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APPLICATION NUMBER:

214697Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 214697

APPEAL DENIED

ARS Pharmaceuticals, Inc.
C/O Pacific Link Consulting
Attention: Richard Lowenthal
CEO and President
11682 El Camino Real, Suite 120
San Diego, CA 92130

Dear Richard Lowenthal:

Please refer to your new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Neffy (ARS-1, epinephrine nasal spray), 2 mg/0.1 mL.

I also refer to your November 27, 2023, formal dispute resolution request (FDRR), received on November 28, 2023. The appeal concerns the September 19, 2023, Complete Response letter (CRL) issued by Kelly Stone, M.D., Ph.D., Associate Director for Therapeutic Review, Division of Pulmonology, Allergy, and Critical Care (DPACC). In the FDRR, you specifically:

1) "Disagree with the Agency's requirement in the CRL that ARS conduct an additional PK/PD clinical study with repeat-dose nasal allergen challenge (NAC) to support the efficacy and safety of the product under review, as a condition of approval" (FDRR at 1). Accordingly, you "seek FDA's agreement that the requested EPI 18 study to provide PK and PD data with twice dosing after NAC is not necessary for NDA approval" (FDRR at 29). You also believe that "the application should be returned to the division to complete package labeling and take final steps towards approval" (FDRR at 30).

2) "Disagree with the Agency's requirement in the CRL for testing of nitrosamine impurities in the ARS-1 2 mg product, as a condition of approval" (FDRR at 2).

I also refer to the meeting held between FDA and ARS Pharmaceuticals, on January 3, 2024, where the issues raised in your request for formal dispute resolution were discussed.

I have carefully reviewed the materials you submitted and referenced in support of your appeal. I have also reviewed the materials for the May 11, 2023[1] Pulmonary-Allergy

[1] *See* May 11, 2023: Pulmonary-Allergy Drugs Advisory Committee Meeting Announcement, available at:https://www.fda.gov/advisory-committees/advisory-committee-calendar/may-11-2023-pulmonary-allergy-drugs-advisory-committee-meeting-announcement-05112023.

Drugs Advisory Committee (PADAC) Meeting, including briefing documents and a recording of the PADAC discussions. Additional information reviewed includes the CRL, Post Action Type A meeting materials and Type A meeting minutes issued on November 08, 2023. I have also consulted with staff in DPACC, the Office of Clinical Pharmacology (OCP), and the Office of Pharmaceutical Quality (OPQ).

I have completed my review of your request for formal dispute resolution and deny your appeal. I describe below the basis for my decision and provide recommendations for a possible path forward.

I will briefly outline the relevant background, and then discuss in detail the issues that you have raised in your FDRR.

My denial does not in any way prevent your resubmission of NDA 214697 with an appropriate response to the September 19, 2023, Complete Response letter; an appropriate review of such a response would be expected as part of standard FDA procedure.

I. Background and relevant regulatory history

You submitted NDA 214697 pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act on August 19, 2022, for epinephrine nasal spray (ARS-1, also referred to as neffy in your submission).

The application proposed an indication, similar to that for the epinephrine injection products:

- "For the indication of emergency treatment of allergic reactions (Type I), including anaphylaxis, in adult and pediatric patients who weigh ≥30 kg"

The proposed dosing, also similar to that for epinephrine injection products, provided for a second administration of ARS-1, if needed:

- "One spray of neffy (2 mg/0.1 mL of epinephrine) administered into one nostril."
- "Administer second dose of neffy with a new nasal spray after approximately (b) (4) minutes in absence of clinical improvement or (b) (4) after initial dose."

In your NDA submitted pursuant to section 505(b)(2), you included the following data and information agreed upon with the division pre-submission:

- Chemistry, manufacturing, and controls information
- Device-related information
- Human Factors results
- Clinical and clinical pharmacology program:
  - Single and repeat dose administration of ARS-1, in contralateral and ipsilateral nares, in healthy subjects, Study EPI 15
  - Self-administration study in healthy subjects, Study EPI 17

- Single dose in patients following nasal allergen challenge (NAC), Study EPI 16
- Single dose, single treatment PK/PD trial in pediatric subjects ≥ 30 kg (interim analysis), Study EPI 10

To discuss the complexities of this application, the Agency convened a PADAC Meeting on May 11, 2023.[2]

In response to information requests, you submitted amendments received on May 20, 2023, and June 5, 2023, which constituted a major amendment to the application. The user fee goal date was extended to September 19, 2023. On September 19, 2023, FDA issued a CRL citing two deficiencies:

- Clinical/Clinical Pharmacology Deficiency (Excerpt):

  "Due to the complex interaction between allergen-induced acute rhinitis and local pharmacologic effects of epinephrine, adequate PK/PD data assessing durability of effect in patients with allergen-induced acute rhinitis are needed to have confidence in the results sufficient to support approval.

  Information to Resolve Deficiency

  In order to resolve the above deficiency, provide PK/PD data assessing repeat doses of ARS-1 compared to repeat doses of epinephrine injection product(s) under allergen induced allergic rhinitis conditions. Include an assessment of PK/PD findings when the second dose of ARS-1 is administered in the ipsilateral and contralateral naris."

- Product Quality Deficiency (Excerpt):

  "Your NDA does not include data or information, such as a risk assessment, and/or confirmatory testing data as needed, demonstrating that you have ascertained the presence of NDSRIs in your drug product, including specifically (b) (4)

  Information to Resolve Deficiency

  Provide information to FDA regarding potential NDSRIs in your application, specifically with respect to (b) (4)

A Post-Action Type A meeting occurred between the FDA and ARS on October 24, 2023.

[2] *Id.*

II. Discussion

A. Clinical Deficiency

Summary of my understanding of the division's assessment and conclusions

The review team concluded that the submitted data do not provide substantial evidence of effectiveness for the use of ARS-1 for its proposed indication because of limitations of the data that preclude fully establishing a scientific bridge to the clinical efficacy and safety of the marketed epinephrine injection products, which is the basis to support this regulatory submission. These limitations include the lack of adequate data with repeat dosing in patients under NAC conditions. In addition, there were concerns with the discordance of the PK/PD profiles between healthy subjects and patients following NAC where in subjects with allergen-induced acute rhinitis, ARS-1 demonstrated a more rapid absorption phase during the first 10 minutes, compared to Adrenalin, followed by a more rapid decline in epinephrine plasma concentration, with epinephrine mean plasma concentrations dropping below Adrenalin starting around 20 minutes post dose, demonstrating lower PK sustainability. The limitations of the submitted data result in significant residual uncertainty regarding the effectiveness of ARS-1 when repeat dosing is needed. This residual uncertainty around the effectiveness of repeat dosing is of great concern given that patients who fail to improve clinically after a first dose are at significant risk for adverse outcomes and death. Therefore, while the need for repeat administration of ARS-1 may be relevant for only a minority of patients with anaphylaxis, given the potential consequences, the safety and efficacy of repeat dosing must be assured for this potential life-threatening condition. Based on these considerations, the review division concluded that a repeat dose trial in subjects undergoing NAC is necessary to address concerns of durability of effect from a single dose, and to demonstrate sustained PK and PD for patients with severe and persistent anaphylaxis who may require a repeat dose, consistent with the proposed conditions of use.

Comments on specific points raised in the FDRR

My review will first focus on your arguments as they pertain to the deficiencies identified in the CRL.

You state that "the basic scientific rationale and Sponsor position that the requested twice-dosing NAC study is unnecessary for approval is primarily supported by the benefit-risk assessment for approval of neffy in Type I allergy patients 30 kg or greater" (FDRR at 11). In support of this rationale, you have included the following points for consideration:

- You assert there is a significant unmet need.

  The review team and I agree that there is a clear unmet need for additional treatment options for the management of anaphylaxis, including needle-free alternatives to epinephrine injection products to potentially

improve compliance, promote early and more timely administration of epinephrine, and mitigate emotional and physical trauma that may be associated with epinephrine injection products. We also agree that ARS-1 may potentially address such an unmet need. However, I note that the ARS-1 clinical program was not designed to directly assess most of these implied benefits, i.e., improve compliance, promote early and more timely administration of epinephrine, or improve outcomes; rather, it was designed to establish a scientific bridge to the safety and efficacy of the epinephrine injection products in healthy subjects and in patients with NAC, but not in patients with anaphylaxis.

- With respect to the durability of effect, you state that "This matter was specifically considered by the PADAC members at the request of the Agency and dismissed as lacking any scientific basis for concern" (FDRR at 11). You also argue that any possible outcome of the required repeat dose study in NAC, "at best, would inform labeling on an extreme condition as a worst-case challenge to nasal administration" (FDRR at 4). You further state that the "PADAC concluded that an additional NAC study was not necessary and would provide no additional useful information to support efficacy or safety of the product," and that "the PADAC members did not see this study as necessary for approval" (FDRR at 2).

  While the advisory committee discussion and voting are critical for the Agency to obtain input from broader external panel of experts, I remind you that the PADAC is advisory, like other FDA Advisory Committees, and FDA makes the final decision. The team and I have carefully considered the input and advice from the PADAC. I note that while many PADAC panelists expressed the opinion that they were willing to accept the uncertainties of the PK/PD bridging approach to establishing efficacy of ARS-1, few specifically commented on the durability of effect consideration. Your expert, Dr. Jay Lieberman, commented on this issue and stated, "Does it matter? The answer is no one knows." (Dr. Jay Lieberman, May 11, 2023, PADAC meeting official transcript, p. 116).[3] Dr. Lieberman continued to say that this question is "a little bit academic" because if a response is not observed, a second dose of epinephrine is administered, and if a sustained response isn't there, patients are referred to the emergency room (Dr. Jay Lieberman, May 11, 2023, PADAC meeting official transcript pp. 116-117).

  On the other hand, some panelists expressed concerns with accepting the uncertainties, referring to inconsistent PK/PD findings between healthy subjects and patients under NAC conditions, lack of bridging to clinical outcomes, and lack of data in the relevant population of patients with anaphylaxis. These concerns underscore the uncertainties with ascertaining the efficacy in a condition for which there is little to no margin

[3] I note that Dr. Lieberman was not a member of the PADAC Roster. *See* Pulmonary-Allergy Drugs Advisory Committee (PADAC) Roster, available at: https://www.fda.gov/media/167984/download.

for error, which is particularly relevant to patients with severe and persistent anaphylaxis who require a repeat administration. In this context, the durability of effect consideration is important as the drop off in PK in subjects with rhinitis compared to subjects without rhinitis could lead to more patients requiring a repeat administration. The available data cannot reliably rule out this possibility, which could impact more patients than the approximately 10% who require repeat administration of epinephrine injection products. I agree with the review team that adequate PK/PD data assessing repeat doses of ARS-1 compared to repeat doses of epinephrine injection product(s) under allergen-induced allergic rhinitis conditions, and an assessment of PK/PD when the second dose of ARS-1 is administered in the ipsilateral and contralateral naris, could address these uncertainties and inform the effectiveness, safety, and labeling of repeat administration of ARS-1.

