Questions From PQRI Webinar:
Holistic QbD to Enable Product Quality
October 10, 2019

	Question Asked	Answer Given	Answerer
1	How would QbD principles lead to Established Conditions that ICH Q12 will refer to when finilized?	QbD with enhanced process and product understanding is a key contributor to defining ECs. ICH Q8, Q9, Q10 are all enablers of EC concepts.	Rakhi Shah
2	PSD can be included in the drug substance specification as a control strategy?	Drug substance specification typically does include particle size distribution limit(s).	Ajit Narang
3	If USP monographs available then also agency ask for tighter specification??	USP monographs provide a minimal quality standard. Additional controls, including tighter specifications, may be requested depending on the product and associated risk.	Rakhi Shah
4	Why pvp has been selected?	Among all the excipients screened for entecavir solubility enhancement, PVP was the best. It also acted as a binder. Therefore, based on dual roles PVP could play, it was selected in the formulation.	Divyakant Desai
5	Are the PB-PK studies acceptable to agencies as an alternate for BE stidues?	The FDA and EU accept biowaivers on the basis of PBPK modelling. The model has to comply to current guidelines (cf. links in the slides presented)	Xavier Pepin

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6	Dr. Shah, Does DOE allow a range of excipients in the formula to be approved(e.g. % surfactant on slide 36). Thank you .	The example given was mainly for a post approval change if necessary, not necessarily for a range of excipients in the approved formula.	Rakhi Shah
7	How would you evalute the added value to have Qbd in case of quality global crisis such as Nirosamine management for example in particular term of control strategy?	QbD helps evaluate the effect of raw materials variability, changes in manufacturing process and how it impacts the product quality. Thus, it is of great value to understanding important material attributes and developing a control strategy that can maintain the manufacturing process under a state of control	Rakhi Shah
8	To Dr. Shah, where should we draw a line between CBE0 and CBE30.	CBE supplements are appropriate for changes that have a potential to have a moderate impact to quality. In certain cases, FDA has identified changes that are appropriate for submission as a CBE-0. Please see various FDA guidance documents on this topic, including “Changes to an Approved NDA or ANDA” and those that start with “SUPAC” for more information.	Rakhi Shah

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9	Is there a reason why you chose such a large tablet weight (200 mg and 400 mg) for such a low potency per unit dose? Would pursuing a lower tablet weight have helped with you CU issues (although I am sure it would not have resolved them)?	The main reason for the large tablet weight was to ensure that all the PVP solution containing drug is absorbed. Additionally, some additional water used to rinse tubings and PVP-drug container is also absorbed.	Divyakant Desai
10	Is dissolution RTRt model a topic considered as emerging technology to seek ET engagement? (Q for Rakhi Shah)	Only innovative element that the firm is proposing is a model based RTRT approach for dissolution, then it doesn't by itself qualify for being included into the ETT program. However, firms can reach out to the agency early on i.e. prior to submission of the application to discuss their proposed modeling approach with the agency. They can do this via a standard Type C meeting request.	Rakhi Shah
11	How much is the acceptability of PBPK models by FDA in recent submissions?	In terms of numbers, most reviewed/accepted PBBK models cover DDI studies, but there are some PBPK models related to DS and DP quality. This is a field that the FDA is very interested in as it follows on the QbD principles and patient-centric approach.	Xavier Pepin

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12	PBPK modeling, how is it important to do the right in vivo predictive dissolution? or QC dissolution method acceptable for weak acidic drugs? you did work on gastric pH but will it be important for acidic drugs? I feel it is more important for basic drugs	All dissolution methods are theoretically acceptable as long as they are biopredictive (or clinically relevant), ie if they allow to predict clinical outcomes when used as input to PBPK modelling. For immediate release formulations, an approach such as P-PSD or z-factor is preferrable as it is more mechanistic and will be able to capture the effect of system parameters like GI tract pH, volumes and transit times. The gastric pH is indeed more important for weak bases as for a very low solubility base, that is the only chance (if the pH is acidic) to dissolve. For weak acids a higher pH value may lead to more rapid dissolution and absorption, but if the solubility is enough in the small intestine, the drug will dissolve and be absorbed with a small delay (due to gastric residence time)	Xavier Pepin

Moderator: Chris Moreton, Ph.D., FinnBrit Consulting
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