STANDARD REGULATION FOR STEM CELL PRODUCTS IN INDONESIA

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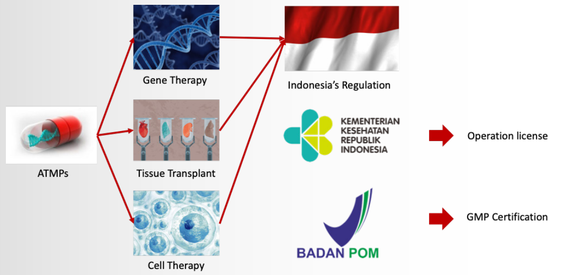
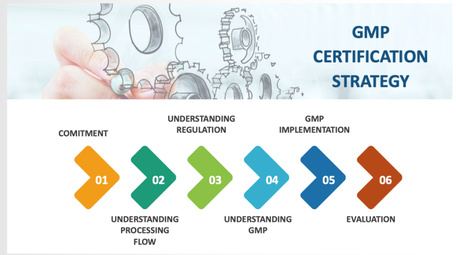
Background

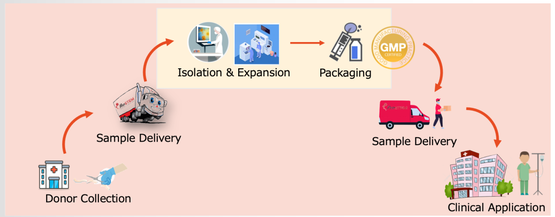
Advanced Therapy Medicinal Products (ATMPs) are genes, tissues, or cell-based medicines for human use. Currently, there has been a constant increase in the number of clinical trials evaluating ATMPs, with a focus on Cell-Based Medicinal Products (CBMPs), including stem cell-based medicinal products for regenerative medicine.



However, the scientific assessment of stem cells product is still challenging according to the regulatory perspective. It is important to standardize the manufacturing process because cells can be impacted by various factors during their isolation and processing. In complying with standard regulation for clinical-use stem cell manufacturing in Indonesia, a laboratory should establish an operational permit according to Indonesia's Ministry of Health Regulation, PERMENKES No 50 tahun 2013 about Operation of Stem Cell Processing Laboratory for Clinical Application. Accordingly, public manufacturing laboratory should be GMP certified by the local FDA, Badan Pengawasan Obat dan Makanan. Strategy is need in the process of GMP certification.



During UC-MSC production, raw material, packaging material, production flow, facilities, equipment, human resources are maintained and should comply with the local standard to ensure the quality of the product and the patient's safety. Upon the certification process, both the qualification of laboratory facilities and equipment and the manufacture validation process shall be completed. The validation process includes the donor qualification, isolation and expansion of stem cells, cryopreservation and thawing, packaging, and delivery process.



Aims

In this study, we would like to describe the validation process in Umbilical Cord-Mesenchymal Stem Cells (UC-MSC) manufacturing that comply with local GMP regulation in Indonesia.

Method

ProSTEM laboratory has conducted qualification of facilities and equipment in normal condition and worst-case scenarios with three replications. After qualifications have been passed, the validation process of Umbilical Cord-Mesenchymal Stem Cells (UC-MSC) is performed in the facilities. UC-MSC obtained from qualified donors who passed medical screening.

Cells are isolated and the propagated until passage 5 using validated protocol. All materials used in the process should pass all the acceptance criteria. In each passage, cell counting, viability, and sterility testing is done. The last passage (P5) is classified as the final product and packaged as required. Then, quality control testing is performed including endotoxin, mycoplasma, immunophenotyping, differentiation, viability, sterility, and genomic stability.

UC-MSC is wrapped in primary and secondary packaging for delivery. Product stability of UC-MSC is also conducted in five days consecutively. After 5 days, viability, sterility, endotoxin, mycoplasma, immunophenotyping, and differentiation are evaluated.

Result and Discussion

Three umbilical cord donors showed negative result for HBsAg, Anti-HCV, Anti-HIV, Anti-Toxoplasma IgM, and Anti-CMV IgM screening. Supporting documents such as doctor registration certificate, laboratory agreement, medical history, and storage consent form have been completed. The pre-sterility result showed a negative result and all samples produced more than 4.5 x 10^6 cells in the first passage (P0).

The cryopreservation process for UC-MSC does not affect the viability of cells because viability recovery after cryopreserved and recovery cell after thawing showed results of ≥ 80%. In-process QC testing such as sterility showed negative results, while quality control testing results for final product are negative endotoxin; negative mycoplasma; surface marker (CD73+, CD90+, CD105+) greater than 80%; able to differentiate into osteocyte, chondrocyte, adipocyte; and normal karyotype.

Primary and secondary packaging of UC-MSC showed negative results for sterility. All three packaging for delivery able to manage temperature of 2-8˚C up to 18 hours. Cell culture after storage at 2-8˚C can attached well compared to cells 15-25˚C and 37˚C. Overall, our product can maintain its characteristics at best at 2-8˚C.

Conclusions

Qualification and Validation is important process required in GMP certification process.