- You further assert that the most critical need in the community that results in improved clinical outcomes and lower rates of morbidity and mortality is early intervention with dosing of epinephrine as soon as symptoms of an allergic reaction are detected. You then propose the potential for early intervention using ARS-1 more often and dosed more quickly after symptoms of an allergic reaction are detected, than with current injection products.

  While I do not disagree that this could be a potential benefit, I also must acknowledge that this benefit is assumed because the clinical program was not designed to assess this claim. I also note that some PADAC members placed significant weight on this potential benefit in their benefit-risk deliberations and voting considerations without addressing the fact that the program did not specifically assess this potential benefit.

- You further assert that “neffy is dose proportional” and “twice dosing with injection products does not result in a dose proportional increase in epinephrine exposure and results in only about a 30-40% increase in exposure after the second dose due to physiologic response to epinephrine. Thus, when subjects are severe, neffy can provide more efficient administration of epinephrine” (FDRR at 11, 12).

  I note that this statement implies that a repeat administration with ARS-1 would result in improved clinical outcomes compared with repeat dose with epinephrine injection products. This is a speculative assertion considering that the clinical program was not designed to assess this claim. In addition, the discordance of the PK/PD profiles between healthy subjects and patients following NAC, in the absence of adequate data with repeat dosing in patients under NAC conditions, further underscores the uncertainties with this assertion.

- You further argue that the "currently approved injection devices, such as EpiPen (either pre-approval or post-approval), were never required to do PK studies under challenge conditions (e.g., NAC or other) or even twice dosing studies at all, despite labeling allowing for repeat dosing and nasal conditions being well known in these indications" (FDRR, p. 12).

  I note that in the case of ARS-1, one key scientific consideration justifying the unique need for studies with repeat nasal administration of epinephrine and under NAC conditions, is the impact of potential local changes in the nasal mucosa with anaphylaxis on the absorption of epinephrine, as well as the local PD effect of epinephrine on the absorption of a second dose under nasal allergen conditions. Unlike for ARS-1, the PK/PD for epinephrine injection is not expected to be impacted by nasal vasoconstriction with single or repeat administration to necessitate studies under NAC. Given that the considerations for your appeal pertain to the ARS-1 development program, I will not comment on the data needed to support the epinephrine injection products, except to note that the use of these products has been informed by a significant body of literature reporting roughly 100 years of clinical use and well-documented pharmacologic effects of epinephrine for the treatment of anaphylaxis.

- You state that "Even with exposures after 20 minutes, the plasma concentrations of epinephrine remained above 100 pg/mL (suggested by FDA as a benchmark efficacy measure) for 60 minutes post-dose" (FDRR, p. 12).

  I note that the therapeutic threshold for epinephrine in the treatment of anaphylaxis is unknown. There are some data in healthy subjects to inform the relationship between real-time epinephrine plasma concentrations and change from baseline values for SBP (increase), DBP (decrease), and HR (increase)[4] and the magnitude of vital sign changes which was generally proportional to epinephrine plasma concentration from the threshold of 80 to 200 pg/mL up to approximately 1000 pg/mL.[5] However, there is uncertainty in target thresholds that correlate with efficacy for treatment of anaphylaxis and whether the PD responses can be extrapolated to patients with anaphylaxis. Therefore, the approach of bracketing around the PK/PD of the epinephrine injection products was adopted to bridge to the efficacy and safety of these products, and the data from Study EPI 16 indicates that under NAC conditions the PK of ARS-1 decreases below the reference epinephrine injection products after about 20 min post-dose. Thus, even if the arithmetic mean plasma concentrations of ARS-1 remained above 100 pg/mL after 20 minutes,

[4] Westfall, TC, 2011, Adrenergic Agonists and Antagonists, The Pharmacological Basis of Therapeutics, Goodman, L. S. and A. Gilman, 12th edition 282-285.
[5] Clutter, WE, DM Bier, SD Shah, and PE Cryer, 1980, Epinephrine plasma metabolic clearance rates and physiologic thresholds for metabolic and hemodynamic actions in man, J Clin Invest, 66(1):94-101.

there is uncertainty with respect to the anticipated effectiveness of ARS-1 beyond that timepoint.

- You also rely on other supportive nonclinical and clinical data and assert there is little risk that various conditions will negatively affect absorption:

  I acknowledge the additional contextual information you have included in the NDA and the FDRR. This information includes: 1) PK/PD data and the effect of hypotension during anaphylaxis in a GLP dog anaphylaxis model, 2) PK/PD data in patients with allergic rhinitis following NAC in Study EPI 16, 3) PK/PD data in patients with upper respiratory tract infection, Study EPI 14, and 4) PK/PD data in patients with allergic rhinitis in Japan, Study EPI JP01. Based on this information, you assert that "there is little to no concern about congestion (related to rhinitis or edema caused by the Type I allergic reaction) or other nasal conditions" (FDRR at 21). I do not agree with this assertion. As discussed above, the data from Study EPI 16, which I view as an important study in the ARS-1 clinical program, indicate a discordance of the PK/PD profiles between healthy subjects and patients following NAC, underscoring the uncertainties with extrapolating data from healthy subjects or other settings to patients with anaphylaxis who would have both systemic cardiovascular and local vascular and mucosal abnormalities related to anaphylaxis. I further note that the data provided from all of these additional studies reflect using a single administration of the product. Thus, the additional information provided is not sufficient to mitigate or address the clinical/clinical pharmacology deficiency.

- You also propose that: (1) ARS-1 avoids the risk of IV bolus or partial IV bolus injections into blood vessels (can occur up to 14% of the time with EpiPen based on ARS clinical studies), (2) ARS-1 has a very benign safety profile and low risk of serious events that can occur with injection products, which will also help avoid hesitancy to dose, and (3) ARS-1 has the potential to address many of the unmet medical needs as a needle-free option to current injection devices.

  While I do not disagree that these could be potential benefits, I also must acknowledge that the clinical program was not designed to demonstrate such benefits. Similar to the potential for early intervention using ARS-1, some PADAC members placed significant weight on these potential benefits in their benefit-risk deliberations and voting considerations without addressing the fact that the program did not specifically assess this potential benefit.

- You argue that the required additional PK/PD clinical study with repeat-dose NAC has not been required for any of the other emergency use nasal products.

  These examples are context-specific and based on the individual circumstances of each product at issue. A determination of whether submitted data satisfies the substantial evidence of effectiveness standard is made on a case-by-case basis. From my perspective, one key scientific consideration justifying the need for repeat nasal administration of epinephrine is its local PD effect on the nasal mucosa, which is unique to ARS-1 and can impact the absorption and thus safety and effectiveness of ARS-1 compared to other approved intranasal products. As noted previously, there are concerns regarding changes in the nasal mucosa during anaphylaxis and there were differences in absorption of ARS-1 noted with NAC versus healthy volunteers. Unlike epinephrine, none of these other emergency nasal administration products have the PD effects of local vasoconstriction that could potentially impact the systemic absorption of a second dose, and thus the safety and efficacy of the drug in patients with severe reactions who may need repeat dosing of epinephrine. A repeat dose study under NAC conditions will also likely inform optimal administration of the second dose – whether it would be best administered in the ipsilateral naris, contralateral naris, or either, and thus inform the benefit-risk assessment and labeling of repeat dosing of ARS-1 for the proposed indication. An additional product-specific consideration is that the epinephrine therapeutic and safety window is much narrower than those for other products for intranasal administration referenced in your FDRR.

Summary of my assessment of the clinical program and FDRR

Next, I summarize below my assessment of the clinical program and your appeal of the Clinical/Clinical Pharmacology Deficiency.

Epinephrine injection products are used as the current standard of care for emergency treatment of allergic reactions (Type I), including anaphylaxis, and are based on roughly 100 years of clinical experience. Developing an alternative to these products has been challenging due to the nature of this rapidly developing and potentially life-threatening condition. Given the challenges with conducting a traditional clinical development program to independently establish the safety and effectiveness of ARS-1, the FDA review team and you have agreed on the alternative approach of PK/PD bracketing as a bridge to the clinical efficacy and safety of the marketed epinephrine injection products, which is the basis to support this regulatory submission. In addition, during the development, to address the concern that the absorption phase of the PK could be different in subjects with nasal edema, which could occur in subjects with anaphylaxis, the FDA review team and you have agreed to evaluate the PK/PD in patients with allergen-induced allergic rhinitis following NAC, as a reasonable model to address this

concern. Thus, to support the agreed upon bridging strategy and to allow for the bridge to be established, the review team considered it critical to have a complete understanding of the PK/PD of ARS-1, including the PK/PD with repeat administration of ARS-1 following NAC. Acknowledging the limitations of the clinical development program, the majority of the PADAC panel opined that the potential benefits from using a needle-free alternative to epinephrine injection products outweigh these uncertainties, a position referred to as taking a "leap of faith" by one panel member at the PADAC discussion (Dr. Susanne May, May 11, 2023, PADAC meeting official transcript, p. 367), and reiterated by others. On the other hand, some of the committee members expressed concern about taking this leap without additional clinical data.

The review team and I agree that there is a clear unmet need for additional treatment options for the management of anaphylaxis, including needle-free alternatives, to potentially improve adherence, promote early and more timely administration of epinephrine, and mitigate emotional and physical trauma that may be associated with injections. The FDA review team and I also agree that ARS-1 may address such an unmet need. I note that the ARS-1 clinical program was not designed to address these points. Rather, it was designed to establish a scientific bridge to the safety and efficacy of the referenced epinephrine injection products. Acknowledging the limitations and uncertainties of the development program in the context of the unmet need, the review division and I are also aligned with ARS and the PADAC assessment that this scientific bridging approach may be reasonable to inform the expected effectiveness of ARS-1 and that the data and information in the submission are adequate to support a favorable benefit-risk assessment in the majority of patients who may need to administer *only one dose* of ARS-1.

However, because ARS-1 is indicated for the emergency treatment of anaphylaxis, and the literature suggests that approximately 10% of patients with anaphylaxis require administration of a second dose of epinephrine injection products, ARS-1 is also proposed for administration of a second dose in the absence of clinical improvement or [redacted] (b) (4) after initial dose, consistent with guideline recommendations for the management of anaphylaxis.[6,7] I note that for patients who require a repeat dose administration, i.e., patients with severe and persistent anaphylaxis, the risks for adverse outcomes and death are significantly greater than those for the broader population for whom a single dose may have been sufficient to treat a Type I allergic reaction.

