Appendix no. 14

No.	Questions	Answers
1	**Refer below question received from our bioanalytical team upon evlauting the feasibility:** We have validated assay method for [redacted] having calibration curve range 1.00 pg/mL to [redacted] pg/mL and 0.25 pg/mL to [redacted] pg/mL. We have validated assay method for [redacted] having calibration curve range 2.00 pg/mL to [redacted] pg/mL. We have validated assay method for [redacted] having calibration curve range 0.2 pg/mL to [redacted] pg/mL. We are unable to find the exact mean Cmax data of said formulation for single dose. Literature shows steady state Cmax data for said formulation. So, kindly provide the said formulation single dose Cmax data to judge the our existing linearity range suitability. After availability of data from sponsor, we will further conclude feasibility in-line with our validated assay methods. As product is FDC, we have to perform few qualitative experiments in presence of [redacted] in [redacted] assay methods and vice-versa.	Please be informed that we do not have any in-house data on the Cmax of [redacted] following a single inhaled dose. The following publication was identified as a potentially relevant source of information: "Pharmacokinetics of [redacted] administered as an [redacted] in Japanese and Caucasian healthy subjects." This was a single-centre, open-label, two-treatment crossover study with a 21-day washout period. Japanese and Caucasian healthy subjects received [redacted] (medium dose) or [redacted] once daily (high dose) for 14 days in each treatment period. Pharmacokinetics were characterized up to 24 hours post-dose **on Days 1** and 14. Based on the reported Cmax values, it appears that the analytical method range for [redacted] would need to be increased. Additionally, the Cmax values for [redacted] following a single dose are presented in the article:"Pharmacokinetics (PK) of single doses of [redacted] delivered via [redacted] devices in healthy subjects." **In this study, the reported Cmax values were lower** and it should be noted that [redacted] was not a component of the investigational product. According to "A Review of the Unique Drug Development Strategy of [redacted] A First-in-Class, Once-Daily, [redacted] Treatment for Asthma": *"As a result of a pharmaceutical interaction within the [redacted] formulation, **there was an increase in the [redacted] fine particle mass in this FDC compared** to the same nominal [redacted] dose in [redacted]. Hence, [redacted]80 µg o.d. (medium-dose strength) and 160 µg o.d. (high-dose strength) in the [redacted] formulation provided comparable [redacted] efficacy/dose strength to [redacted]160 µg o.d. (medium-dose strength) and 320 µg o.d. (high-dose strength) in the [redacted] formulation, respectively."* We have also noted that some bioanalytical sites have a ULOQ of 350 pg/mL for [redacted] Please be informed that the quotation should include all additional costs associated with the bioanalytical methods if needed. Furthermore, the validated methods should be fully established and ready before start the clinical part of the study.
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