| Wyzer BioPharma | Request For Proposal |
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# Request for Proposal:

## *Curemumab* GMP Production

## for

## Phase I Clinical Trials

**November 2017**

1. **Introduction**

This information is a request for proposal (RFP) for the production of an IgG1 monoclonal antibody, *Curemumab*, Drug Substance (DS). Wyzer BioPharma is requesting a cost estimate through project completion. Costs should be all inclusive, and should include resin and raw material estimates as well as complete costs for performing 3rd party testing, if needed. Please provide a cost breakdown for the staged activities listed below and a detailed project plan with time estimates (Gantt Chart). The project is expected to begin in 4Q17.

**Contact information:** Please relay all questions and completed proposal to:

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| Senior Director, External Supply<br>Wyzer BioPharma<br>San Diego, CA USA | Sourcing Lead, Global Procurement<br>Wyzer BioPharma<br>Sandwich, UK |

2. **Scope**

Wyzer BioPharma will supply the Vendor / Contract Manufacturing Organization (CMO) with cell bank vials to perform the activities needed to produce and deliver both non-GMP and GMP DS. The project goal is to provide materials and documentation capable of supporting an analytical method development standard of DS, formulation development, and a Phase 1 clinical trial per applicable US requirements. Wyzer BioPharma will supply the cell line, a developed DS manufacturing process with related knowledge, and developed analytical methods. CMO will provide facilities, materials, manufacturing expertise and labor, testing of all materials and DS (as specified in Section 10), and related documentation sufficient to meet requirements for approval to manufacture DS for use in Phase 1 clinical trials. Wyzer BioPharma will be responsible for formulation development, DS analytical standard and methods development, producing drug product, and all clinical trial protocols and execution.

Wyzer BioPharma's platform processes and methods will be provided to the CMO. The CMO will perform studies at small (bench-top) scale to confirm the platform process suitability. Additional optimization studies may be required depending on the outcome.

3. **Deliverables**

The project goal is to manufacture non-GMP and GMP DS by processes provided by Wyzer BioPharma:

- Development supplies: 50 to 75 g of non-GMP material for formulation development work (formulation development to be performed by Wyzer BioPharma)
- IND-enabling non-human safety studies (Reg-Tox) supplies: non-GMP, 2 x 500 L scale
- DS intended for human clinical trials: GMP, at least 2 x 2,000 L scale

As the project may be considered for further development, it is expected that the process will be designed such that an increase to commercial scale can be reasonably achieved with standard development. Activities will be considered complete upon Wyzer BioPharma's acceptance of material and all required documentation. All reports should be written with sufficient detail to explain methods and process development recommendations, and to support Regulatory filings, as applicable.

4. **Timing**

Pre-MCB vials will be provided to initiate process confirmation and non-GMP Reg-Tox production. Fully released GMP MCB vials will be made available for GMP production. Delivery of non-GMP Reg-Tox material should be prioritized as this event is typically critical path for IND filing.

5. **Cell Bank Vials**

Cell bank vials will be provided to the CMO. Please describe the total number of vials needed, and the minimum vial testing requirements for development work and GMP production, respectively. Pre-MCB vials may be provided to enable non-GMP process development work.

*6.* ***Candidate Cell Line Screening (Not in scope for Case Study)***

Three cell lines will be provided to CMO. Each cell line will be fermented and purified at the 2 L scale in duplicate according to Wyzer BioPharma's platform process. The results will be used to identify the lead candidate for further development. Selection criteria will be based on cell culture growth characteristics, metabolic profiling, titer, and purified mAb Critical Quality Attributes (CQA). Based on cell culture and purification performance, additional process development may be requested described below. Process development would be performed on only one selected cell line.

7. **Development Supplies**

Provide 50 to 75 g of purified mAb for formulation development activities which will be performed by Wyzer BioPharma. The development supply does not have to be manufactured by an optimized or final process. It is anticipated that a single 100 L run would provide enough material, assuming 2 g/L titer and a 50% purification yield from Wyzer BioPharma's platform 2-column process.

8. **Cell Culture Process Confirmation & Development**

**8A)** Vendor will scale up the process using the Wyzer BioPharma's platform process. It is expected that small- to mid-scale runs (e.g., 2 L to 100 L) will be required to confirm parameters necessary to execute 500 L and 2,000 L fermentations. Please provide detail for the number and scale of fermentations anticipated to enable 2,000 L production.

***8B) (Not in scope for Case Study)***

Additional upstream process development may be required based on the outcome of Section 6. If required, a DOE approach would be used to perform 3 rounds of fermentation, 6 x 2 L for each round evaluating set points provided by Wyzer BioPharma, for a total of 18 fermentations. Each fermentation would require that a small portion be harvested and purified by Protein A purification, then subjected to size-exclusion HPLC analysis to determine aggregate level and acidic species. It is understood that this would delay Reg-Tox & GMP production; please provide an alternate timeline in case section **8B** activity is required.

9. **Purification Process Confirmation & Development**

**9A)** Vendor will use Wyzer BioPharma's platform purification process, a two-column process (Protein A and anion exchange [AEX]).

***9B) (Not in scope for Case Study)***

Additional AEX process development may be required based on the outcome of the initial evaluation. Wyzer BioPharma would provide a protocol defining conditions for three AEX runs. Each run would require 0.5 g of Protein-A purified mAb to be loaded onto a 3 mL scale AEX

column. Purified samples would be then subjected to size-exclusion HPLC analysis to determine aggregate levels and acidic species via imaged capillary electrophoresis. The icIEF method would be provided by Wyzer BioPharma.

10. **Analytical Methods Development for IPC and Release Testing**

CMO is responsible for performing in-process control testing (IPC) as required by suitable methods. Wyzer BioPharma will supply IPC protocols as needed, as well as any assay required to evaluate upstream/downstream process performance. The majority of Release and Stability testing will be performed by Wyzer BioPharma or an approved 3rd party, with the exceptions listed below.

The CMO will be responsible for release testing of the cell culture harvest (*Mycoplasma*, Minute Virus of Mice, Electron Microscopy for retroviral particles, *in vitro* Adventitious Virus, and Bioburden). For final Drug Substance, CMO is responsible for the following tests: Appearance, pH, Concentration (by UV scan), Bioburden, and Endotoxin. Compendial methods should be used when possible.

11. **Formulation Development**

Not required for this project.

12. **Non-GMP Pilot Bulk Drug Substance Manufacture**: 2 X 500 L

Reg-Tox manufacture should be performed at the 500 L scale. Please include raw material and resin estimates separately.

13. **Viral Clearance**

Collect samples from the appropriate run (TBD) per approved sampling plan. Wyzer BioPharma will be responsible for 3rd party Viral Clearance testing.

14. **GMP Bulk Drug Substance Manufacture**: 2 x 2,000 L

GMP manufacture should be at the 2,000 L scale. Please include raw material and resin estimates separately.