This was a central point in the considerations by the review team that resulted in the clinical/clinical pharmacology deficiency in the September 19, 2023, CRL. Following the NDA submission, based upon the review of the results of the nasal allergen challenge study (Study EPI 16), the review team identified a knowledge gap in the understanding of ARS-1 performance, when a repeat dosing is needed for the management of anaphylaxis. Most of the data supporting the application, and respectively the PADAC discussion, were based on comparing the PK and PD profiles of single administration.

[6] https://pubmed.ncbi.nlm.nih.gov/32001253/
[7] https://pubmed.ncbi.nlm.nih.gov/21377030/

There are PK/PD data with repeat administration in healthy subjects in both the ipsilateral and contralateral naris (Study EPI 15), which appear to support the comparable exposures between ARS-1 and the reference injection products. As the team noted, however, the nasal route of administration creates additional complexity in translating the findings from healthy subjects to patients with anaphylaxis who may have underlying local (nasal) pathological changes that could impact the PK/PD profile of repeat administration in the setting of anaphylaxis.

This complexity is illustrated by the different PK/PD profiles between healthy subjects (Study EPI 15) and patients with underlying local pathology induced by nasal allergen challenge (Study EPI 16). The PK results from Study EPI 16 demonstrate an earlier peak (Tmax) epinephrine concentration with ARS-1 compared to the Adrenalin comparator, but concentrations are not sustained, falling below those of Adrenalin starting at around 20 minutes (FDRR Figure. 4 at 23). A repeat dose after approximately (b) (4) minutes, as proposed in the Dosage and Administration section of labeling, may mitigate some of the concerns with the uncertainty regarding the declining epinephrine concentration with ARS-1 observed under NAC conditions. I also acknowledge the observations of comparable PD (systolic blood pressure, diastolic blood pressure, and heart rate) between patients treated with intramuscular epinephrine and those with ARS-1 under NAC conditions, which is reassuring (FDRR Slide CO-66). However, there are no data with repeat administration in patients following NAC (i.e., the effect of nasal epinephrine administration on absorption of a second dose in the setting of acute rhinitis is not known) to inform the assessment of the repeat administration proposed for labeling to adequately assure the effectiveness of ARS-1 upon repeat administration. Further, it is not known if the repeat dose should be administered in the ipsilateral or contralateral naris under these conditions, which may be critical information on the safe and effective use of repeat ARS-1 administration. As there are no clinical data in patients with anaphylaxis, who would have both systemic cardiovascular and local vascular and mucosal abnormalities related to anaphylaxis, it is unclear whether the declining epinephrine concentrations observed for ARS-1 following NAC may result in more patients needing a repeat dose.

Given the challenges of conducting clinical trials in patients with anaphylaxis and that there are concerns regarding the translation of PK/PD data from healthy subjects to patients with anaphylaxis, I note that the PK/PD data from the NAC model was an agreed upon and required component of the ARS-1 development program to assess the PK/PD of ARS-1 in a model that has allergen-induced changes to the nasal mucosa that could impact epinephrine absorption. In this context, the PK/PD data from the NAC model are not just supportive information; rather, they are essential to support the demonstration of effectiveness of ARS-1 with repeat administration of ARS-1 and therefore critical to the benefit risk assessment for the product. Data from the repeat dose PK/PD study following NAC, evaluating results when ARS-1 is administered in the ipsilateral or contralateral naris, are also necessary for labeling to inform the safe and effective use of repeat ARS-1 administration.

Notwithstanding the recognition that ARS-1 may address an unmet need for a needle-free alternative to epinephrine injection products, based on the above considerations, I agree with the review division's conclusion that additional data from a PK/PD trial(s) assessing PK/PD following a repeat dose of ARS-1 compared to repeat doses of epinephrine injection product(s) under acute, allergen-induced rhinitis conditions are needed to support the demonstration of substantial evidence of effectiveness for repeat administration of ARS-1.

You have also expressed concerns that, "despite the PADAC recommendation for approval based on data in the NDA, and agreement with the PADAC and Agency that the EPI 18 study would be a PMR study, the Agency decided in the final week before the PDUFA date and without discussion with the Sponsor that the study would be a Pre-Approval requirement" (FDRR at 5). The regulatory history for NDA 214697, as summarized in the FDRR, indicates ARS' commitment over the years to addressing the scientific challenges with developing ARS-1 as an intranasal epinephrine product and I understand why the complete response action may have been unexpected in this context. As I indicated at the Type A meeting on January 03, 2024, a regulatory decision is not final until the action is taken and, in this case, the deficiencies that were determined at the end of the review cycle had not been communicated to ARS prior to the action. I note that during the review, the team had elevated the need for such additional data from a post-marketing commitment (PMC), to a post-marketing requirement (PMR) study (referred to as Study EPI 18), to ultimately a pre-approval requirement, which reflects the team's evolving thinking on the criticality of these data for establishing the scientific bridge to the effectiveness and safety of the marketed epinephrine injection products not only for the initial administration, but also for the repeat administration of ARS-1 in patients who have severe and potentially life-threatening reactions. It is not unusual for such determinations to be made as part of an ongoing review. Based on this evolving assessment, the FDA team has concluded, and I agree, that such data are needed to inform the safe and effective use of ARS-1 for the repeat administration, as proposed in the product labeling and as likely to be needed in the actual clinical setting.

You have also requested that if the arbiter of this FDRR "determines that this proposed solution is not acceptable, ARS requests that it first speak to key experts on the FDA PADAC about their opinions of this matter." (FDRR at 30). The review and considerations on the FDRR include sufficient input from both internal and external subject matter experts (i.e., at the PADAC meeting) and I have concluded that additional consultation with the recommended PADAC members or other experts is not necessary for my review of your appeal.

Path forward for addressing the clinical/clinical pharmacology deficiency:

As a path forward, I recommend that you continue your collaborative work with the review division to:

- Provide PK/PD data assessing repeat doses of ARS-1 compared to repeat doses of epinephrine injection product(s) under allergen-induced rhinitis conditions. Include an assessment of PK/PD findings when the second dose of ARS-1 is administered in the ipsilateral and contralateral naris. As I understand from the Type A meeting discussion, you are planning to submit this information (Study EPI 18) in a re-submission in March 2024. It is also my understanding from the October 23, 2023, Type A meeting discussion that the review division indicated they would expedite the review of the resubmission as resources allow (October 23, 2023, Type A meeting minutes, p. 5).

- Alternatively, if you believe that addressing the deficiency through labeling has not been sufficiently explored and can be adequately addressed, e.g., a revised condition of use and/or dosing recommendations, based on a favorable benefit-risk, consider engaging with the review division to explore the feasibility of such an option. Based on the October 23, 2023, Type A meeting discussions, it appears that some of these considerations have been explored and not thought to be practicable, i.e., a dosing regimen that provides for use of back-up epinephrine injection product when a repeat dose is needed (October 23, 2023, Type A meeting minutes, p. 4). Thus, I would encourage you to keep working with the review division and submit the data from Study EPI 18 to facilitate their expedited review.

B. Product Quality Deficiency

In the FDRR, you state: "[the NDSRI] Guidance was issued approximately 11 months after the ***neffy*** NDA submission and after the original PDUFA date. Testing for nitrosamines was conducted using the most current guidelines for FDA and EMA at the time of the NDA submission (August 2022) and original PDUFA date (June 2023). This guidance is not a regulation and does not require compliance until 1 August 2025. ARS therefore, does not see this CRL comment as an approvability issue and believes this should be a PMC, at most, given the low risk based on prior testing and the acute emergency use nature of ***neffy***." FDRR at 7 (emphasis in original). Similarly, you state: "the recent guidance is indeed a nonlegally binding guidance. It does not have the effect of law. Furthermore, the guidance requires compliance by August 1, 2025." FDRR at 30 (emphasis in original); see also FDRR at 2, 10.

Your API, epinephrine, is at risk of forming the nitrosamine-drug substance related impurity (NDSRI) N-nitroso-epinephrine (b) (4). Nitrosamine compounds are potent genotoxic agents in several animal species and some are classified as probable or

possible human carcinogens [redacted] NDSRIs are a class of nitrosamine impurities that share [redacted] which is a significant quality/purity concern. However, your NDA does not include data or information, such as a risk assessment with supporting data that [redacted] in your drug product, or confirmatory testing data in your drug product, demonstrating that you have ascertained the presence (and, if applicable, levels) of [redacted] in your drug product.

The Product Quality Deficiency in the Complete Response Letter (CRL) dated September 19, 2023, was based on FDA's statutory and regulatory requirements for approving drug products. Under section 505(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), if FDA finds that "the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its . . . quality and purity," it "shall issue an order refusing to approve the application." Section 505(d)(3) of the FD&C Act; see also 21 CFR 314.125(b)(1). Accordingly, under FDA's regulations, an NDA "is required to contain" a chemistry, manufacturing, and controls (CMC) section, that includes, among other things, a description of the manufacturing and packaging procedures and in-process controls for the drug product, and the specifications necessary to ensure the quality and purity of the drug. 21 CFR 314.50(d)(1).

As explained above, [redacted] may form in your drug product. Your NDA lacks adequate information on the presence/levels of [redacted] in your drug product.[11] You have not provided adequate information on [redacted] (e.g., a risk

[redacted]

[11] You state that your NDA includes some information on nitrosamines and you state it shows "that there were no nitrosamines detected at any level of concern" and that there is a "low risk based on prior testing." (FDRR at 30). However, the confirmatory testing results you submitted were limited to [redacted]

assessment with supporting data that [redacted], or confirmatory testing data in your drug product demonstrating that the levels of [redacted] are at or below FDA's recommended acceptable intake (AI) limit or another scientifically justified AI limit), to demonstrate the quality and purity of your drug product. Consistent with the conclusions of the CRL, I find that without this information FDA cannot determine that the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of your drug are adequate to preserve its quality and purity, and thus your NDA fails to meet the standard of approval under the FD&C Act and its implementing regulations. See Section 505(d)(3) of the FD&C Act, 21 CFR 314.125(b)(1), and 21 CFR 314.50(d)(1).[12]

In your FDRR, you state that "the Agency is now applying new guidance issued in August 2023" and you state multiple times that the NDSRI Guidance "is not a regulation."[13] (FDRR at 2, 7, 10, 30). I agree that the guidance is not a regulation; it provides nonbinding recommendations. As explained above, FDA's finding that your NDA lacks the necessary information for approval is grounded in the FD&C Act and its implementing regulations. The guidance "provides manufacturers and applicants of drugs… with a recommended framework for predicting the mutagenic and carcinogenic potential of [NDSRIs] that could be present in drug products and recommends

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this information you concluded that this testing "demonstrates no nitrosamine products are detected above [redacted] ng/mL, well below the [redacted] ng/day acceptable intake (AI) level equal to the class-specific limit for nitrosamine impurities based on the most potent, robustly tested nitrosamine, [redacted] (Quality Information Amendment dated 8-21-2023). You have not provided a risk assessment [redacted]

You also state that ARS "does not see this CRL comment as an approvability issue and believes this should be a PMC, at most, given the low risk based on prior testing and the acute emergency nature of *neffy*." (FDRR at 7). However, a post marketing commitment is not appropriate. As noted above, the "prior testing" you submitted did not include information on NDSRIs, including [redacted] FDA has determined that you need to address NDSRIs [redacted] pre-approval in order to show that your product meets the approval standard.

