN*]:
Does the agency agree that the results of HRT001-PK01 supports the approval of HRT-001 for the treatment of known or suspected opioid overdose?

**In a correspondence dated March 22, 2021, the Sponsor officially withdrew this question as the topline results of its bioavailability study were not available.*

3.0 ADDITIONAL COMMENTS*:*

To ensure that all components of your eventual NDA are submitted in accordance with the applicable regulations and guidances, we refer you to 21 CFR 314.50 and various guidance documents noted below that are relevant to NDA submissions. Note that a searchable website for FDA guidance documents can be found at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

In an effort to assist you in preparing your application, each review discipline has provided some additional recommendations regarding expected submission contents for your eventual NDA. Note that these recommendations are intended to highlight aspects of your application that are required that you did not ask about; however, our comments are not necessarily comprehensive. You alone are responsible for the completeness of your submission.

Clinical Pharmacology

Before you submit your NDA, we recommend that you ensure that we have adequate opportunity to review the results of your comparative bioavailability study to determine that the study will be sufficient to support NDA filing. We recommend a Type C meeting as the most appropriate pathway for submitting your results and obtaining FDA feedback. In the interim, we refer you to comments previously provided (see the Type B Pre-IND Written Responses dated August 10, 2017 and meeting minutes from the Type B Pre-IND meeting held on November 15, 2018):

- *To fulfill the 505(b)(2) regulatory requirements, you must establish a scientific bridge (e.g., via a comparative bioavailability study) between your proposed product and a product approved in the United States upon which you plan to rely. Although the reference product, Narcan injectable (NDA 016636), is no longer marketed, you may still rely upon FDA's findings of safety and efficacy for that product. In this situation, you must use an approved generic product (i.e., ANDA) to Narcan, listed in the Orange Book, as the comparator in your proposed comparative bioavailability study. We recommend that you use a reference standard (RS) drug as the comparator at an approved dose and by an approved route of administration in its labeling. You must still identify the NDA product as the listed drug and patent certify against that NDA product in your application.*

- *Your product must demonstrate comparable or higher systemic exposure and comparable or quicker onset of action (i.e., by examining Tmax, Cmax, and partial AUC values) to the reference drug given at an approved dose and by an approved route of administration in your comparative bioavailability study. Because rapid onset of action is critical for reversal of opioid overdose, your proposed product must demonstrate comparable or higher exposure to the comparator in the comparative bioavailability study during the early absorption*

phase. The partial AUC 0-2.5min, AUC 0-5min, and AUC 0-10min need to be calculated and compared.

- *If your product demonstrates a substantially higher systemic exposure than the reference product, then additional data or justification may be required to assure that the higher exposure does not represent a safety concern (e.g., from literature or pharmacokinetic data for the reference naloxone product administered at higher doses).*

- *The final to-be-marketed product (including both formulation and device) needs to be used in the pharmacokinetic (PK) studies intended to support your NDA. Otherwise, you must provide adequate bridging information or justification for why the study results using a different formulation apply to your final to-be-marketed product.*

We would like to further emphasize that rapid onset of action is critical for reversal of opioid overdose, so your proposed product must demonstrate comparable or higher early exposure (e.g., AUC0-2.5min, AUC0-5min, AUC0-10min).

In your NDA submission, include the following data and information:

- *PK datasets for free naloxone (i.e., unconjugated naloxone), including raw PK and PK parameter datasets, and bioanalytical validation and bioanalytical study reports for your comparative bioavailability study.*
- *Clearly state whether the final to-be-marketed product (including formulation and device) was used in the comparative bioavailability study. If not, you must provide adequate bridging information or justification why the study results using a different formulation apply to your final to-be-marketed product.*

Clinical Efficacy

We refer you to the following guidance documents:

- *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document – April 2009, available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/integrated-summaries-effectiveness-and-safety-location-within-common-technical-document*

- *Integrated Summary of Effectiveness – October 2015, available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/integrated-summary-effectiveness*

Provide a Summary of Clinical Efficacy (SCE) that discusses any basis for supporting efficacy of your product. In addition to the SCE, submit an Integrated Summary of Effectiveness (ISE) in Module 5. If you believe that the SCE in Module 2 otherwise

fulfills the regulatory requirements for an ISE, you may submit an ISE in Module 5 that references and links back to the SCE.

