Responses to Clarifications requested by FDA on 03 November 2014.

**Question 1:**
Confirm that there were no changes to the fill process as a result of the facility modifications.

**Response to Question 1:**
Amgen confirms that there were no changes to the filling process as a result of facility modifications. The changes were associated with and limited to the introduction of the (b) (4)

**Question 2:**
Clarification of the filling duration discussed in table 3 in section **3.2.P.3.5 Process Validation** of the BLA and its relation to exposure time duration for the Drug Product (b) (4) in table 3 in section **3.2.P.3.3** (b) (4) **Filling, and Freezing** of the BLA.

**Response to Question 2:**
The Drug Product (b) (4) is filled directly after manufacture. The time when the (b) (4) as stated in Table 2 of **3.2.P.3.3** (b) (4) **, Filling, and Freezing** in the BLA) is one of the parameters tracked during the filling step, as well as the duration established by the media fills (as originally stated in table 3 of **3.2.P.3.5 Process Validation** and updated per the 26 November 2014 responses in Table 6). The filling operation is stopped before one of the following parameters is exceeded: 1) (b) (4) are listed in table 2 in **3.2.P.3.3** (b) (4) **, Filling, and Freezing**, copied below and clarified for ease of review in Table 1 below.
Per Agency request Table 2 in **3.2.P.3.3** (b) (4) **, Filling, and Freezing** of the BLA, will be amended to clarify and match Table 1 below.

**Table 1. Key Filling Operating Parameters for Drug Product** (b) (4)

| Parameter | Acceptable Range | Units |
|---|---|---|
| | | (b) (4) |
| | | |
| | | |
| | | |

**Question 3:**
Why is there a difference in media fill duration between Table 3 in section **3.2.P.3.5 Process Validation** of the BLA and Table 6 in response # 3 filed 26 November 2014.

**Response to Question 3:**
The purpose of a media fill is to simulate the aseptic manufacturing conditions and ensure those conditions are maintained for filling operations which include the routine interventions and incorporating worst-case activities (non-routine interventions) and conditions that provide a challenge to aseptic conditions.

The difference observed between the previous submitted media fill duration time and the new (b) (4) qualified duration time is a reflection of the introduction of the (b) (4) which allowed for a (b) (4) aseptic processing time.

The media fill duration demonstrates aseptic conditions can successfully be maintained for a time equal or exceeding the maximum expected filling time. The challenges include routine interventions at a representative frequency and non-routine interventions (i.e. line stoppages, equipment adjustments). The duration of the media fill qualification is expected to vary due to the time required for different non-routine interventions challenged in each media fill qualification.

Media Fills do not challenge product specific parameters that have been previously validated and/or characterized (i.e. control room temperature exposure time of (b) (4) ). These product specific parameters do not impact the ability to maintain aseptic processing conditions for filling activities. Media Fills simulate as close as possible the actual production operation at full batch size and duration and confirms that filling operations can be performed aseptically within the duration times obtained during media fills. Media fills are performed (b) (4) .

**Question 4:**
Explain why there is a range for the vial fill line speed.

**Response to Question 4:**
A range rather than a single value was provided for the fill speed for the (b) (4) because the fill speed is a result of the individual times associated with the several independent filling steps, including filling, stoppering, capping, and advancing of vials between the stations on the filling line. The fill speed can vary slightly due to minor changes to filler operational parameters. The parameters have been characterized and qualified resulting in fill speeds of (b) (4) respectively. As part of the routine operations, staff ensures that each station on the filler is working effectively within allowable ranges.
The operating ranges are specified in the operating procedure and used for both media fill and product filling operations.