Genentech
A Member of the Roche Group

October 16, 2019

Dear HFA and NHF,

We are following up to provide a response to your letter dated October 11, 2019.

Patient safety is Genentech's top priority and we are grateful for your help in our efforts to share information with the hemophilia community and for providing us a platform to establish additional clarity around the manufacturing monitoring and quality control processes we have in place.

Please provide a detailed timeline of when Genentech discovered the particles, and the steps Genentech took following that discovery to investigate the matter. -and- Please describe what sort of inspection revealed the presence of the particles.

As part of our industry-standard, quality assurance process, a routine inspection beginning on February 5th found translucent (hardly visible) particles within a single batch of Hemlibra® (emicizumab-kxwh), outside of particle specification. The first step was to identify the composition of the particle and ensure patient safety. Within one day's time, our manufacturing technicians were able to confirm the particles were a combination of Hemlibra protein and silicone oil, and that the level and make-up of the particles did not constitute an immediate safety concern, but instead represented a deviation from our predetermined specification.

Silicone oil is a non-toxic, organic polymer that has wide-ranging uses fundamental to medicine and medical device manufacturing, as well as some consumer food and cosmetic products. The particles found are not contaminants (e.g. viruses or bacteria) and if they had constituted a safety signal, our team would have rapidly communicated to the community, healthcare professionals and health authorities, prior to and during our subsequent detailed investigations.

Additional testing confirmed the particles were inherent to Hemlibra, meaning they are a part of the product formulation, and present in multiple batches dating back to product used during the initial clinical trials. Further comprehensive safety and toxicology assessments were conducted and confirmed there was no change to the benefit/risk profile.

Next, a root cause analysis was initiated, which determined that the particles could have been derived from contact with manufacturing parts lined with or containing

pharmaceutical-grade silicone oil, commonly used during the manufacturing of injectable medicines.

In March, in accordance with regulatory requirements and within mandated timelines, our team filed its safety and toxicology assessment and initial root cause analysis report with health authorities, including the FDA, EMA, Swissmedic, Health Canada and MHLW health authorities. We submitted additional follow-up reports to these health authorities in April/May, July and September/October providing updates on the root cause analysis.

Please provide information on what level of particle formation would constitute a safety risk. -and- Please summarize the existing evidence on the safety and/or risks of human exposure to silicone oil.

The particles found are inherent and made up of a combination of Hemlibra protein and silicone oil, with the available data pointing to their presence in product dating back to our comprehensive clinical trial program. A cumulative review of our safety database did not demonstrate an emerging safety signal associated with the particles leading to the conclusion that the benefit/risk profile of Hemlibra is unchanged. Genentech and Roche will continue to perform routine pharmacovigilance to look for emerging safety signals.

With the particles containing both Hemlibra protein and silicone oil, an assessment of the potential toxicity of silicone oil was conducted. The WHO has established the acceptable daily oral intake (ADI) of silicone oil to be 1.5mg/kg body weight/day, or 97.5mg/day (based on an average body weight of 65 kg).[1] However, the ADI of silicone oil administered subcutaneously has not been determined. As such, an established scientific conversion using a 10-fold safety margin for the subcutaneous route was applied, making the ADI for subcutaneous silicone exposure 0.15mg/kg/day, or 9.75mg/day (based on an average body weight of 65kg). By comparison, the maximum amount of silicone oil a heavier patient requiring 5mL of Hemlibra would potentially be exposed to is 0.0005mg (0.0001mg/mL) based on the concentration in the vials that we've determined to be out of specification. This specific silicone oil exposure is more than 20,000 fold *below* the WHO limit. Given this, the particle levels identified are well below the limits that would be considered a concern for toxicity.

What should patients do if they discern particles in their vials of Hemlibra?

Should patients or healthcare professionals in the United States have any product quality or side effect concerns with Hemlibra, we ask that they follow the guidance provided in Hemlibra's prescribing information, discard the vials in question and report such concerns.

Please describe what resources are available for Hemlibra users who want to communicate concerns and/or product issues to Genentech.

Product quality issues with Hemlibra vials should be reported to Genentech Product Complaints at (800) 334-0290. Side effects should be reported to the FDA at (800) FDA-1088 or www.fda.gov/medwatch, or to Genentech at (888) 835-2555.

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.

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All regulatory bodies have agreed with our assessment via communication per their established protocols. We received an emailed response from the EMA, Health Canada and Swissmedic, all which supported our assessment that the benefit/risk profile of Hemlibra remains unchanged, and support the continued distribution of Hemlibra to patients to avoid therapy interruption. Per FDA and MHLW protocol, they will only communicate if there is a benefit/risk profile change. We have received no such communication.

Please describe what if any steps Genentech is taking to eliminate or reduce the presence of particulate matter in the manufacture of Hemlibra. -and- Please describe Genentech's anticipated timeline for implementing any corrective measures.

Our final report outlined corrective measures to minimize traces of silicone oil in Hemlibra. We will be implementing these corrective measures before year end, and aim to discuss with the health authorities any update on our particle specification following the change.

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?

Given that there has been no change to the benefit/risk profile of Hemlibra, we do not foresee a need for a pause in production, nor do we anticipate a product shortage.

We remain committed to communicating proactively and transparently any updates that impact the benefit/risk profile of Hemlibra.

Sincerely,

Daud Chaudry
Head of Hemophilia, US

References:
1 WHO Technical Report Series 966: Evaluation of Certain Food Additives and Contaminants. 74th report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva 2011

***Roche/Genentech data on file.*