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IMPACT OF POLOXAMER 188 VARIABILITY ON BIOLOGICS MANUFACTURING: MITIGATIONS AND CAUSAL INVESTIGATION

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Poloxamer 188 (P188), a water-soluble, synthetic copolymer with hydrophilic as well as lipophilic properties, is widely used as a cell protectant for bubble-induced shear during cultivation of suspension-adapted mammalian cells for large-scale production of protein-based therapeutics. Poor cell growth and lower product yield has been recently observed at commercial scales in more than one Chinese hamster ovary-based manufacturing process within Roche network when specific lots of P188 were used. An investigation is being conducted to unearth the root cause of “poor-performing” P188 lots and to identify means to mitigate the product supply risks. P188 raw material is currently sourced from a single vendor with additional supply constraints and risks associated with the impending change in the vendor manufacturing facility and location. These factors further exacerbate the supply risks for the drugs produced by Roche. A multi-pronged approach has been undertaken. A small-scale bioreactor based screening assay was developed where a model commercial cell line was subjected to a relatively high shear stress environment to differentiate between good-performing and poor-performing lots. To discern the root cause for the lot-specific loss of P188 functionality, analytical fingerprinting methods have been used to test different hypotheses including presence of high molecular weight species¹. Pilot-scale fractionation was performed using good- and poor-performing P188 lots to isolate fractions with different molecular weight and characterized using methods including LC-MS/MS and 2D NMR. The structure elucidation results were further evaluated to discern the cell-protective functionality of the different fractions. Lastly, in order to ensure uninterrupted supply of our medicines to patients, a comprehensive evaluation of an alternate manufacturer of poloxamer 188 was performed. Taken together, the findings from this investigation provide insights to understanding a long-standing risk in biopharmaceutical manufacturing.

¹ Weiwei Hu, Pluronic F68 cell culture raw material evaluation: Scale down model development and mechanism investigation, Biogen Idec, Cell Culture Engineering XIV, 2014