[13] You also state that the NDSRI Guidance "does not require compliance until 1 August 2025." (FDRR at 7). At the outset, the NDSRI Guidance is not legally binding. The guidance merely provides recommended timelines for risk assessments, confirmatory testing, and submission of required changes for NDSRIs (if applicable). However, I also note that ARS misinterprets the applicability of the August 1, 2025 recommended timeline. The guidance "recommends different implementation timelines for manufacturers and applicants depending on the regulatory status of the drug product." [redacted]. The recommended August 1, 2025 date is applicable only for approved or marketed drug products – not pending applications. [redacted] The NDSRI Guidance separately explains the Agency's recommended timeline for drug products subject to applications pending with the Agency. With respect to applications pending before the Agency, the NDSRI Guidance states that "[a]pplicants with pending applications should conduct a risk assessment for NDSRIs expeditiously and inform FDA if confirmatory testing finds NDSRI levels above the AI limits recommended in this guidance. If an NDSRI is detected above the recommended AI limit, the applicant should amend the application as appropriate." [redacted] The different recommended timelines in the NDSRI Guidance reflect different statutory and regulatory provisions and policy considerations implicated by the review of pending applications versus already approved applications.

acceptable intake (AI) limits for NDSRIs." [redacted]. As stated in the guidance, applicants can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. For example, to address the purity of your drug product, you could have provided information to show that the level of [redacted] in your drug product is at or below FDA's recommended limit of [redacted] ng/day or you could have followed an alternative approach, such as providing a scientifically justified rationale to support a different AI limit and address the quality and purity of your drug product. However, you have done neither; your NDA does not include any information on NDSRIs [redacted].

You also state that "ARS, in fact submitted nitrosamine testing per guidance in place at the time of the NDA submission" (FDRR at 2) and that "[t]esting for nitrosamines was conducted using the most current guidelines for FDA and EMA at the time of the NDA submission (August 2022) and original PDUFA date (June 2023)." Additionally, you note that "[the NDSRI] Guidance was issued approximately 11 months after the ***neffy*** NDA submission and after the original PDUFA date." (FDRR at 7). FDA makes its decisions on applications based on the scientific information before it, and whether the applicable statutory and regulatory standard has been met, at the time of the approval decision. I also note that, as reflected in the administrative record, FDA alerted you of the potential presence of a nitrosamine impurity several times, as early as February 1, 2023.[14] After the publication of the NDRSI Guidance, FDA issued you another information request letter on August 21, 2023 to advise you of the publication of the NDSRI Guidance and FDA's recommended AI limit of [redacted] ng/day for [redacted] and to seek information that had not been submitted. Instead of providing the requested information, you responded by providing a copy of a Risk Assessment completed in May 2023 and testing results for [redacted], not NDSRIs. As explained earlier (see footnote 5), the information/testing you submitted does not address NDSRIs [redacted] and it is insufficient to address the agency's concerns about [redacted]

In sum, I agree with the conclusions of the CRL and consider the lack of information and adequate resolution regarding the potential NDSRI to be a deficiency that supports the complete response action. In the absence of adequate information on [redacted] FDA cannot find that the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of your drug are adequate to preserve its quality and purity. Therefore, I do not agree that your application can be approved without the resolution of this issue.

[14] See Information Request e-mail dated February 1, 2023. ("We acknowledge that you assessed potential nitrosamine impurities in active ingredient and excipients. The risk assessment identified that the [redacted] drug product during shelf-life. Provide nitrosamines analysis results for drug product on stability, or provide other justification to support that the risk is acceptably low (e.g., absence of [redacted] in the formulated drug product).")

Path forward to addressing the product quality deficiency:

To resolve this deficiency, I recommend that you refer to the CRL issued on September 19, 2023. In your FDRR, you state "ARS is moving diligently to do this additional testing so that results are available by first quarter of 2024." FDRR at 30. Thus, it appears that ARS is already working towards resolving this deficiency. If the generation of such data may impact your plans to submit the response to the CRL in March, as you had indicated during the October 23, 2023, Type A meeting discussion, I believe that the data can be submitted during the review of that resubmission so as not to delay the planned resubmission.

III. Conclusion

The review team and I acknowledge the public health importance of a needle-free alternative to epinephrine injection products. However, I agree with the review division's concerns regarding the uncertainties with the durability of effect from a single dose, and the sustainability and strength of PK/PD for patients with severe persistent anaphylaxis who may require a repeat dose, which is a proposed condition of use. I believe the division has outlined a reasonable path forward to address this deficiency and you have also indicated your intent to provide the data to address the clinical/clinical pharmacology deficiency in a resubmission in March 2024 (October 23, 2023, Type A meeting minutes, p. 5).

I also agree with the team's conclusion of the CRL regarding the nitrosamine-related deficiency and consider the lack of information and adequate resolution regarding the potential NDSRI to be a deficiency that supports the complete response action. In your FDRR, you state "ARS is moving diligently to do this additional testing so that results are available by first quarter of 2024." (FDRR at 30). Thus, it appears that you are already working towards resolving this deficiency.

Questions regarding next steps as described in this letter should be directed to Ji Hyun LaRose, Regulatory Project Manager, Division of Pulmonology, Allergy, and Critical Care, Office of Regulatory Operations at either ji.larose@fda.hhs.gov or (301) 796-9017.

This constitutes the final decision at the Office of Immunology and Inflammation level. If you wish to appeal this decision to the next level, your appeal should be directed to Peter Stein, M.D., Office Director, Office of New Drugs, Center for Drug Evaluation and Research. The appeal should be sent to the NDA administrative file as an amendment, and a copy should be sent to the Center's Formal Dispute Resolution Program Manager, Melissa Sage. Any questions concerning your appeal should be addressed to Melissa Sage at either Melissa.Sage@fda.hhs.gov or 301-796-6449.

Sincerely,

{See appended electronic signature page}

Nikolay P. Nikolov
Director (Acting)
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

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/

NIKOLAY P NIKOLOV
02/02/2024 04:21:20 PM

IND 139091

MEETING MINUTES

ARS Pharmaceuticals, Inc
8195 Run of the Knolls Court
San Diego, CA 92127

Attention: Richard E. Lowenthal, MS, MBA

Dear Mr. Lowenthal:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Neffy (Epinephrine Nasal Spray).

We also refer to the teleconference between representatives of your firm and the FDA on June 28, 2021. The purpose of the meeting was to discuss the set of Neffy data, including reanalysis of EPI 03 and EPI 07, and results of EPI 11B trial intended to support the filing of an NDA for the emergency treatment of allergic reactions (Type I) including anaphylaxis based on the listed epinephrine IM injection (needle and syringe), and to also confirm that the stability data available for the new formulation of Neffy dose will be adequate for filing an NDA.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-9017.

Sincerely,

{See appended electronic signature page}

Ji Hyun LaRose, PharmD
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Pulmonology, Allergy, and Critical Care
Office of Immunology and Inflammation (OII)
Center for Drug Evaluation and Research

[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.

Enclosure:

- Meeting Minutes

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: June 28, 2021 @ 2:00 PM to 3:00 PM EST
Meeting Location: Teleconference

Application Number: 139091
Product Name: Neffy (Epinephrine Nasal Spray)

Sponsor Name: ARS Pharmaceuticals, Inc.
Regulatory Pathway: 505(b)(2)

Meeting Chair: Sally Seymour, MD
Meeting Recorder: Ji Hyun LaRose, PharmD

FDA ATTENDEES

Sally Seymour, MD, Division Director, Division of Pulmonology, Allergy, and Critical Care (DPACC)
Kelly Stone, MD, PhD, Associate Director for Therapeutic Review (ADTR), DPACC
Miya Paterniti, MD, Clinical Team Leader, DPACC
Jennifer Lan, MD, Clinical Reviewer, DPACC
Yunzhao Ren, PhD, Clinical Pharmacology Acting Team Lead, Division of Inflammation and Immune Pharmacology (DIIP), Office of Clinical Pharmacology (OCP)
Suneet Shukla, PhD, Clinical Pharmacology Reviewer, DIPP, OCP
Xiaochun Chen, PhD, Pharmacology/Toxicology Reviewer, Division of Pharmacology and Toxicology for Immunology and Inflammation (DPT-II)
Carol Galvis, PhD, Pharmacology/Toxicology Team Leader, DPT-II
Yongman Kim, PhD, Team Leader, Division of Biometrics II, Office of Biostatistics (OB)
Ji Hyun LaRose, PharmD, Regulatory Project Manager, DPACC

SPONSOR ATTENDEES

Richard E. Lowenthal, MSc, MBA, President, ARS Pharmaceuticals
Sarina Tanimoto, MD, PhD, Chief Medical Officer, ARS Pharmaceuticals
Brian Dorsey, MSEL, Chief Operating Officer, ARS Pharmaceuticals

(b) (4)

1.0 BACKGROUND

ARS Pharmaceuticals submitted a meeting request dated March 18, 2021, requesting a Pre-NDA meeting to discuss Neffy (Epinephrine Nasal Spray). The meeting was granted for June 28, 2021. We also reference an Information Request sent on June 7, 2021 to which ARS submitted a response on June 11, 2021. ARS Pharmaceuticals specific questions from the briefing document dated May 28, 2021 are listed below in *italics* and the FDA responses are provided in normal font.

FDA sent Preliminary Comments to ARS on June 21, 2021.

2.0 DISCUSSION

INTRODUCTORY COMMENTS

You propose to submit a 505(b)(2) New Drug Application (NDA) for Neffy (intranasal epinephrine) for the treatment of allergic reactions (Type I) including anaphylaxis. In your meeting package, you summarized the pharmacokinetic (PK)/pharmacodynamic (PD) results of your repeat dose range finding trial (EPI 11b) assessing differing epinephrine and Dodecylmaltoside (DDM) doses along with reanalysis of the PK results from your previous trials. Based on these results, you propose a higher epinephrine dose (1 mg to 2 mg) and DDM dose ((b) (4) % to 0.275%) to be used in future clinical trials. You propose to conduct a repeat self-administration trial (EPI 13), a single and repeat dose trial (EPI 15), and a new upper respiratory tract infection trial (EPI 14). After data is obtained with the 2 mg dose of Neffy in adult trials, you also plan to reinitiate the pediatric PK trial (EPI 10) with the higher epinephrine and DDM dose formulation. Based on the data you provided, we have some safety concerns regarding the potential higher epinephrine systemic exposure of this dose selection. EPI 11b showed that the epinephrine AUC0-t following the 2 mg dose is around 50-70% higher than following EpiPen 0.3 mg injection. It is unclear if this is due to the variability of epinephrine PK or relatively small sample size and whether a larger sample size may present a different result. It is also unclear if the proposed 8-day washout period is adequate to account for the carry over effect (see response to Question 2c).