Clinical Safety

Provide a Summary of Clinical Safety (SCS) that includes a discussion of the safety findings in the context of what is known about the safety of naloxone products for adults and pediatrics. In addition to the SCS, submit an Integrated Summary of Safety (ISS) in Module 5 to your application.

In your presentation of clinical safety, you will need to provide information from all of your clinical PK study(ies), including: summaries of the study protocols, analyses of adverse events (AE), and narratives and analyses of any serious adverse events (SAE), deaths, and discontinuations due to AEs.

Additionally, ensure that your NDA includes a comprehensive review of the available postmarketing safety information for marketed single-ingredient naloxone products. In your submission, include a summary of your findings as well as your analyses and conclusions of the postmarketing safety information from each of the following safety data sources:

- *FDA Adverse Events Reporting System (AERS)*
- *World Health Organization's (WHO) International Drug Monitoring Program*
- *National Poison Data (NPDS) from American Association of Poison Control Centers (AAPCC)*
- *A review of published medical literature relevant to the clinical safety of naloxone, including a table listing the references with the type of study, objectives, population and principal results.*

You may limit the above database searches to the previous seven years with a cutoff date approximately 6 months prior to your NDA submission.

For each database listed above, include:

- *An overall analysis of cases involving any single-ingredient naloxone product, including:*
    - *Numbers of cases of nonserious versus serious adverse events by years of reporting*
    - *An evaluation of the most common system organ classes (SOC) and preferred terms (PT) associated with all reported cases*
    - *An evaluation of the most common SOC/PTs associated with cases with serious outcomes*
- *Analyses of AEs associated with naloxone products by intended setting of use (hospital versus community naloxone)*
- *Analyses of AEs associated with community use naloxone products by route of administration (nasal versus injection)*

- *Analyses of AEs associated with intranasal naloxone products by the following age groups: age less than 2 years, between 2 and up to 12 years, 12 to 18 years, and greater than 18 years old*
- *Narrative summaries of deaths, if available, and analyses provided if death was reported as related to use of the naloxone product or another cause*
- *Safety topics of interest for intranasal naloxone formulations only:*
    - *Product ineffective and the reason (if available)*
    - *Rebound opioid toxicity*

Also, provide a discussion of the worldwide experience of naloxone products. In your discussion, include the following information:

- *A list of countries where naloxone is marketed, including the marketing status of the product as prescription, nonprescription, or other. Include certified English translations of foreign nonprescription labels.*
- *Whether naloxone has been withdrawn from any foreign markets due to safety or regulatory reasons.*
- *If possible, provide an estimate of domestic and worldwide postmarketing patient exposure as roughly calculated based on worldwide sales volume.*

A 120-day safety update will be expected during the NDA review (21 CFR 314.50(5)(vi)(b). Additional data may be requested upon review of your marketing application.

Social Science

Refer to the Advice Letter dated February 19, 2021 and the July 28, 2020 teleconference held with FDA. In the most recent submission of your Drug Facts label (DFL) (submitted December 3, 2020 along with your proposed Human Factors (HF) Validation Study protocol), we noted that you made substantive changes to the FDA naloxone model DFL. We remind you that any changes made to FDA's model DFL beyond those directions that are specific to your product and "Call 911" will need to be supported with data from a pivotal Label Comprehension Study (LCS). Alternatively, if you revert to the FDA model DFL, you may test your product specific directions and proposed "Call 911" modifications in your HF study. Submit your latest DFL to FDA so that we can offer our best advice on the contents of your application.

Division of Medication Error Prevention and Analysis

We note that you intend to conduct your HF validation study in Q2 2021; however, it is unclear if you intend to conduct remote HF testing. We remind you of our previous comments provided in our February 20, 2021 advice letter in which we strongly urged you to update and submit your HF study protocol before commencing any remote HF testing. We also remind you to refer to our draft guidance Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications – October 2018, available at: https://www.fda.gov/regulatory-

information/search-fda-guidance-documents/contents-complete-submission-threshold-analyses-and-human-factors-submissions-drug-and-biologic to ensure that you provide a complete HF validation study report. Note that Appendix D, within the draft guidance, provides a hypothetical example of the results and associated analysis of human factors validation study data in a tabular format that can facilitate an efficient review.

