Validation of Cell Substrate

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The goal of validation of a cell substrate is to provide sufficient information to enable a manufacturer to identify the cell and demonstrate stability and purity of the substrate. Apart from the recommendations from KFDA, the validation of a cell substrate is a practical aspect of good manufacturing practices. The validation of the cell substrate provides that information to enable a manufacturer to exercise a degree of control over a biological system that is the first step in a production system. There are several issues to satisfy the requirements for validation of a cell substrate. First, the history of a cell line should include not only its passage history, but also the origin of the cell. Isolation method, cloning and subcloning procedures, culture conditions and media used for propagation and storage should also be described. Second, another major objective in the validation of a cell line is establishing the phenotypic characteristics of the MCB (Master Cell Bank) The phenotype of a cell line can then be used to monitor batch-to-batch variation during production and to verify the identity of the WCB (Working Cell Bank). The method used to establish or confirm identity may include morphology, doubling time, production expression rates, karyology, isoenzyme analysis, and other markers that may be relevant within the culture process. The characterization of the plasmid or gene insert certainly contributes to the identity of the cell line. Third, the genotypic characterization of a cell line should provide a detailed description of the vector and inserted gene, its state within the host cell, the copy number of the gene per cell, restriction maps and nucleotide sequence of the cloned gene. These data provide not just a means to identity or characterize the cell, but also, provide a basis to verify directly the stability of the cell line and thereby, the safety of the product system.

In the mammalian cell system, the virus validation is another important issue in the safety of the production. The objective for the virus validation is to assure product safety by minimizing the potential for viral contamination. Because of the enormous number of potential agents that could contaminate a culture, the validation must be both broad and flexible enough to address the potential. There is a wide range of potential virus species that can contaminate a cell line. There are endogenous viruses, such as the retroviruses, that endanger a number of species concerns. Exogenous adventitious viruses may contaminate a culture from laboratory technicians or from

tissue culture reagents, such as trypsin or serum. Therefore, because of the diversity of routes of contamination and types of agents, it is essential that the screening strategy cover as broad a range of adventitious agents as possible. If a suspected agent is detected, it is essential that the viral species be identified with additional testing. Validation of the purification process to remove or inactivate the contaminating virus should be considered as part of the total process validation study.

This talk will mention the requirements of the cell substrate by KFDA and then discuss the limits of the requirements for the approval of recombinant DNA products.