Due to the uncertainty in dose selection and the proposed washout period we recommend conducting your EPI 15 trial first before initiating your other trials. We also recommend splitting EPI 15 into a single dose and a repeat-dose trial and conducting a nasal allergen challenge trial. We have further comments regarding the individual trials in the responses below.

Meeting Discussion:
ARS discussed that clinical trials have been conducted with Neffy and three different epinephrine injection products. The results showed that the different injection products have relatively different pharmacokinetic profiles, depending on the device used and technique of administration. ARS stated that the Intramuscular (IM) injection with

needle-syringe, the standard treatment in hospitals and clinical settings, generally demonstrates a lower epinephrine systemic exposure compared to EpiPen. On the other hand, the PK profiles from some subjects following EpiPen IM injection demonstrated rapid spikes which the Sponsor believes is likely due to injection into blood vessels or the mechanism of injection. ARS stated the epinephrine systemic exposure following the initial administration of 1 mg Neffy is at the lower end of the range of injection products. In order to ensure efficacy and safety in the treatment of Type 1 allergies and anaphylaxis, ARS proposes to double the dose of Neffy to target the middle range of the injection products. ARS asked if this bracketing approach of targeting the middle of the range of injection products based on C_{max}, t_{max}, and partial early AUC to support the 2 mg Neffy dose is reasonable. Specifically, they would reference the exposure and safety of EpiPen and the exposure and efficacy of IM injection with a needle syringe.

The FDA stated that the approach to bracket PK from Neffy 2 mg between two approved listed injection products (IM injection with needle-syringe and EpiPen) was acceptable. The acceptability of the study results will be a review issue. The FDA clarified that with a bracketing approach, PK/PD and safety would all be reviewed and compared to both IM injection and EpiPen. We would not take the approach of delineating one listed product for efficacy and another listed product for safety. ARS agreed to this clarification.

The FDA asked ARS to clarify the length of the washout period for any future studies that involve multiple administrations via intranasal route. ARS agreed to have a minimal 12-day washout period between any of two intranasal administrations for the same naris. The FDA agreed.

Further, ARS proposed that it is likely the DDM component of the intranasal product that causes the carry-over effect of Neffy in the previous studies. However, the FDA relayed that at this time it is still not clear exactly what is contributing to the carry-over effect, whether it is DDM or epinephrine itself, as literature reported that accidental local injection of high amounts of epinephrine was known to cause some local tissue damage. ARS agrees that they have not fully assessed if any other component may be contributing to the carry over effect. FDA relayed if ARS is interested in pursuing the mechanism of the carry-over effect, FDA encourages more in vitro or animal studies to tease out the potential contribution from epinephrine. ARS reported understanding.

Self-Administration Study (EPI 13)

Question 1a:

Based on the outcomes of EPI 09 and EPI 12 showing ease of use of Neffy and very low risk of dosing errors relative to approved injection products for community use, does

the Agency believe that an additional Self-administration ('Real World') study is required with the higher 2 mg formulation of Neffy?

FDA Response:
Yes, the additional self-administration trial is required with the 2 mg Neffy product. Based on the results provided, Neffy 1 mg showed significantly decreased epinephrine systemic exposure PK results when compared to the listed drugs in the self-administration trial. You will need to confirm that this is solely due to formulation and carry over effect and not also secondary to self-administration technique. Also, depending on the results of the single dose part from Study EPI 15, you may need to enroll more subjects in EPI 13 to justify the potential safety concerns that may be related to the potential higher AUC0-6 of the 2 mg Neffy product.

Question 1b:
If an additional self-administration ('real-life') study is required with the 2 mg dose of Neffy, ARS is proposing the EPI 13 study design which is essentially the same as that previously agreed to with the Agency and conducted with EPI 09 and EPI 12. Given the low error rates (zero dosing errors in 89 subjects with the Aptar UDS in EPI 09 and EPI 12, as well as zero errors in the Human Factor Validation study completed with Neffy), does the Agency agree that the EPI 13 study can be powered based on pharmacokinetic considerations only, as was done in EPI 12, with an overall sample size of 42 persons (to complete at least 36 in all arms)?

FDA Response:
We recommend powering EPI 13 to account for the PK considerations and potential safety considerations. Pending results of the single dose part of EPI 15, you may need more subjects in EPI 13 to justify the potential safety concern. See response to Question 1a. We recommend discussing the sample size of Study EPI 13 with the Agency when the results of EPI 15 are available.

Meeting Discussion:
To justify the relatively higher epinephrine AUC_{0-t} values following the 2 mg Neffy product, ARS stated their studies showed the epinephrine AUC_{0-t} is a highly variable parameter regardless of the drug products and the route of administration. Endogenous epinephrine approximately 2 hours after the administration likely contributes to the high variability in AUC_{0-t}. A cross-study comparison showed that the epinephrine AUC_{0-t} value of the 2 mg Neffy from EPI 11b is within the range of AUC_{0-t} of injection products from other studies. ARS also stated the pharmacology and cardiovascular toxicity of epinephrine is primarily driven by peak concentrations. For this reason, ARS stated they believe early partial AUC is most important, especially the first 20 to 30 minutes.

FDA agreed that partial AUC is more critical than AUC_{0-t} for potential efficacy consideration. It will be acceptable if partial AUC is listed as one of the primary PK endpoints. However, some previous studies demonstrated that the median Tmax

following different epinephrine products could be between 30 minutes and 60 minutes. Therefore, using AUC_{0-20} or AUC_{0-30} is inappropriate. The FDA recommend that ARS use partial AUC with a later time point for PK comparison. ARS agreed. In addition, the FDA stated that AUC_{0-t} value should be calculated and compared as one of the secondary PK endpoints.

Regarding the sample size of the self-administration Study EPI 13, the FDA and Sponsor agreed to leave the decision open until the PK results from Study EPI 15 are available. ARS noted if in the EPI 15 study that the AUC_{0-t} of the IN is greater than IM with needle-syringe or EpiPen, ARS is willing to include a 0.5 mg epinephrine IM injection as a listed product in the nasal allergen challenge study (EPI 16) to provide a potential safety coverage for the high AUC_{0-t} value. The FDA agreed that inclusion of 0.5 mg IM would help create a wider bracket and appreciated ARS's suggestion.

The FDA asked if ARS agreed to perform Part 1 of the EPI-15 study (i.e. single dose cross-over) before the other studies. ARS confirmed that the plan is to first conduct EPI-15, Part 1; and other studies would not be initiated until confirming the results of the single 2 mg Neffy compared with the listed injection products from EPI 15, Part 1.

Single and Repeat-dose Study (EPI 15)

Question 2a:
Does the Agency agree that [in the repeat-dose study (EPI 15)] it is adequate to compare exposures to a single dose of IM and single dose of EpiPen to bracket the variability of injection products, given dose proportionality of Neffy is expected, and repeat exposures of injection products were determined in previous clinical studies?

FDA Response:
We do not agree. We recommend including a repeat dose IM injection comparison arm in the proposed EPI 15 trial. Given the results from EPI 11b that the AUC0-t value following Neffy 2 mg is higher than that of EpiPen, we expect a repeat dose of Neffy and a repeat dose of the epinephrine injection product in EPI 15. For details, see response to Question 2c.

Question 2b:
If repeat dosing of an injection is more desirable, does the Agency agree to use IM injection with a needle-and-syringe (the RLD) dosed both once and twice in EPI 15?

FDA Response:
We agree that you need to evaluate and compare the epinephrine PK/PD following the repeat dose for the 2 mg Neffy product with a listed IM injection product. However, selection of the IM injection product will be at your discretion.

Question 2c:

Does the Agency agree that the EPI 15 study is adequately designed to obtain the data needed to characterize single and repeat dosing with Neffy 2 mg?

FDA Response:
We recommend you consider splitting EPI 15 into a single dose and repeat-dose trial due to multiple logistical considerations in EPI 15 trial as outlined below:

1. You will need 6 treatments for Study EPI 15 due to an additional repeat dose IM injection treatment. This may exceed the maximum blood sampling volume to be collected in a clinical study.

2. We acknowledge your justification for sufficiency of a washout period of 7-8 days (IR response received on 6/11/21). However, the justification is based on extrapolation of PK data from 2-day or 4-day washout periods in EPI 03. The scientific basis of extrapolation of only two sets of data points (2 days or 4 days) based on R^2 values or Linear Mixed Effect Model is not clear. Although we agree there is a trend for the effect of washout length on epinephrine PK for Neffy, there are uncertainties for the 8-day washout period suggested by your model which is supported by the limited observed results. We recommend using a longer washout period (for Neffy administration to the same naris) similar to that of EPI 11b. However, this approach may substantially elongate the duration of EPI 15.

3. The objectives of the single dose PK comparison (leaning towards stricter PK comparison criteria) and repeat dose PK comparison (leaning towards PK trends and understanding potential safety concerns of repeat-dosing) are different.

Given the above considerations, we have the following recommendations for splitting EPI 15 into a single and repeat-dose study:

Single-dose Study

- Conduct a single-dose study with only one treatment period for Neffy. This design will provide the cleanest PK/PD profile of 2 mg Neffy for comparison to injectable epinephrine. You can use two listed products for bracketing purpose. Since Neffy will only be administered for one treatment period and washout is only necessary to cross-over Neffy to injectable epinephrine, the washout period of this study can be short. We expect the sample size of this study close to that of EPI 03.

Repeat-dose Study

- Conduct a repeat-dose study focusing on the PK/PD comparison of repeat dose administration in two scenarios (same naris and opposite nares). You only need one IM injection product as the listed product. To shorten the long wash out period required between intranasal dosing periods, consider two

sequences (intranasal – IM – intranasal) so that IM injection will be administered during the washout period. The sample size of this study will be at your discretion.

Meeting Discussion:
The Division asked ARS to clarify the sample size in study EPI-15 and if subjects would be encouraged to roll over from part 1 to part 2 of the study. ARS explained that the same 42 patients are planned for both Part 1 and Part 2 to get consistent data and that the blood volume to be collected from 6-period treatments would be acceptable according to IRBs. Any dropouts after Part 1 or any patients that don't qualify when they return to the site, would be replaced to enroll 42 patients in Part 2. The FDA agreed that this was reasonable.

