October 11, 2019

Daud Chaudry
Head of Hemophilia, US
Genentech
One DNA Way
South San Francisco, CA 94080

Re: Announcement of Particulate Matter in Emicizumab (HEMLIBRA)

Dear Daud,

We are writing to follow up on Genentech's announcement of October 5, 2019, regarding the identification of translucent particles in Hemlibra, outside Genentech's particle specification. We appreciate the time you and your team have spent on the phone with us in recent days, and are writing today with a number of questions prompted by or discussed during the course of those conversations:

1. You advised us that the discovery of particles in Hemlibra is not an issue of product contamination, but rather is an issue of deviation from the manufacturing specifications that Genentech submitted as part of its application dossier to the US Food and Drug Administration (FDA). You state that a lookback investigation conducted by Genentech shows that particles have been present in some but not all batches of Hemlibra dating back as far as the clinical trials for the product; however, the presence of those particles was only recently identified.
    a. Please provide a detailed timeline of when Genentech discovered the particles, and the steps Genentech took following that discovery to investigate the matter.
    b. Please describe what sort of inspection revealed the presence of the particles.
2. You stated that there have been no safety signals or indications of any change in Hemlibra's risk/benefit ratio.
    a. Please provide information on what level of particle formation would constitute a safety risk.
    b. Please summarize the existing evidence on the safety and/or risks of human exposure to silicone oil.
3. What should patients do if they discern particles in their vials of Hemlibra?
4. Please describe what resources are available for Hemlibra users who want to communicate concerns and/or product issues to Genentech.
5. You stated that Genentech informed the FDA and other regulatory bodies (Europe, Japan, Canada, etc.) of the presence of the particulate matter in March 2019. You further stated that the FDA typically does not respond to this type of communication from manufacturers if no safety signals are present.
    a. Please describe your communications with the US and overseas regulators regarding the discovery of particulate matter in Hemlibra, and please describe what if any reply the regulators made to Genentech.

5. Please describe what if any steps Genentech is taking to eliminate or reduce the presence of particulate matter in the manufacture of Hemlibra.
    a. Please describe Genentech's anticipated timeline for implementing any corrective measures.
    b. Please advise what, if any, impact the manufacturing and/or quality control changes will have on Genentech's production of Hemlibra. Does Genentech foresee needing to pause production and/or take any other steps that could result in a product shortage?
6. As you know, MASAC made the following recommendations on October 7, 2019:
    a. MASAC expects that Roche/Genentech will conduct a full review of their manufacturing and quality control processes to determine how they may better ensure that all product meets their industry standard on the limits to particulate matter in HEMLIBRA.
    b. MASAC has requested notification of any regulatory feedback of this manufacturing issue that changes the risk-benefit assessment and has requested any follow up on this matter after Roche/Genentech have completed their manufacturing process and quality control review.
    c. The current recommendation regarding no change in prescribing practice and no interruption in the use of emicizumab is an interim recommendation pending our assessment of the full review by Roche/Genentech of their manufacturing and quality control.

    Please continue to update NHF and HFA as well as MASAC as Genentech develops answers to MASAC's recommendations, and as Genentech receives further regulatory feedback regarding this matter.

We look forward to your response with answers to these questions and we would like to keep open lines of communication on this matter. Please contact Michelle Rice, Chief External Affairs Officer for NHF (mrice@hemophilia.org) and Kim Isenberg, Vice President – Policy, Advocacy and Government Education at HFA (k.isenberg@hemophiliafed.org) with any responses.

Sincerely,

Val Bias
Chief Executive Officer
National Hemophilia Foundation

Sharon Meyers, M.S., CFRE
Interim President & CEO
Hemophilia Federation of America