Interdisciplinary Science

In your NDA, be sure that any clean labeling that is submitted to Module 1.14.1.1 is free of private or proprietary information, such as ink color codes and contractor names. Any and all approved labeling would be publicly displayed at Drugs@FDA, https://www.accessdata.fda.gov/scripts/cder/daf/.

Annotate your labeling with format specifications required in 21 CFR 201.66(d). For instance, you may include a legend that denotes type sizes and character spacing with each label.

Each label represents an individual record; thus, an individual file needs to be submitted for each record. Refer to the required eCTD specifications as described in our guidance document Providing Regulatory Submissions in Electronic Format - Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications – February 2020 and the eCTD Technical Conformance Guide– July 2020, available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM333969.pdf and https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf.

Chemistry, Manufacturing, and Controls

Provide Chemistry, Manufacturing, and Controls (CMC) information per eCTD (electronic Common Technical Document, available at: https://www.fda.gov/downloads/drugs/ucm163175.pdf) to module 2 (Quality Overall Summary) and Module 3 (Quality).

Some critical information include:

1. *Drug substance:*
   a. *Provide a letter of authorization for the drug substance drug master file (DMF) (b) (4).*

2. *Drug product:*
   a. *Provide raw material specifications for all components of the drug product.*
   b. *Provide detailed manufacturing process and in-process controls (IPC) information for the drug product.*

c. *Provide the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug product.*
d. *Provide structures of the impurities and degradants of the drug substance and drug product, especially for those impurities that are above the Identification Threshold and qualify any impurities that are above the Qualification Threshold, per ICH Q3B. In addition, refer to ICH Q3D for elemental impurities in the drug product.*
e. *Provide rationale for choosing critical quality attributes (CQA) and justification of specifications.*
f. *Provide appropriate studies (compatibility and safety; extractable and leachable studies, etc.) to qualify container closure systems for the drug product.*

3. *Process and Facilities:*
   a. *Facility information on 356h form need to be consistent with module 3 and include detailed responsibilities of drug substance (e.g., active pharmaceutical ingredient (API) and critical intermediates) and drug product manufacturers, contract testing laboratories, and contract packaging facilities (e.g., primary and secondary). Note all facilities should be ready for inspection when the application is submitted.*
   b. *If there is scale up in commercial production, provide the list of the equipment used for registration batch and commercial batch production with information on make, model, and capacity. In addition, provide a table listing the processing parameters used for registration batches and proposed commercial batches, along with the IPC observed in the registration batches and the IPC acceptance criteria proposed for commercial production.*

4. *Product Quality Microbiology (based on information provided in the IND and the meeting package submitted on 15 March 2021):*
   a. *Provide a description of the manufacturing and* (b) (4) *process parameters.*
   b. *Provide method suitability study reports for microbial limits (Total Aerobic Microbial Count TAMC and Total Combined Yeasts and Molds Count TYMC) per USP <61>, test for specified microorganisms Staphylococcus aureus and Pseudomonas aeruginosa per USP <62>, and test for Burkholderia cepacia Complex (BCC) per USP <60>, demonstrating the recovery of challenge microorganisms in the presence of the drug product. Note that per USP <61> both Soybean-Casein Digest agar (for TAMC) and Sabouraud Dextrose Agar (for TYMC) need to be used for challenge microorganisms Candida albicans and Aspergillus brasiliensis. Also note that per USP <60> test strains of microorganisms for suitability testing include Burkholderia cepacia, Burkholderia cenocepacia, Burkholderia multivorans, P. aeruginosa, and S. aureus.*

c. *Regarding the control for the presence of BCC in your product, in addition to including a release and stability specification for the absence of BCC in the drug product per USP <60>, you need to also consider identifying potential sources for introduction of BCC during the manufacturing process and describe the steps to minimize the risk of BCC organisms in the final drug product. We recommend that potential sources are examined and sampled as process controls. These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.*

d. *Regarding the release and stability specifications for microbiological quality testing, we recommend updating the acceptance criteria for microbial limits including TAMC of not more than (NMT) (b) (4) cfu/mL (rather than (b) (4) cfu/mL) and TYMC of NMT (b) (4) cfu/mL (rather than (b) (4) cfu/mL), absence of S. aureus in (b) (4) mL, absence of P. aeruginosa in (b) (4) mL, and absence of BCC in (b) (4) mL (rather than absence of S. aureus, absence of P. aeruginosa and absence of BCC) (b) (4).*

e. *The draft labeling for the finished drug product was not included in the meeting briefing package.* (b) (4)