Upper Respiratory Tract Infection Study (EPI 14)

Question 3a:
Does the Agency agree that the existing Neffy 1mg data that demonstrate an increase in Cmax of approximately 30% with congestion caused by Seasonal Rhinitis is acceptable and that this study does not have to be repeated with the 2 mg dose of Neffy?

FDA Response:
No, we do not agree. Your model demonstrated that after a 4-day washout period, the epinephrine Cmax following Neffy treatment may still be around 32% higher than the initial dose. Meanwhile, EPI 04 showed that the epinephrine Cmax following Neffy treatment (3-day washout) with nasal allergen challenge was only 14% higher than the Cmax without nasal allergen challenge. There is a concern that the epinephrine Cmax following initial dose under nasal congestion condition is approximately 20% lower than the Cmax without nasal congestion condition. For these reasons we recommend repeating the nasal congestion allergen challenge study with the new formulation of Neffy. See also response to Question 3b.

Question 3b:
ARS does not believe that the etiology of the nasal congestion will influence the increase in Cmax observed. Thus, if data is required on the 2 mg dose of Neffy, does the Agency agree that the EPI 14 clinical study, which will evaluate absorption in subjects with congestion resulting from an URTI, would provide adequate data to characterize the 2 mg dose of Neffy in subjects with congestion?

FDA Response:
The reanalysis of EPI 04 observed data and modeling indicates a potential lower epinephrine exposure with nasal congestion compared to without congestion. This is different than what we initially saw for EPI 04. Due to this unexpected outcome, we recommend a nasal allergen challenge trial to assess the effect of allergic triggered

nasal congestion on Neffy absorption. The nasal allergen challenge study design can be two-way crossover design with a longer washout period.

It's unclear if the upper respiratory infection study will fully explore the effects of nasal congestion due to potential differences in nasal congestion in subjects with an upper respiratory infection compared to a nasal allergen challenge. Due to this uncertainty including an additional upper respiratory infection trial in your development is at your discretion.

Meeting Discussion:
ARS described the nasal allergen challenge study design with a single injection comparator and asked if the FDA agreed or had any further comments.

The FDA agreed that the sample size, the partial randomization sequence (Neffy > IM > Neffy) and a washout period of at least 12-days between Neffy doses are reasonable.

The FDA stated the all the comparator products used in the planned clinical studies should be US approved products. ARS agreed that this was the current plan.

Pediatric PK Study (EPI 10)

Question 4:
ARS has completed treatment of 24 pediatric subjects with the 1 mg formulation of Neffy in the EPI 10 clinical trial. Given the plan to increase the dose of Neffy, ARS has placed the EPI 10 clinical trial on hold until adult data is obtained with the 2 mg dose of Neffy. ARS plans to reinitiate EPI 10 with the 2 mg dose of Neffy and enroll an additional 20 subjects with body weight of 30 kg or greater. Does the Agency agree with this plan and that 20 pediatric subjects with body weight of 30 kg or greater is adequate to support inclusion of this population in the planned NDA?

FDA Response:
We agree with keeping EPI 10 on hold until adult data is obtained with the 2mg dose of Neffy. It is premature to provide advice on the sample size as the adequacy of the proposed sample size in pediatric subjects with body weight of 30 kg or greater will depend on the results of the adult trials.

Meeting Discussion:
The FDA inquired about the pediatric study plans and whether ARS was planning on filing the NDA with pediatric data. ARS stated the NDA will likely be submitted in April/May 2022 with 6 months stability data, and the pediatric data at least for the >30 kg pediatric subjects. ARS stated the full cohort of >30 kg group is expected be included in the initial NDA but could not commit with certainty that the full data from children 15 to <30 kg will be included in the initial NDA submission. The FDA encouraged submitting as much pediatric data in the NDA package as possible.

ARS noted the number of pediatric subjects in EPI 10 will be increased to assess the 2 mg Neffy dose in children 30 kg and over and 1 mg dose in children 15 to <30 kg. The original PSP was 10 subjects in each group, (b) (4) (b) (4) Thus, ARS is anticipating to enroll at least an additional 10 pediatric subjects in the 15 to <30 kg group and 20 additional subjects in the 30 kg and over group.

The FDA commented that due to the lack of inclusion of listed products in the pediatric studies, the approvability of the pediatric dose will rely on the comparison of epinephrine PK parameters between children and adults following the Neffy products. ARS acknowledged the importance of PK matching between pediatric subjects and adults for the pediatric program.

Question 5:
ARS is also planning on utilizing the current 1 mg dose of Neffy for the pediatric population from 15 kg to <30 kg body weight (age 4 and greater). ARS plans to enroll an additional 10 subjects with the 1 mg dose in this population. Does the Agency agree that characterization of the pharmacokinetics of the 1 mg dose in children from 15 kg to <30 kg is adequate to support expansion of use to this lower body weight population?

FDA Response:
It is premature to provide advice on the sample size for pediatric subjects. See response to Question 4.

Meeting Discussion:
No discussion occurred

Chemistry, Manufacturing, and Controls (CMC)

Question 6:
ARS has demonstrated that Neffy 1 mg is stable for more than 18 months at 25°C/60% RH (b) (4) (b) (4) (b) (4) *ARS is proposing to file the planned 505(b)(2) NDA with 24 months supportive data from the original 1 mg formulation of Neffy as well as 6 months stability data at 25°C/60% RH and 40°C/75% RH for the 2 mg formulation of Neffy with three new registration/validation lots. ARS anticipates requesting an 18 month expiration date at the time of NDA approval. Provided that the stability of the higher concentration formulation is at least as good or superior to that of the 1 mg formulation, does the Agency agree that the planned*

505(b)(2) NDA can be filed with 6 months stability data on the new formulation with an ongoing commitment to continue stability through 36 months?

FDA Response:
In general applicants are expected to follow the recommendations of ICH Q1A and provide a minimum of 12 months of long term and 6 months of the accelerated stability data from at least three primary batches of their drug product in the NDA. Also, applications are expected to be complete at the time of submission and the Agency cannot guarantee that we will have the resources to evaluate additional unsolicited amendments that are submitted during the review period. We acknowledge your proposal to include supportive stability data for the lower strength formulation and your expectation that the stability of the higher strength with the limited data will meet or exceed that of the lower strength formulation. Your proposed approach does have risk in terms of the length of the expiry period that may eventually be granted upon approval. The expiration dating period of your drug product will be determined during NDA review based on the totality of the stability data in your NDA and the principles of ICH Q1E.

Meeting Discussion:
No discussion occurred

Nonclinical

Question 7:
Considering the higher 2 mg dose of Neffy, the safety margins from the previously conducted GLP toxicology study were re-evaluated and provide a safety margin of over 15 fold epinephrine and over 100 fold for DDM in the rat. Does the Agency agree this study is adequate to support the higher dose of Neffy (2 mg) and that additional nonclinical studies are not required to support the change in dose?

FDA Response:
Yes, we agree. We note that you proposed a maximal intranasal (IN) dose of 4 mg Neffy [2 sprays of 2.0 mg/100 µL ARS-1, spaced 10 minutes apart] in EPI-15. Based on our calculation, the local and body-surface-area -based systemic safety of epinephrine for the proposed 4 mg Neffy is supported by the single IN dose toxicity study of Neffy in rats, and no additional nonclinical study is needed to support this dose change.

For DDM, no additional safety qualification is needed for your proposed maximal IN dose of 4 mg Neffy with an estimated maximal exposure of (b) (4) mg DDM. We note that the new formulation contains 0.275% DDM which equals to 0.275 mg/100 µL, but not (b) (4) mg/100 µL as you used for safety margin calculation in Table 46. Correct this to avoid confusion in the future.

Meeting Discussion:
No discussion occurred

The following comments are from the *Center for Devices and Radiological Health* (*CDRH*)

Question 8:
Other studies completed with the Neffy Aptar UDS device (e.g., Human Factors Validation, Reliability) are unaffected by the change in dose, given the device is identical, and thus should be suitable for submission without repeating these studies. Does the Agency have any other suggestions or requirements necessary for the (b) (4) *of Neffy prior to filing the planned 505(b)(2) NDA?*

FDA Response:
You stated that you intend to (b) (4) Changes in the manufacturing process and (b) (4) of the drug product can impact the device performance. After completing the initial reliability report, future design changes and manufacturing process changes may occur that necessitate re-evaluation of reliability to ensure emergency-use device reliability. To determine when the reliability data may need to be updated, the impact of the change should be evaluated based on the existing reliability model. You should consider if the change impacts the design output specifications of the emergency-use nasal spray or the basic events of the fault tree analysis. If it is determined that the change does impact these aspects, creates new design outputs, or creates new risks, then the emergency-use device reliability testing should be re-evaluated for all design inputs that may potentially be impacted (e.g. essential performance requirements) and included within your premarket submission. Such potential changes in performance should be re-evaluated as reliability verification testing should be conducted on the final finished combination product after considering the appropriate preconditioning and use conditions over shelf life. In summary, consider the following approach:

1. Define all changes in the drug product and process
2. Determine changes in risks impacted by the change(s) in drug product and the manufacturing process
3. Determine how reliability testing is impacted by the change in design input, process, risk, or specification
4. Re-evaluate any performance impacted by the change

Meeting Discussion:
No discussion occurred

3.0 ADDITIONAL INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[2] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of

[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

reproductive potential.

- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*. Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as

part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[6] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[7]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999).[8] In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov.[9]

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any

[6] https://www.fda.gov/media/84223/download
[7] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[8] 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.
[9] http://www.regulations.gov

aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such

reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
(1) Example: Published literature	*Nonclinical toxicology*
(2) Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
(3) Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
(4)	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA

investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[10]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

None

[10] https://www.fda.gov/media/85061/download

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/

JI HYUN LAROSE
07/09/2021 03:47:49 PM

IND 139091

MEETING MINUTES

ARS Pharmaceuticals, Inc
8195 Run of the Knolls Court
San Diego, CA 92127

Attention: Richard E. Lowenthal, MS, MBA

Dear Mr. Lowenthal:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ARS-1 (epinephrine nasal spray).

We also refer to the meeting between representatives of your firm and the FDA on October 30, 2019. The purpose of the meeting was to obtain Agency's input on the completed clinical studies with 1 mg ARS-1 and analyses conducted and confirm that the data available for the 1 mg ARS-1 dose is adequate for filing an NDA for the emergency treatment of allergic reactions (Type 1) including anaphylaxis based on the RLD epinephrine IM injection (needle and syringe).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-9017.

Sincerely,

{See appended electronic signature page}

Ji Hyun LaRose, PharmD
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Pulmonary, Allergy, and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: October 30, 2019 @ 3:00 PM - 4:00 PM
Meeting Location: White Oak, Building 22 Room 1313

Application Number: 139091
Product Name: ARS-1 (epinephrine nasal spray)
Indication: emergency treatment of allergic reactions (Type 1) including anaphylaxis
Sponsor: ARS Pharmaceuticals, Inc.

