CMC Request for Information

February 2, 2015

We are providing the following detailed **request for information** on some of the issues identified in the mid-cycle review for additional clarity. Please provide all the requested information by the 10th of February, 2015.

1. Regarding retest procedures, please explain how the following historical test failures would be handled under Amgen's current policy that will be in effect for commercial manufacturing. Please also indicate how these types of test results would be reported on the certificate of analysis, under Amgen's current policy that will be in effect for commercial manufacturing.
   (b) (4)

2. The SOP that you submitted on 12/23/14 (Lab investigations and handling of OOS and unexpected results) is only applicable to tests performed at Woburn and Abingdon. Please provide information on how OOS/UR are investigated and resolved for tests performed at contract testing labs.

3. Please describe all instances where a clinical lot of talimogene laherparepvec initially failed a <u>valid</u> lot release test. Please describe in detail any investigations and retests that were performed in such instances. Please describe the final disposition of any such lots, and how the test result was reported on the COA.

4. Please describe your procedures to qualify neutralizing antiserum for performing the *in vivo* (b) (4) .

5. Regarding release testing of (b) (4) :
   a. For the (b) (4) tests, please provide a detailed description of the test method and results for (b) (4) tests (b) (4) . The provided test report (4798-00268) does not include sufficient information for us to evaluate this test, and the test report 4798-00269 was not provided. Please also specifically address:
      i. Why two different (b) (4) tests were performed.
      ii. Whether either of the (b) (4) tests included (b) (4)

b. For the *in vitro* (b) (4) assay, please provide a detailed description of the test method and results. The provided test report (4798-00270) does not include sufficient information for us to evaluate this test. Please specifically address:

   i. Why the COA indicates that (b) (4) cells were tested, while the test report (4798-00270) indicates that (b) (4) cells were tested.

   ii. Why test report 4798-00270 states that method (b) (4), but only (b) (4) were tested.

c. The report for the *in vivo* (b) (4) (4798-00326) mentions an out of specification report OOS-12-034 and an investigation study report SG12276.6976v3. Please provide these reports.

6. (b) (4)

7. Please provide the reports for OOS, Non-conformance and Deviations identified in COAs for product lots manufactured in 2013. Please provide COAs for product lots manufactured in 2014 with revised DS and DP release specifications.

8. Please revise “acceptable hold time” specifications for in process hold times. Acceptable hold times should not exceed validated times. The hold times may be extended after additional validations are completed and reviewed by FDA as a PAS.

9. Please evaluate leachables and extractables for the final DP container for recommended storage conditions. This may be a part of the ongoing stability assessment.