

**APPROVED**

**By Jean Gildner at 1:20 pm, Oct 12, 2017**

From: [Harman, Christine](#)  
To: [Gildner, Jean](#)  
Subject: Please IR to Portola STN125886/0  
Date: Thursday, September 21, 2017 3:06:25 PM

---

Hi Jean,

As per our discussion yesterday's monthly meeting, please send the following IR to Portola and give them two weeks to respond.

1. Please provide the cleaning validation report VAL-30328.02.1.
2. You indicated in 3.2.S.2.5 Process Validation and/or Evaluation section 9.2 (b) (4) Cleaning Studies that (b) (4) was detected in some of the samples tested, but only present at alert levels. Please provide the alert limit for (b) (4) and actual (b) (4) counts noted during process validation. In addition, please provide information on microbial identification for noted alert limits exceeded.
3. In 3.2.S.2.5 Process Validation and/or Evaluation, sections 9.1 and 9.2 of your CR response, you indicated lifetime studies are currently being performed to support (b) (4) uses of the (b) (4) and the (b) (4). Please provide a description of the how the (b) (4) are cleaned and stored (including maximum storage time between uses), in addition, to how the (b) (4) are routinely monitored (i.e. Normalized Water permeability (NWP), bioburden, TOC etc.).
4. In regards to the Pharmaceutical Development Report: "**Measurement of Equipment Capability for Laboratory and Production Scale Freeze Dryers Relevance of Equipment Capability to the Graphical Design Space for (b) (4)**" provided to support the comparability of the lab-scale lyophilizer to the production scale lyophilizers, please provide and note the following:
  - a. Please provide the mathematical details used to determine the relationship between the process variables (i.e. (b) (4) ) based on the (b) (4).
  - b. Please indicate what pre-determined quality targets (i.e. maximum value of product temperature that influence the critical quality attributes that include (b) (4) ) were used in your development study.
  - c. The stated conclusion "that any cycle that will run on laboratory equipment should run on production scale equipment" based on demonstrating capability in regards to (b) (4) rate between the lab-scale and production scale lyophilizers does not sufficiently support that the cycles will yield the same result in regards to product quality in that the product may not experience the same "thermal history" in the lab-scale lyophilizer as compared to the production scale lyophilizer. This report is deficient in that there is no consideration or supportive data for the effect of scale up on product quality in regards to but not limited to the following:
    - i. Effects of variations in (b) (4) dynamics in the (b) (4) relating to differences in size and geometry of the freeze-dryer
    - ii. Effects of temperature of (b) (4) variations even when same set point is used

iii. Effects of variations in the rate of (b) (4)

iv. Effect of variations in (b) (4)

v. Effect of load configuration differences

Specifically, demonstrating capability of each lyophilizer alone is not sufficient in translating operating conditions between different scales. Please provide details of the scale up correlations in regards to product quality.

- d. In reference to **Table 4: Equipment Capability Curves for Laboratory Scale vs. Production Scale Freeze Dryers**, please indicate why the (b) (4) (lab-scale lyophilizer) has more data points than the production scale lyophilizers. It appears from the graph that the (b) (4) rates of the production lyophilizers were monitored at only (b) (4) points as compared to the lab-scale lyophilizer in which the (b) (4) rates were monitored at (b) (4) points. Additionally, please indicate why the capability studies in regards to (b) (4) rates did not include monitoring of the (b) (4) set at (b) (4) for the production lyophilizers, which is the maximum end of the “Proven Acceptable Range” for the (b) (4) indicated from your DoE studies.
- e. Please provide a detailed geometric comparison of the lab-scale lyophilizer and production scale lyophilizers, specifically including details of the (b) (4).
5. In Section 3.2.P.2.3 Manufacturing Process Development (pg. 27) of your CR response, you indicated that a predictive model (Figure 3.2.P.2.3-6) was determined based on the (b) (4) experiments performed at lab-scale. Please provide the details for how these (b) (4) product temperature models were generated and what data points were used. Additionally, please indicate if these models considered the combined influence of both (b) (4) on product temperature or was the influence of each parameter on product temperature only considered separately in your models. Please provide justification for your approach.
6. In the Table 3.2.P.3.5-12 **Lyophilization Process Parameters and Hold Temperature for the Consistency Lots** provided in the original BLA submission (Section 3.2.P.3.5 Process Validation and/or Evaluation), you indicated a low and high value for each parameter including (b) (4) for each of the process validation runs. Please indicate what these low and high values represent in the validation runs for (b) (4).

Thanks,

*Christine*