Recombinant Source Material: Master/Working Banks

“If there are any reasons to believe the manufacturing or controls for the clinical trial product present unreasonable health risks to the subjects … such as a poorly characterized master or working cell bank.”

CMC reason for the FDA to place a ‘clinical hold’ on a submitted Phase 1 IND\textsuperscript{37}

“Basis for a refusal to file under 21 CFR 601.2(a) … insufficient description of source material (including characterization of relevant cell banking systems) …."

CMC reason for the FDA to ‘refusal to file’ a submitted BLA/NDA\textsuperscript{31}

1. NEEDED: RELIABLE, CONTINUOUS, STABLE GENETIC SOURCE

The genetic source material needed to initiate a biopharmaceutical manufacturing process must be reliable, continuous and stable.
The genetic source material must be reliable in terms of safety and quality so that the desired specific biopharmaceutical product, and only that product, is manufactured, without the introduction of adventitious agents that could harm the patient.

The genetic source material must be continuous in terms of an adequate long-term inventory in order to be able to produce the same biopharmaceutical product over and over again, for extended periods of time.

The genetic source material must be stable in terms of storage so that the biopharmaceutical product produced during the first manufacturing campaign is the same product, both in terms of quality and quantity, as the product produced during the last manufacturing campaign.

When working with a recombinant living host, it cannot be emphasized enough that a manufacturer does not have a truly useable process until a reliable, continuous, stable source of starting material is in hand. Unfortunately, some companies learn the hard way and try to move forward either with a host of very low productivity or with an unstable host. They may be able to manufacture enough product to initiate the clinical development process, but soon enough they will find out that either the manufacturing costs are unacceptable for a commercial process or an inconsistent product quality keeps them away from receiving regulatory agency approval.

1.1. Three Primary CMC Concerns for Banks

To provide this reliable, continuous stable genetic source, a manufacturer will prepare a bank. The ‘master bank’ is a single pool of recombinant organisms prepared from a selected clone, aliquotted and stored under defined conditions. The master bank aliquots provide the characterized common starting source material for production. By the expansion of a master bank aliquot, a ‘working bank’ is prepared. The working bank can then be used for initiating production of the biopharmaceutical.

Regulatory agencies have great concern about the quality and safety of the master and working banks used to produce biopharmaceuticals. Their three primary CMC concerns can be summarized as follows:

1. The quality and safety of the banks impacts the quality and safety of the product

   The old adage of ‘garbage in, garbage out’ applies here.

2. The quality and safety of the banks cannot be fully assessed without adequate, extensive documentation

   The origin and handling of all of the genetic components used to assemble the recombinant organism directly impacts the master bank subsequently prepared from it.

3. The quality and safety of the banks cannot be fully assured without appropriate controls on all aspects of the bank preparation and extensive characterization of the bank