

**From:** Kumar, Vasantha  
**To:** [icastillo@Portola.com](mailto:icastillo@Portola.com)  
**Cc:** [Maruna, Thomas \(Thomas.Maruna@fda.hhs.gov\)](mailto:Maruna,Thomas(Thomas.Maruna@fda.hhs.gov))  
**Subject:** BLA 125586/0 Coagulation Factor Xa (Recombinant), Inactivated. Information Request regarding direct and indirect potency assays  
**Date:** Wednesday, July 06, 2016 12:14:00 PM  
**Importance:** High

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Dear Ms. Castillo,

I am writing on behalf of Thomas Maruna.

We have reviewed the following assays for the (b) (4) drug product and their validation reports submitted under STN 125586/0, and the additional information you provided in 125586/0.45, and have the following Information Request:

### **Direct and Indirect Potency Assays**

1. You stated that the potency of the first reference standard was assigned using the (b) (4) Method and that for the subsequent standards will be determined using the Direct and Indirect Potency assays, using the first standard. However, based on the information you provided, it is not clear to us how you will qualify and establish subsequent reference standards. It is not acceptable if you continue to establish reference standard using the previous reference standard lot because that contributes to significant deviation in potency due to propagation of error. You should qualify and establish one lot of your product as the Primary standard, which should be linked to your clinical outcome. You should qualify all of your subsequent lots using this Primary standard as the standard. In addition, you should perform adequate number of replicate analyses so that the potency of the subsequent standard can be assigned with an acceptable statistical power. Please provide your reference standard qualification protocol to qualify subsequent standards for review.
2. Please explain how qualifying your standard using the Direct Potency assay allows you to assign the potency for the Indirect Potency Assay as these two assays work via completely different mechanisms and are not mutually related. Please provide data in support of your explanation.

**Please provide your response by July 20, 2016.**

Thanks  
Vasantha

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