1. INTRODUCTION

1.1 Viral safety issues for monoclonal antibodies

Therapeutic compounds derived from biological fluids or tissues, or biopharmaceutical products, pose a number of problems for manufacturers and regulatory authorities when considering virus safety. Previous experience has demonstrated the potential for transmission of infectious viruses from a small number of biopharmaceutical products. Examples include the transmission of Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) in blood products, and the transmission of Simian virus 40 (SV40) in vaccines. Monoclonal antibodies intended for therapeutic use pose similar virus safety concerns since the cell culture process used for production of such products can support the growth of adventitious virus particles. These virus contaminants may be inadvertently introduced into the final formulation via raw materials or personnel. For these reasons it has been a regulatory requirement for several decades now that any manufacturer of biopharmaceuticals of human or animal origin assess the safety of the product for use in humans. Although there are several types of potential microbial contaminants of concern, the majority can be removed by standard sterile filtration. Such filtration treatment would have little, or no, effect on the level of virus particles within a product. Therefore, a major
element in the safety assessment of biopharmaceuticals is ensuring, as far as possible, the product's freedom from contaminating viruses. There are three principle complimentary approaches used to control for potential viral contamination of biologicals:

- Selection of the source material
- Testing of source materials and products from various stages of the manufacturing process for the absence of detectable virus
- Testing the capacity of the manufacturing process to remove or inactivate viruses

The latter is referred to as a virus clearance study, or a virus validation study, and plays an important role in establishing the safety of biopharmaceuticals. The regulatory definition of validation of this type is:

"A documented programme, which provides a high degree of assurance that a specific process will consistently manufacture a product, meeting predetermined specifications" (CPMP/ICH/295/95, 1997)

There are inherent limitations in testing both starting materials and bulk product; the sample size sets a statistical lower limit on the level of contamination that can be detected and the assay methods determine the range of viruses that may be revealed. With increasing sophistication of techniques new viruses are being uncovered in biological materials, for instance circoviruses have recently been found as significant contaminants of both human and animal biological materials. The limitations on testing, indicated above, underscore the importance of choosing optimal virus clearance technologies and conducting appropriate virus clearance studies.

Since virus clearance study data would represent a significant part of a submission to a regulatory body for a biopharmaceutical product, an in-depth understanding of the regulatory requirements for virus clearance in different countries, for different product types, and at different phases of development would be required.

To address the virus safety concerns for biopharmaceutical products, and to help manufacturers understand the level of clearance study required for their particular product, world-wide regulatory agencies have prepared guidelines detailing the testing and safety evaluation that should be performed prior to any submission. A number of guidelines from individual regulatory bodies are available which cover specific topics or products. The most relevant guidelines for virus safety assessment of an antibody product are listed in Table 8.1 below: