Purification of the Biopharmaceutical

“The extent of purification of recombinant DNA products should be consistent with the intended use of the product. Drugs and biologics which are to be administered repeatedly or at high concentrations should be adequately pure to prevent the development of undesired immune or toxic reactions to contaminants. The purification process should be designed to specifically eliminate detectable viruses, microbial and nucleic acid contamination and undesirable antigenic materials.”

1985 FDA guidance on the production and testing of recombinant DNA-derived products

1. GOALS: PURITY, RECOVERY AND CONSISTENCY

From the harvested production, the expressed biopharmaceutical needs to be purified in sufficient quantity to produce the bulk active pharmaceutical ingredient (API). Regardless of the type of production system used or its scale, the products will be purified using procedures common to either protein or DNA molecules.

The goal of the purification process is to effectively separate the product from both its impurities and any putative adventitious agent contamination, without unacceptably altering the product.

Each harvested production system presents similar but unique challenges for the purification process; for example, if recombinant mammalian or human cells are used, the
purification process must be robust in its ability to remove viral contaminants. It should be noted that for some gene therapy products (e.g., a patient’s cells which have been genetically altered with a viral vector), purification may not even be possible.

1.1. Two Major CMC Regulatory Concerns for Purification

There are two major CMC regulatory concerns about the purification processes used for biopharmaceuticals:

1. Proper Design

   The purification processes must be adequately designed to sufficiently separate the biopharmaceutical product from the many components present after the harvest of the production process, including the capacity to remove putative viruses that might accidentally contaminate the production system.

2. Consistent Performance

   The purification processes must have adequate procedures and controls in place to ensure that the process is consistently operated, and that it yields a consistent product of the desired quality.

It is the responsibility of each manufacturer to demonstrate to the regulatory agencies that their specific purification process is adequately designed and controlled, yielding the desired product.

Note, the regulatory agencies, in contrast to the manufacturer, are not that concerned about the level of product yield, except when that yield might impact the ability of the manufacturer to produce enough product for market launch.

1.2. Need for High Recovery of a Pure Product

A manufacturer does not really have a useable purification process until it can be shown that the process yields a suitably high recovery (many purification processes provide overall recoveries of the biopharmaceutical in the 60% level or higher) and acceptable product purity (many purification processes are targeted at the 95% purity level or higher), every time the process is run.

Most purification processes at Phase 1 will not meet these criteria, and they are not required to do so. Unfortunately, many biopharmaceutical companies rush into the clinic with a purification process, fail to commit to do process development alongside their clinical development; and if they find clinical value, they are then faced with a purification process that either may not meet regulatory expectations or cannot be run economically. Continual development and improvement of the purification process during the clinical drug development stages is essential for eventual commercial success.