Meeting Chair: Sally Seymour, MD
Meeting Recorder: Ji Hyun LaRose, PharmD

FDA ATTENDEES

Sally Seymour, MD, Division Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Miya Paterniti, MD, Clinical Team Leader, DPARP
Jennifer Lan, MD, Clinical Reviewer, DPARP
Bhawana Saluja, PhD, Acting Team Lead, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP)
Yunzhao Ren, PhD, Clinical Pharmacology Reviewer, DCPII, OCP
Renish Delvadia, Chemistry, Manufacturing, and Controls (CMC) Reviewer, Division of New Drug Products II (ONDP)
Aishah Ali, MD, Clinical Reviewer, DPARP
Lindsey W. Crist, Pharm.D., BCPS, Reviewer, Division of Risk Management (DRISK), Office of Surveillance and Epidemiology (OSE)
Matthew Barlow, RN, BSN, Safety Reviewer, Division of Medication Error Prevention and Analysis, OSE
Ji Hyun LaRose, PharmD, Regulatory Project Manager, DPARP

SPONSOR ATTENDEES

Richard E. Lowenthal, MSc, MBA, President ARS Pharmaceuticals
Sarina Tanimoto, MD, PhD, Chief Medical Officer ARS Pharmaceuticals
(b) (4)
Barry Koplowitz, MSc Statistician, ARS Pharmaceuticals
Brian Dorsey, MSEL, Chief Operating Officer, ARS Pharmaceuticals

(b) (4)

1.0 BACKGROUND

ARS Pharmaceuticals submitted a meeting request dated August 29, 2019, requesting a Pre-NDA meeting to discuss ARS-1 (intranasal epinephrine). The meeting was granted for October 30, 2019. ARS Pharmaceuticals specific questions from the briefing document dated September 30, 2019, are listed below in *italics* and the FDA responses are provided in normal font. FDA sent Preliminary Comments to ARS Pharmaceuticals on October 28, 2019. Sponsor meeting was held on October 30, 2019.

2. DISCUSSION

Introductory Comments:

You propose to submit a 505(b)(2) New Drug Application (NDA) for ARS-1 (intranasal epinephrine) for the treatment of allergic reactions and anaphylaxis. In your meeting package, you summarized the pharmacokinetic/pharmacodynamic program and are seeking Agency agreement regarding whether this is sufficient for submission. Based on what you have provided, we have the following comments in addition to answers to the questions you provided.

1. Because of the lack of regulatory precedence for intranasal epinephrine and your proposal for a PK/PD only program, we discussed the results you provided in your Pre-NDA meeting package more broadly within the Office of New Drugs. Based upon these discussions, we have the following additional recommendations for data to submit in your NDA.

   Your current program assesses ARS-1 in a controlled investigational environment where study site personnel administer ARS-1 to subjects in a reclined position. Because of the controlled administration of epinephrine in these studies, we have concerns about the transferability of the PK results from your current studies to a real-world situation where patients will be self-administering ARS-1. As such, we recommend you assess ARS-1 in a simulated real-world PK/PD study in which subjects self-administer ARS-1 and self-administer a comparator autoinjector.

a. The enrolled subjects should represent the population of intended users.

b. Document use errors and collect PK and PD data at a similar schedule as Trials EPI03 and EPI07 to assess comparable PK/PD upon self-administration.

c. Assess whether different positions (e.g. sitting or head tilting) or administration conditions (e.g. post-dose nose blowing, gentle sniff with administration), affect the ARS-1 PK/PD profile.

d. Power the study based on failure modes commonly used in human factor studies.

e. We recommend submitting this protocol before initiating the study.

2. Given that your product is an emergency treatment via a different route of administration than currently approved products, whether clinical studies will be required will warrant discussion at a Pulmonary-Allergy Drugs Advisory Committee meeting.

3. It is unclear from the protocols in EPI03 and EPI04 which comparator drug was used. Provide this information in your NDA submission.

4. As this product is intended for emergency use, comparison of treatment failures between your product and epinephrine injection comparators should be conducted at an individual level from both a PK (baseline-adjusted and -unadjusted) and PD perspective. Include this evaluation in your NDA submission.

5. We acknowledge the Initial Pediatric Study Plan (iPSP) submitted on October 8, 2019. We plan to review your iPSP and discuss it with the Pediatric Review Committee. Therefore, specific comments on the pediatric development program will be forthcoming.

Discussion:

ARS started the meeting by showing the Aptar UDS device and how to use it. ARS commented that the intranasal epinephrine is proposed to be enclosed by a (b) (4) however only prototypes are available of the (b) (4) ARS then went on with an introduction as to the medical need and current issues in the community with epinephrine autoinjectors.

ARS stated they are willing to conduct an additional PK/PD study where subjects self-administer ARS-1 and comparator injection products if deemed necessary by the Agency. However, this study would not truly be a 'real-world' study as they

would still be in a clinical setting to obtain PK samples and hemodynamic measurements. The sponsor anticipated there would be far more dosing errors in the self-administered injection arms than with intranasal ARS-1 based on previous experience with the Aptar UDS device in other products.

The Agency acknowledged the potential benefit of intranasal epinephrine. The Agency also commented on the need for a self-administration study to ensure that the PK for intranasal epinephrine is comparable to injectable epinephrine taking into account the variability of use with self-administration. The Agency acknowledged the study would not be 'real-world' but rather a 'self-administration' study. The study design was discussed and the Agency commented that one injection comparator would be sufficient for the purpose of this study and it is the sponsor's discretion as to which comparator they use. However, ARS noted their intention to use two injection comparators (EpiPen and Symjepi) in this study.

A population of Type 1 allergy patients (including persons with rhinitis) and dosing in a sitting position was also discussed. The Agency verified assessing the sitting position would be sufficient. The Agency also noted that the proposed sample size of 24 subjects was too small. The Agency advised ARS to base the sample size on 1) the PK variability of epinephrine in an uncontrolled setting, 2) the potential failure rates of ARS-1 and the comparator drug products, and 3) the number of failures anticipated to try and assess the difference in PK results from that failure. ARS agreed to consider the failure rates of EpiPen and Symjepi from the human factor validation study conducted for approval of Symjepi and use that as a basis to establish the sample size.

The Agency stated that they would have to discuss the appropriate training for participants in the self-administration study, but that if the approved comparator injection devices to be used in the study recommend training prior to use, the study subjects should ideally receive such training. ARS agreed to prepare the protocol design and submit to the Agency for review. The Agency confirmed that a Human Factor Validation study would also still be necessary.

ARS expressed concern regarding the Agency's position that an Advisory Committee would have to be convened to obtain concurrence from experts in the field that the development program was adequate to support approval. ARS's position is that the mechanism of action of epinephrine to treat anaphylaxis is well understood. Epinephrine is systemically-acting and the highly similar PK should be the primary factor for approval and further discussion should not be necessary at an Advisory Committee. ARS also stated that they do not understand why an Advisory Committee needs to be held to assess if clinical data is necessary given the Agency's prior approval for intranasal Narcan. ARS relayed that the Pulmonary-Allergy Drugs Advisory Committee members selected currently have no expertise in systemic allergic reactions and anaphylaxis. The

sponsor also emphasized that an Advisory Committee would delay manufacturing as their investors would not be willing to support full scale manufacturing with the uncertainty of an Advisory Committee.

The Agency explained that while they understand the concerns ARS has, an Advisory Committee is an important aspect of the review given the new route of administration for an emergency use product that has clinical efficacy trial feasibility issues. The Agency stated that additional experts with knowledge in anaphylaxis will be invited to participate in the Advisory Committee.
The Agency stated that they would not be planning to bring ARS's application to an Advisory Committee if they did not feel the PK/PD data provided by ARS had potential for review. The Agency reiterated that an Advisory Committee meeting would be necessary.

The Agency acknowledges the path taken to approve intranasal Narcan, but emphasized that there are differences between the Narcan and epinephrine development programs that are important to acknowledge. Narcan has an established minimal threshold of efficacy and no safety concerns with higher exposures of naloxone. There is not an accepted minimal threshold for efficacy of epinephrine for anaphylaxis and there are safety concerns with higher exposure of epinephrine. Furthermore, intranasal Narcan was used in the field prior to approval so there was a degree of comfort regarding this route of administration, which the Agency does not have with epinephrine. These are some of the differences that lead to uncertainties with the intranasal epinephrine program and therefore the request for more data compared to the intranasal naloxone program and an Advisory Committee discussion.

Question 1:
Does the Agency agree that, based on the EPI 03 and EPI 04 studies conducted with ARS-1 (intranasal epinephrine), a single IN administration of 1 mg ARS-1 has comparable pharmacokinetics to that of a single IM injection of 0.3 mg epinephrine (needle and syringe) in the mid-anterolateral thigh in terms of AUC_{0-t} and C_{max}?

FDA Response to Question 1:
Based on Trials EPI03, 04, and 07, we consider that ARS-1 generally demonstrated a comparable to higher C_{max} and comparable AUC_{0-t} for epinephrine systemic exposure compared to 0.3 mg IM products following single dose administration. Whether these results are applicable to real-world use is uncertain. See our Introductory Comment 1.

Discussion:
See Introductory discussions

Question 2:

ARS-1 demonstrates a higher C_{max} with repeat dosing (twice) as compared to 0.3 mg IM injection with a needle and syringe due to its more rapid absorption and more proportional accumulation. However, as compared to EpiPen, two doses of ARS-1 and two doses of EpiPen appear to have a very similar C_{max} (536 vs. 538 pg/mL). The C_{max} from dosing 0.5 mg IM twice was not evaluated in these studies, but is known to be safe in patients experiencing a systemic allergic reaction. The mean C_{max} results observed from two doses of epinephrine by IM or IN (ARS-1) administration are also within published endogenous levels from exercise or other strenuous events. Does the Agency agree that the C_{max} from two doses of ARS-1 (538 pg/mL in EPI 03 and 536 pg/mL in EPI 07) when given (b) (4) *is an acceptable exposure for safety given it is bracketed by the C_{max} exposures seen with two doses of 0.3 mg IM needle and syringe (386 pg/mL) and 0.3 mg EpiPen injection (high 538 pg/mL)?*

FDA Response to Question 2:

Based on your response to Information Request dated October 7, 2019, we consider that ARS-1 demonstrated comparable to higher epinephrine C_{max} compared to 0.3 mg IM products following repeat dose administration. Currently, based on your meeting package, there does not appear to be serious safety concerns with administration in different nares. However, we note the increased Cmax when ARS-1 is administered in the same nares and you will need to provide justification/support for the safety of this potential dosing. We also note our assessment is limited by the summary data available in the meeting package; therefore, the totality of ARS-1 safety will be a review issue. In your NDA submission, provide the change from baseline for heart rate and blood pressure, both the mean and at the individual subject level.

