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Building QbD frameworks retrospectively for commercial products and the use of scale-down model qualification strategies to support continuous improvement

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BUILDING QBD FRAMEWORKS RETROSPECTIVELY FOR COMMERCIAL PRODUCTS AND THE USE OF SCALE-DOWN MODEL QUALIFICATION STRATEGIES TO SUPPORT CONTINUOUS IMPROVEMENT

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A science-based justification for many continuous improvement and post-approval submissions on 'legacy products' (i.e., commercial products developed without a QbD rationale) requires that some of those missing QbD elements in the original filing, be defined retrospectively.

Here we present a new proposal to achieve that, that is general and very capable of supporting the transition of 'legacy' non-QbD into quasi-QbD filings. It is based on (1) a formal criticality analysis to the current process version to support the choice of quality attributes and process parameters in the filing, and identification of additional ones that may impact the quality target-product profile (CQAs, CPPs, QTPPs); (2) risk identification and assessment considering the current design to list all relevant failure modes; (3) a gap analysis of which risks are not addressed by the current CMC strategy; (4) proposing a revised control-strategy in view of currently available technical developments to address and/or mitigate unmet risks in the filed strategy; (5) defining a multivariate operating-space based on available nominal manufacturing data, as sorrogate for a true design-space; (6) challenging with OOT historical events (and OOS when available) the revised CMC strategy and the quasi-QbD rational built retrospectively.

The above framework by its own formulation creates a knowledge-based (KM) and foundation for future change managements as it moves from a simple data- and evidence-driven approach to an holistic (over process and over history) approach. It maps out a commercial process as-is, end-to-end (RMs-USP-USP-BP) and over an extended period of manufacturing history, in such way that we can claim that all relevant information and knowledge are extracted from the available data and evidence through specific tools. Often, during such analysis the need of scale-down confirmation and optimization runs (e.g., through design of experiments, DOEs) is detected as a way to build or increase confidence in the filed ranges and also as a way to establish improvement opportunities. Several strategies can be used to ensure that a good match between conditions at very different scales is obtained (viz., through the use of fingerprinting PAT techniques at each scale investigated) both for USP as well other unit operations, as described in a recent patent filing by us [EP-application Nr. PCT/EP/2014/079152].

As with a true-QbD third stage validation, qualified scaled-down process versions serve to test revised control strategies. Our experience shows that the changes deal either with (1) unmet / uncontrolled risks in the previously filed strategy, (2) operation changes that impact occurrence of a failure mode, and (3) detectability improvements of a known failure mode through improved monitoring.

Our talk discusses the outlined framework and how it can specifically be applied to real processes based on standard CHO-based platforms.