Nonclinical

We remind you of our previous recommendations provided in the meeting minutes from the Type B Pre-IND meeting held on November 15, 2018 regarding the submission of an adequate toxicological safety assessment for your proposed excipients, impurities, and leachables to your NDA. Further, note our additional comments provided in response to your opening IND submission on May 19, 2020, which provided additional guidance regarding the need to justify the levels of drug substance and drug product impurities.

Briefly, provide information on your proposed impurities and degradation products of all active ingredients and refer to ICH guidances for industry Q3A(R2) Impurities in New Drug Substances (June 2008) and Q3B(R2) Impurities in New Drug Products (July

2006) for possible qualification requirements. Ensure that impurities or degradants of active ingredients that are identified as having mutagenic structural alerts are at or below acceptable qualification thresholds to support your NDA as described in the ICH guidance for industry M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (March 2018). Note, that the drug substance specifications are contained in a DMF, which you reference in your IND.

We recommend that you confirm the levels of all drug substance impurities and degradants with the DMF holder. Also, ensure that you have adequate justification for your impurities and degradants to address the risk to humans, addressing risks like genotoxicity/carcinogenicity. Include in your justification an estimate of the total daily intake (TDI) of your impurities and degradants, as determined by the proposed use of your product. In addition to providing the TDI for each impurity, provide a narrative describing how you calculated the TDI.

Finally, ensure that there is a current letter of authorization for the DMF that you propose to rely upon.

Device

When submitting a marketing application for the final finished combination product, provide the following information related to your device:

1) *Design Control (21 CFR 820.30) – The application needs to include design documentation. Your proposal not to include reliability test data in your NDA is inconsistent with 21 CFR 820.30, specifically for lack of design verification information.*

    a. *You need to demonstrate, as you state, "reliability of the combination product…that has been manufactured, assembled, and packaged using the intend-to-market manufacturing and packaging processes, at commercial scale for the proposed reliability study." It is our expectation that you verify your device design. This includes the effects of your end-use conditioning on production-equivalent devices.*

        i. *Provide design verification evidence that is representative of your to-be-marketed device in your marketing submission.*

        ii. *Include your design verification evidence within your FTA in your marketing submission*

        iii. *Also see our comments regarding your control strategy.*

b. *The use of recognized standards and FDA guidance to inform design and testing is recommended, as applicable. For questions about design control documentation, we recommend that you reference the FDA's guidance for industry Design Control Guidance for Medical Device Manufacturers – March 1997; available at: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm070642.pdf. We recommend that the design control information provided in your application include the following:*

   i. *Design Input Requirements (e.g., safety, performance, and reliability requirements of a device that are used as a basis for device design)*

   ii. *Design Output Specifications (e.g., device description, drawings, specifications, bill of materials, etc.)*

   iii. *Design Verification Plan/Summary Report, supporting data and traceability*

   iv. *Design Validation Plan/Summary Report, supporting data and traceability*

   v. *Risk Management File*

2) *Essential Performance – We do not note a clear definition of your essential performance requirements (EPR) in your submission, making it difficult to provide comments regarding your planned testing. See our comments regarding your control strategy as well and design controls and identify EPRs for the device. For each identified EPR, your marketing application needs to include verification and validation information of EPR specifications. While the final set of EPRs needs to be based on your design control process, we are providing the following example EPRs for your device type. This is not an exhaustive list and product specific factors need to influence your EPR selection.*

   Example nasal spray EPRs:
   - *Pump Delivery (Spray Weight)*
   - *Spray Pattern and Plume Geometry Shape*
   - *Spray Content Uniformity (SCU)*
   - *Droplet / Particle Size Distribution*
   - *Actuation Force*

   Refer to the FDA guidance for industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation – July 2002; available at: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070575.pdf for more details.