Discussion:

In order to further address the potential safety concerns related to high Cmax resulting from repeat administration in the same nares, ARS provided some additional data at the meeting (See Section 6 below) showing that both heart rate and systolic blood pressure change from baseline values reached a plateau phase when epinephrine Cmax reaches a certain value. ARS also explained that if a second dose of epinephrine is needed then a higher exposure may be warranted given the increased severity of the reaction.

The Agency expressed that these results are preliminary and review of the data and justification will be a review issue.

Question 3:

Given the more rapid pharmacokinetic profile of ARS-1 (t_{max}, time to 100 mg/mL, proportion of subject with t_{max}≤20 minutes) that leads to a more rapid and greater hemodynamic response (systolic blood pressure, pulse rate/heart rate) as compared in injection, does the Agency agree that these data support that the hemodynamic effect of

ARS-1 is at least as good as that of IM epinephrine injection and acceptable as a surrogate market for efficacy to support the planned NDA?

FDA Response to Question 3:
We acknowledge the hemodynamic response following intranasal epinephrine; however, we do not necessarily agree that a hemodynamic response in healthy volunteers is a surrogate marker for efficacy in patients with anaphylaxis. We also note that it is unclear why ARS-1 has a comparable or lower PK (lower C_{max} and lower AUC_{0-6h}) compared to epinephrine 0.5 mg IM, yet results in a higher PD response. In your NDA submission provide justification/support for this increased hemodynamic response. Whether the hemodynamic response in healthy volunteers is acceptable as a surrogate marker for efficacy in patients with anaphylaxis will be discussed at an Advisory Committee meeting. See also Introductory Comment 1.

Discussion:
See introductory discussion

Question 4:
Does the Agency agree that observations of mild nasal irritation, discomfort, and pain associated with ARS-1 (intranasal epinephrine) reported from clinical studies are not clinically meaningful and (b) (4) (b) (4) *for the drug product?*

FDA Response to Question 4:
Based on the results provided, it does not appear that there are serious nasal related adverse events associated with ARS-1. However, it is premature at this point to discuss (b) (4)

Discussion
No discussion occurred

Question 5:
Does the Agency agree that, based on the results from Study EPI 04, nasal congestion or edema in at-risk patients would not negatively impact the efficacy or safety of IN administration of epinephrine as ARS-1?

FDA Response to Question 5:
Based on the summary information you provided, in Study EPI 04, ARS-1 administered during nasal congestion demonstrated an earlier T_{max}, higher C_{max}, and lower AUC. As such, we do not have serious concerns regarding the impact of nasal congestion on the PK and PD profile of ARS-1. However, as stated previously, whether the PK and PD data are sufficient to support the efficacy and safety of ARS-1 for treatment of anaphylaxis will be a review issue.

Discussion
No discussion occurred

Question 6:
Does the Agency agree that the propose PK/PD analysis is adequate to support submission of the proposed NDA for ARS-1 based on the completed studies to date?

FDA Response to Question 6:
No, we do not agree. See Introductory Comment 1.

Discussion:
See introductory discussion

Question 7:
Based on the results of the EPI 03, EPI 04 and EPI 07 clinical studies, does the Agency agree that these PK/PD studies provide sufficient data to support submission and review of the proposed 505(b)(2) NDA for ARS-1?

FDA Response to Question 7:
No, we do not agree. See Introductory Comment 1. Whether clinical trials will be needed in addition to the PK/PD studies will be a question for an Advisory Committee with key opinion leaders.

Discussion
See introductory discussion

Question 8:
Does the Agency agree that the planned marketing authorization application for ARS-1 (intranasal epinephrine) to the U.S. FDA may be filed under the 505(b)(2) regulatory pathway using Adrenalin® (epinephrine) solution (1 mg base/mL) (NDA 204200; Par Sterile Products LLC) as the Reference Listed Drug?

FDA Response to Question 8:
Your proposal to submit your application through the 505(b)(2) pathway appears reasonable. The Agency typically does not advise a sponsor on the selection of a particular listed drug that may be relied upon to support approval of a proposed product. However, your proposal to rely on Adenalin appears acceptable. Please refer to the section below on the **505(b)(2) REGULATORY PATHWAY** for additional information.

Discussion
No discussion occurred

Question 9:
Does the Agency agree that the indication for 1 mg ARS-1 (intranasal epinephrine) in the planned NDA, namely, "emergency treatment of allergic reactions (Type I) including anaphylaxis; (b) (4) for the >30 kg body weight population is appropriate?

FDA Response to Question 9:
We disagree with your above indication. Given the dosing for (b) (4) is not the same as that for anaphylaxis, we do not agree with the treatment of (b) (4) (b) (4) as part of your indication. Moreover, the weight-based indication would imply approval of your product for pediatric patients weighing 30 kg. As the pediatric development plan is still under discussion, we do not agree with the weight-based dosing at this time. We recommend that your proposed indication be limited to adults pending finalization of your pediatric development plan. See Introductory Comment 5.

Discussion
The Agency explained that it was premature to comment on the iPSP as this was currently under review. Once the iPSP is reviewed, the Agency will provide advice on the pediatric plan. The Agency relayed concern regarding how pediatric nasal anatomy differences may affect drug absorption. ARS reiterated it would be extremely difficult and unethical to obtain PK data in the pediatric population given the indication. They also indicated that for intranasal diazepam (Valtoco), which is currently being reviewed by the Agency, (b) (4) The sponsor asked if ARS-1 would be indicated based on weight in concurrence with epinephrine autoinjectors. The Agency noted the pediatric program will need to be discussed with the Pediatric Review Committee and it may be possible that there could be a weight and age cut off.

Question 10:
Does the Agency agree that based on the stability of ARS-1 ((b) (4) (b) (4)) that it is acceptable to file the propose 505(b)(2) NDA based on three registration lots of 1 mg ARS-1 with (b) (4) months stability data?

FDA Response to Question 10:
No, we do not agree. The long-term testing should cover a minimum of 12 months duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life. Refer to ICHQ1E for recommendations regarding the extrapolation to extend the shelf life beyond the period covered by long-term data submitted in the application.

Discussion
No discussion occurred

Question 11:

Provided that the outcome of the EPI 08 study demonstrates similar pharmacokinetics between a 0.65 mg dose of ARS-1 and a 0.15 mg IM injection, does the Agency agree

(b) (4)

FDA Response to Question 11:

No, we do not agree. At the time of submission, a minimum of 12 months of long-term and 6 months of accelerated stability data for at least three primary batches of (b) (4) mg/mL strength should be submitted. The stability testing should be continued for a period of time sufficient to cover the proposed shelf life.

Additional Pharmacology and Toxicology Comments:

Your meeting package did not address the nonclinical portion of your planned NDA submission. We note that no response has been received for nonclinical advice and requests for information conveyed during the development program. In order to be considered a complete submission suitable for review, your NDA will need to address the following comments:

1. Your NDA submission should include final study reports (or right of reference) for all relevant pharmacology, pharmacokinetics, and toxicology studies conducted with Intravail A3. This would include any study described in your Investigator's Brochure (IB). Justification should be provided for any study not conducted in compliance with U.S. GLP.

2. An audited draft report of the GLP single-dose rat study (#2555-002) was provided in the IND submission on December 19, 2018. In the Study May Proceed letter dated February 12, 2019, the final report was requested to be submitted within 120 days (consistent with *Guidance for Industry Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products*). A complete and final GLP study report will be required in the NDA submission.

3. A number of potential deficiencies with study 2555-002 were identified in the Study May Proceed letter dated February 12, 2019: no organ weight data; no toxicokinetic data; no dosing formulation analysis; and lack of epinephrine-only group to facilitate assessment of toxicological interaction between epinephrine and Intravail A3. In addition, we note that a limited battery of organs and tissues appears to have been collected (page 363 of draft study report). The recommendations to evaluate a full battery of organs and tissues as well as the toxicological interaction between epinephrine and Intravail A3 were originally

provided in the Meeting Minutes dated July 3, 2018. Each of these deficiencies should be specifically addressed in the NDA submission.

4. You are proposing to use Intravail A3 (N-dodecyl-β-maltoside, DDM) at (b) (4)%, to augment the bioavailability of epinephrine when administered via the intranasal route. Your IB states that "The ARS-1 formulation was found to have an optimal bioavailability with the addition of (b) (4)% Intravail A3" but no nonclinical data supporting this claim have been submitted to the IND. We note that a non-GLP rat PK study ((b) (4)-285503) is briefly described in Module 2.6.5, but no study report has been submitted to the IND. Quantitative formulation details were not provided, but the study appears to have included only two groups that received Intravail A3 and there were other formulation differences between these two groups. On face, this study does not appear adequately designed to support the claim made in the IB. Submit the report for study (b) (4)285503 in the NDA submission. We note that additional animal studies would not be warranted if the clinical program with the selected formulation adequately achieved the objectives in terms of safety, efficacy, and pharmacokinetics.

5. ARS-1 formulated drug product solution is filled into type I glass vials and then assembled into the nasal actuator. A safety assessment of extractables and leachables should be provided in the NDA for all primary container closure components of the device that are in contact with the drug product during storage as well as secondary container closure components where there is a potential for migration of leachables into the drug product. See USP Chapters for 1663 and 1664 for the design of extractables and leachables studies, respectively. In addition, see Chapter 1664.1 that is specific to orally inhaled and nasal drug products. Your NDA submission should include the full reports of extractables and leachables studies and not just summary data.

6. Provide structures of any impurities and degradants of the drug substance and drug product in your NDA submission. Monitor impurities and degradation products of all active ingredients and refer to ICH Guidance Q3A(R) and Q3B(R) for possible qualification requirements. Impurities or degradants of active ingredients that are identified as structural alerts should be at or below acceptable qualification thresholds to support an NDA as described in the ICH M7(R1) Guideline, Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (March 2018).

Discussion
No discussion occurred

Post Meeting Comment:

As we anticipate your NDA submission for September 2020, we remind you that an overall reliability specification selected and corresponding confidence interval need to be provided in your submission. The Agency is working towards having all emergency use devices to provide a reliability/CI of 99.999%/(b) (4)% for delivered dose and we encourage you to aim to that level of reliability.

3.0 ADDITIONAL INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[5]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[6]

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

[5] http://www.fda.gov/ectd
[6] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999).[7] In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov.[8]

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but

[7] 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.
[8] http://www.regulations.gov

not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
(1) Example: Published literature	*Nonclinical toxicology*

(2) Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
(3) Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
(4)	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

NONE

5.0 ACTION ITEMS

NONE

6.0 ATTACHMENTS AND HANDOUTS

SEE ATTACHED

10 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JI HYUN LAROSE
11/20/2019 06:59:34 PM