DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Melina Dass, Vice President
Regulatory Affairs
Evolus, Inc.
520 Newport Center Drive, Suite 1200
Newport Beach, CA 92660

RE: BLA 761085
JEUVEAU® (prabotulinumtoxinA-xvfs) for injection, for intramuscular use
MA 559

Dear Melina Dass:

The U.S. Food and Drug Administration (FDA) has reviewed the promotional communication, a professional newsletter, "Science Behind Jeuveau" (US-JUV-2500066) (newsletter) for JEUVEAU® (prabotulinumtoxinA-xvfs), for injection, for intramuscular use (Jeuveau) submitted by Evolus, Inc. (Evolus) under cover of Form FDA 2253. FDA has determined that the newsletter is false or misleading. Thus, the newsletter misbrands Jeuveau and makes the distribution of the drug in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

The newsletter includes the following claims (bolded emphasis original, underlined emphasis added):

- "MANUFACTURING MATTERS-NOT ALL TOXINS ARE CREATED EQUAL"
- "ENSURE PATIENTS GET THE **FULL BENEFITS** OF TREATMENT"
- "Consistency and efficacy starts with manufacturing. Trust vacuum-dried Jeuveau®, a 900 kDa BoNT/A that <u>utilizes the full complex with active accessory protein for full efficacy</u>."

The newsletter is misleading because it includes claims and representations that suggest that because of its manufacturing process and formulation, Jeuveau offers benefits over other botulinum toxin products, when this has not been demonstrated. Jeuveau is one of multiple FDA-approved botulinum toxin products classified as "acetylcholine release inhibitor and neuromuscular blocking agents." These products are approved for the temporary improvement in the appearance of moderate to severe glabellar lines and all are produced from *Clostridium botulinum*. We are not aware of any head-to-head studies comparing Jeuveau to other botulinum toxin products for this use that could be used to support claims that Jeuveau has any unique or added benefits contributing to "full efficacy" or "full benefit" of treatment. If you have information or data to support the suggestion that Jeuveau's manufacturing process or formulation offers an advantage over other botulinum toxin

products in the temporary improvement of moderate to severe glabellar lines, please submit them to FDA for review.

The newsletter includes the following claims regarding nontoxin accessory proteins (NAPs), which are part of Jeveau's formulation (emphasis original):

- "**NAPs play an active role** in BoNT/A [botulinum neurotoxin type A] activity…"
- "BoNT/A with NAPs **effectively reduce glabellar strain** vs non-complexed formulation"
- "The field effect of the **900 kDa molecule** may contribute to the **precision profile**, supporting the theory larger structures **may diffuse less"**

In the context of this promotional newsletter for Jeuveau, these claims create a misleading impression that Jeuveau's formulation, which contains NAPs and has a 900 kDa molecular weight, offers additional benefits compared to other botulinum products with differing characteristics, when this has not been demonstrated. These claims are not supported by the cited review article[1] that summarizes various manufacturing processes and describes in vitro, in vivo and clinical studies. The article only theorizes about the generalized impacts to BoNT/A products and does not evaluate or provide evidence to support the comparative advantage claims above. Thus, claims implying Jeuveau offers additional benefits due to its formulation are misleading. This is especially concerning considering the claim, "900 kDa molecule[s]…may diffuse less" which also minimizes the serious risk of distant spreading of toxin effects detailed in the BOXED WARNING associated with Jeuveau.

The following claims regarding Jeuveau's manufacturing process exacerbate the misleading suggestion that Jeuveau offers additional benefits compared to other botulinum toxin products:

- "Avoids crystal formation, helping maintain integrity of the toxin, including accessory proteins, for efficacy with less risk of antibody formation.[2]"
- "In clinical studies, vacuum-dried toxin formulations produced no antibodies after exposure.[3]"

These claims suggest that Jeuveau's manufacturing process reduces or eliminates the formation of antibodies and thus, reduces the risk of immunogenicity, when this has not been demonstrated. Articles by Kauffman-Janette, et al. and Beer KR, et al. are cited in support of these claims. Kauffman-Janette, et al. describes the results from a phase II safety study where two subjects developed treatment-emergent antibodies with a lyophilized/freeze-dried formulation of Jeuveau. However, this reference does not provide support for representations regarding Jeuveau's risk of antibody formation and merely theorizes about the association between differences in manufacturing processes and subsequent risks for antibody formation. Beer KR, et al. details the results of the phase III pivotal trials for Jeuveau which

[1] Avelar R. Botulinum toxin accessory proteins: Are they just an accessory? Dermatol Surg. 2024;50:S38-S41.
[2] Kaufman-Janette J, Avelar RL, Biesman BS, et al. The first of two one-year, multicenter, open-label, repeat-dose, phase II safety studies of prabotulinumtoxinA for the treatment of moderate to severe glabellar lines in adult patients. Aesthet Surg J. 2021:1-14.
[3] Beer KR, Shamban AT, Avelar RL, et al. Efficacy and safety of prabotulinumtoxinA for the treatment of glabellar lines in adult subjects: results from 2 identical phase III studies. Dermatol Surg. 2019;45:1381-1393.

utilized the final vacuum-dried commercial formulation of Jueveau. The reference states that no subjects, who were negative for antibodies at baseline, tested positive on any of the repeat tests throughout either phase III trials. While this may be the case, according to the ADVERSE REACTIONS, Immunogenicity section of the FDA-approved Prescribing Information (PI) for Jeuveau:

> As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to prabotulinumtoxinA-xvfs in the studies described below, with the incidence of antibodies in other studies, or to other products may be misleading.

Thus, the newsletter minimizes the risk of immunogenicity with Jeuveau treatment and misleadingly suggests Jeuveau offers additional benefits compared to other botulinum products due to manufacturing processes.

Conclusion and Requested Action

For the reasons described above, the newsletter misbrands, Jeuveau and makes the distribution of the drug in violation of the FD&C Act.

This letter notifies you of our concerns and provides you with an opportunity to address them. FDA requests that Evolus take immediate action to address any violations (including, for example, ceasing and desisting promotional communications that are misleading as described above). Please submit a written response to this letter within 15 working days from the date of receipt, addressing the concerns described in this letter, listing all promotional communications (with the 2253 submission date) for Jeuveau that contain representations like those described above, and explaining your plan for the timely discontinuation of such communications, or for ceasing distribution of Jeuveau.

If you believe that your products are not in violation of the FD&C Act, please include in your submission to us your reasoning and any supporting information for our consideration within 15 working days from the date of receipt of this letter.

The concerns discussed in this letter do not necessarily constitute an exhaustive list of potential violations. It is your responsibility to ensure compliance with each applicable requirement of the FD&C Act and FDA implementing regulations.

Please direct your response to the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266**. A courtesy copy can be sent by facsimile to (301) 847-8444. Please refer to MA 559 in addition to the BLA number in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter. You are encouraged, but not required, to submit your response in eCTD format. All correspondence submitted in response

to this letter should be placed under eCTD Heading 1.15.1.6. Additionally, the response submission should be coded as an Amendment to eCTD Sequence 1554 under BLA 761085. Questions related to the submission of your response letter should be emailed to CDER-OPDP-RPM@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

George Tidmarsh, M.D., Ph.D.
Director
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/

CARTER M BEACH
09/09/2025 05:12:40 PM
On behalf of George Tidmarsh, M.D., Ph.D