3) *Stability (ICH Q1) – Your stability program needs to include endpoints to verify that device essential performance is maintained at expiry. You may exclude certain EPRs from the stability study if you can provide scientific rationale that the excluded EPR is unlikely to change over time. We note your intent to change your labeled expiration information. We advise you to determine your final to-be-marketed labeled expiry information and design your stability program accordingly.*

4) *Shipping – We acknowledge your intent to utilize* (b) (4) *State the assurance level you are performing your testing to and justify the adequacy of your approach. Provide documentation for the final finished product to demonstrate that the device EPRs are met after shipping.*

5) *Control Strategy – Your described intent to begin process validation following NDA approval would prevent you from providing adequate control strategy information. Provide a control strategy that ensures that the final finished combination product maintains its EPRs The control strategy may consist of, but is not limited to, process validation, lot release, in-process, control of incoming materials, purchasing controls, etc.*

6) *Quality System – The marketing application needs to contain a complete summary of your base operating system as described in the FDA guidance for industry and FDA staff Current Good Manufacturing Practice Requirements for Combination Products –January 2017; available at: https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf.*

Additionally, we have the following submission specific comments:

1) *We note your intent to meet your EPRs following worst-case conditioning in a reliability study. "As reliability of the combination product can be impacted by not only the design but also the manufacturing and inspection processes, it is advantageous to use the RiVive combination product that has been manufactured, assembled, and packaged using the intend-to-market manufacturing and packaging processes, at commercial scale for the proposed reliability study." We agree with these comments and advise that your FTA considers worst-case conditioning on your to-be-marketed device. We also advise you perform a complete assessment of the "reliability of the combination product…that has been manufactured, assembled, and packaged using the intend-to-market manufacturing and packaging processes, at commercial scale for the proposed reliability study." We continue to advise that you submit a draft FTA protocol for FDA review as discussed in our August 5, 2020 written responses and consider how you will demonstrate that the dose is delivered at 99.999% reliability and 95% confidence at expiry at your boundary conditions of use.*
2) *We note your intent to use* (b) (4) *in your assessment of your device's function.* (b) (4)

(b) (4)

ustify the adequacy of using this standard or provide testing relevant for your device constituent and your use-case in your future NDA.

3) *We note you provide significant data in this submission. The review of data is more appropriately handled in your future NDA.*
4) *We advise that you discuss failures encountered in your reports and your FTA adequately presents the totality of data contained in your reports.*
5) *We advise that you justify sample sizes based on statistical confidence and reliability and your confidence and reliability selections for sample size are driven by your risk documentation.*
6) *We advise that conditioning and choices made during your testing are representative of worst-case/boundary conditions of your product. Your reliability assessment/FTA needs to adequately identify, justify, and discuss your boundary conditions of use.*
7) *While not applicable to your device constituent, you need to consider recommendations from FDA's draft guidance Technical Considerations for Demonstrating Reliability of Emergency-Use Injectors Submitted under BLA, NDA, or ANDA – April 2020; available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/technical-considerations-demonstrating-reliability-emergency-use-injectors-submitted-under-bla-nda when developing reliability protocol and FTA.*

Combination Products

Combination products are subject to the current good manufacturing practices (CGMP) requirements applicable to each constituent part (drug, device, biological product) of the combination product. However, as reflected in the final rule on CGMPs for combination products (21 CFR Part 4), manufacturers have the option to demonstrate compliance both with the drug CGMP regulations (21 CFR Parts 210, 211) and with the device quality system (QS) regulation (21 CFR Part 820) through a streamlined approach. If utilizing a streamlined approach, you must demonstrate compliance with either the drug CGMPs or the QS regulation in its entirety and also with those provisions specified in Part 4 from the other of these two sets of requirements. Alternatively, you may demonstrate compliance with both the drug CGMPs and QS regulation in their entirety (non-streamlined approach). Further information on 21 CFR Part 4 is accessible at https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products. A related final guidance Current Good Manufacturing Practice Requirements for Combination Products – January 2017 is accessible at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm.

