

## Review on the Tocilizumab Bioprocessing Proposal for COVID-19<sub>1</sub>

Tamara et al proposed a novel bioprocessing design for the Tocilizumab (Actemra) treatment for severe COVID-19 patients in the U.S. It is a repurposed monoclonal antibody that targets the IL-6 receptor to suppress the immune-inflammatory response. Designed and engineered by Genentech, a member of the Roche group, Tocilizumab is currently under phase III clinical trials, and its positive results indicate the effectiveness of the drug, and the company most likely needs a practical plan for manufacturing the product to meet the mass market demand.

As a recombinant humanized IL-6R monoclonal antibody, Tamara et al found literature that classified Tocilizumab as an IgG1 antibody, and the variable region is engineered to be IL-6R specific. The mechanism of action (MOA) entails how the monoclonal antibody competitively inhibits the IL-6 binding sites on the cell surface and lowers the patient's inflammatory response.

In regard to the product profile, Tamara et al explicated that the drug is single-use, needs to be intravenously administered, has an up to 2-year shelf life (stored at less than -50 °C), and viable under an acidic environment (pH 6-6.5, with a tolerable variation up to 40%). As for the control quality attributes(CQA), Tamara et al emphasized the purity of the final product is crucial, and the team aimed for an impurity concentration less than 100ng/mg and impurity aggregates less than 5%. A note brought up by the faculty audience was that the concentration of the final product (50-60 mg/mL)was somewhat inconsistent with the target concentration (20 mg/mL) specified in the product profile, which should have a further explanation to avoid misunderstandings.

There were several highlights related to the upstream and downstream processing. In order to meet the demand of the whole patient population in the U.S, there was a proposed 2400kg of Tocilizumab produced yearly in WAVE bioreactors that are 80% filled and have a 50% yield. The host cells are derived from CHO DXB11 and will be transferred with CHO V4. The upstream processing would be more sophisticated if there were additional steps to check if the viral transfection was successful before moving onto the downstream steps. For the downstream processing, the team planned to use disk stack centrifugation to remove solids, clarify liquid components, and perform microfiltration, with a pore size of 0.05-8um, to attain the permeate. Next, viral inactivation would be achieved by disrupting viral envelopes and capsules. One caution is the pH level that the environment shouldn't be too acidic that it might potentially denature the mAb products. Then, a protein A chromatography would be used to capture IgG mAbs. After a series of purification steps (cation exchange chromatography, ultra-diafiltration, and nanofiltration), the final drug is purified and aliquot, along with injection mixture, into type 1 clear glass vials, which would be a stopper and crimp sealed, and ready for shipment to hospitals nationwide.

The final product price was placed at \$350 per vial, which was way cheaper than what it would cost in a real-world scenario, and the faculty suggested to have the price increase to at least \$1,500.

1. Tamara M., Albert L., Lea O., Milena K., Cole A., Keziah K., Juliet C., Ramiro A., Joelyn V.