Information to include in NDA Form 356h: List the manufacturing facilities for the combination product and its constituent parts and identify what activities occur at each site (e.g., assembly, filling, sterilization, packaging other) involving which constituents parts (e.g., drug only, device only, both drug and device). For facilities that have

manufacturing activities for both drug and device constituent parts, you need to identify which CGMP operating system is being used at the site for the combination product (streamlined or non-streamlined) and if it is a streamlined system, whether it is a drug-CGMP-based or QS-regulation-based system.

Information to include in your application: If you are using a drug-CGMP-based system, you must demonstrate compliance with the following provisions from the QS regulation. Provide the following information in your marketing application with respect to these requirements. You are not required to provide this information, but we encourage you to do so. Its review will enable the agency to determine whether inspection is needed with respect to these requirements and, if so, to enhance the efficiency of this inspection. Using the eCTD format, this information needs to be provided in Section 3.2.P.3.

- *Management Responsibility (21 CFR 820.20)*
  Provide a summary of how your firm's management has established responsibility to assure that the combination product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4). Also, provide a description of the functions and responsibility of each facility involved in the manufacturing of the combination product and its constituent parts.

- *Design Control, General (21 CFR 820.30)*
  Explain how you utilized the design control process to develop the combination product under review and provide a description of your design control procedures. The description must include how requirements for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file are fulfilled. Provide a copy or a summary of the plan used to design the combination product.

- *Purchasing Controls (21 CFR 820.50)*
  Provide a summary of the procedure(s) for purchasing controls. The summary needs to:
  a. *Describe your supplier evaluation process and describe how it will determine type and extent of control you will exercise over suppliers.*
  b. *Define how you maintain records of acceptable suppliers and how you address the purchasing data approval process.*
  c. *Explain how you will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.*

  Explain how the procedure(s) will ensure that changes made by contractors/suppliers will not affect the final combination product. Provide a description of how you apply the purchasing controls to the suppliers/contractors used in the manufacturing of the combination product. (e.g., through supplier agreement).

- *Corrective and Preventive Action (21 CFR 820.100)*
  Summarize the procedure(s) for your Corrective and Preventive Action (CAPA) System. The CAPA system requires:
  a. *Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;*
  b. *Investigation of nonconformities and their causes;*
  c. *Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and*
  d. *Verification or validation of the actions taken.*

- *Installation (21 CFR 820.170) and Servicing (21 CFR 820.200)*
  If installation and service requirements apply based on the type of device constituent part included in your combination product, the following information needs to be provided:
  a. *Installation -- If applicable for the combination product, provide a summary of how your firm has established installation, inspection instructions, and test procedures for the installation of the combination product.*
  b. *Servicing -- Where servicing is a specified requirement for the combination product, provide a summary of how your firm has established and maintained instructions and procedures for performing and verifying that servicing of the combination product meets the specified requirements.*

For location of device constituent part and combination product information, we refer you to our guidance document Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications – July 2020, available at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf.

Division of Pediatric and Maternal Health

Submit your Agreed iPSP with your NDA. In your NDA, provide a complete pediatric assessment consisting of data supporting the dosing, safety, and efficacy of your product in the full pediatric age range. Your assessment must address the following:

- *The safety and effectiveness of the proposed dose of naloxone for all pediatric age ranges, including neonates*
- *Justification for the proposed dosing volume in all pediatric patients, including neonates*
- *Justification for why the absorption of drugs through the nasal mucosa will not be different in pediatric patients, including neonates, compared to adults*
- *Justification that the device can appropriately deliver the drug product to all pediatric patients, including neonates (e.g., achieve correct placement of device, evidence that device is appropriately sized, evidence that the correct volume is delivered)*

Your assessment may be based on published literature, practice guidelines, and approved labeling for a reference product.

4.0 SELECTED SUGGESTED ACTION ITEMS

Prior to NDA submission
Submit draft Reliability Protocol and request meeting e.g., Type C WRO
Submit topline results of comparative bioavailability study and request meeting e.g., Type C WRO
Submit final draft Drug Facts Label for FDA comment
Submit final draft of Human Factors Validation trial
Provide approximate timing of anticipated NDA

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/

NUSHIN F TODD
05/04/2021 06:12:07 PM