BIO Manufacturing

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Introduction

The manufacturing process is characterized by a number of overall activities like:
The design and layout of the manufacturing facility
Raw materials utilized in the manufacturing process
The manufacturing process itself
The training and commitment of personnel involved in all aspects of the manufacturing operation
The highest quality standards in all aspects of manufacturing. The production of pharmaceuticals needs to comply with the guides to good manufacturing practice (GMP) and include substantive documentation requirements.

The manufacturing facility includes production, quality control and storage areas.
Labelling and packaging may be conducted in the manufacturing facility as well.

Expression systems

The sources of biopharmaceutical proteins are cDNA or genes inserted into recombinant cells or Transgenic organisms.

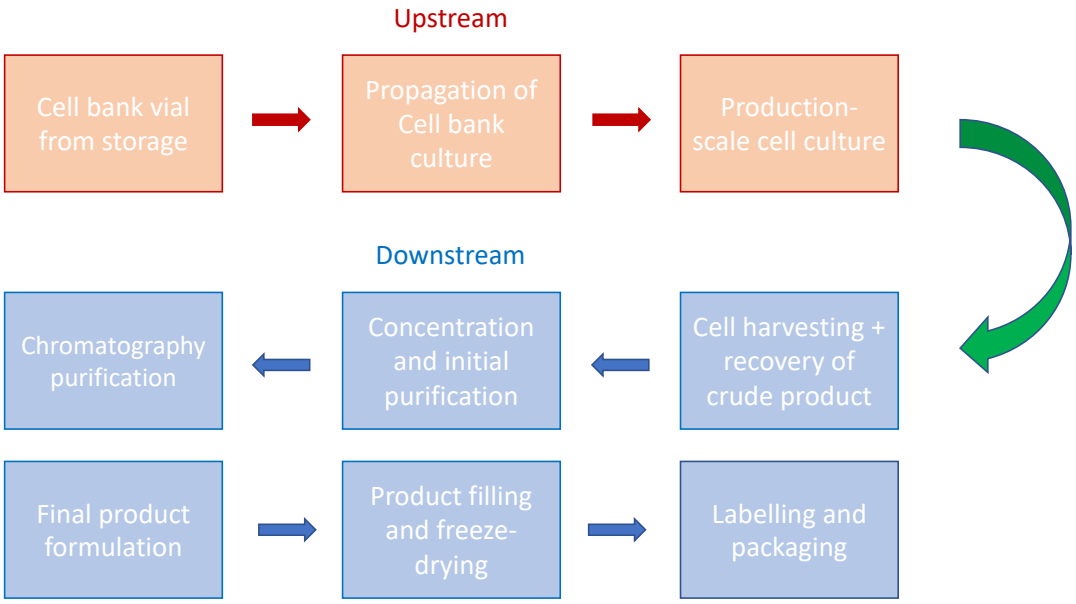
The producer recombinant cells are most frequently:
Bacterial cells: *E.coli, Bacili*
Yeast or fungi cells
Animal cell cultures (CHO chinese hamster ovary cells and BHK baby hamster kidney cell lines)
Insect cell culture systems

Transgenic organisms are:
Transgenic animals (in milk)
Transgenic plants

The production system

The production system is divided upstream processing and downstream processing.

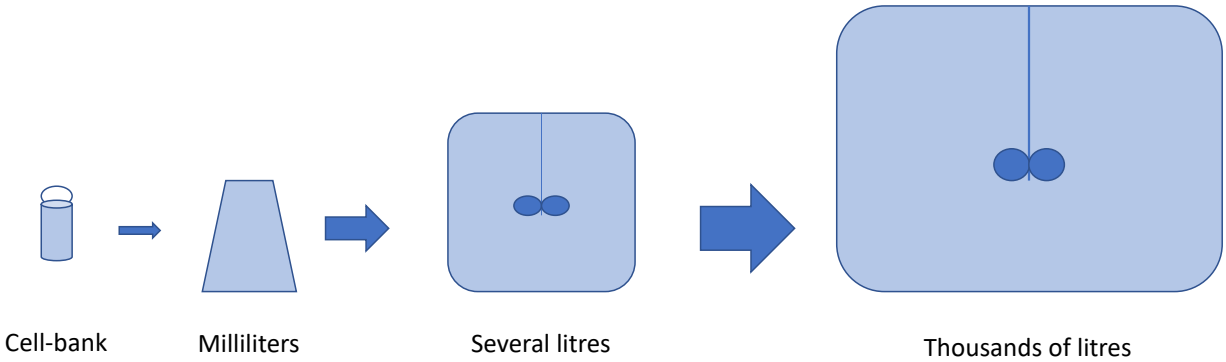
Production process for a biopharmaceutical product



The upstream processing process includes the expression systems and the initial fermentation process. A vector system is added to a culture of producer cells (cell bank).

The cells divide in the cultivation period and thus expand in volume. The expanding cultures are transferred to increased volume tanks. The tanks show variation in configuration some are roller-bottle systems.

Up-stream cell-cultivation



The media composition, fermentation conditions and time are unique for each production system. Mammalian cell lines require more complex media. Cells may grow on microcarriers.

All produces seek to increase the expression levels of the recombinant production system.

The downstream processing system includes purification and generation of the finished product format. The more detailed activities include

- Removal of product from cells
- Addition of virus inactivating agents
- Adjustment of product potency
- Formulation (stablisation and possibly freeze drying)
- Labelling and packaging

The challenges regarding biological activity of proteins include proteolytic degradation of the protein, covalent alterations of the protein and alteration of glycosylation patterns

The final product needs to be analysed in different ways:

- *Quality Control testing of contaminants, removal of altered proteins.*
- *Product potency with Bioassays.*
- *Determination of protein concentration*
- *Detection of impurities*
- *Pyrogenic contaminants*
- *DNA contaminants*
- *Microbial and viral contaminants*

There are a number of variations in this overall outline of the manufacturing process for some biological products.
Classical virale vaccines are produced in fertilized chicken eggs.

Manufacturing problems and inefficient supply chains are unfortunately not rare and this leads to shortage of specific pharmaceutical products from time to time.

Manufacturing of other biological products

Some biopharmaceuticals are more demanding in the delivery chain and include a cold-chain in order to prevent degradation (some vaccines and insulin as an example).

Nucleic acid drugs are different from protein based drugs and require chemical synthesis for oligonucleotides. Their
delivery may be challenging in relation to their stability, their access to the cell nucleus and their access to cell membranes.

Cell-based therapy (like stem cell treatment) production are again different from protein manufacturing. Cell lines, short lived cells or cells from patients are expanded in cultures of different time periods. If delivered to a patient, cell lines may need an encapsulation to prevent the patient immune system to reject the cells.

Manufacturing of plant medicines

The formulation and manufacture of plant medicines are again different from the manufacture of biopharmaceuticals.
Drugs obtained directly from plant sources are notably alkaloids, glycosides and phenolic compounds. Plant material is also a favoured source of volatile (essential) oils.
The problems involved with the use of collected wild plant material include dramatic variability in quality as a result of the genetic variability of the wild stock. Transport delays is a problem if you depend on fresh plant material.
Both fresh and dried plant material may be used.
Quality control of crude plant drugs is more complex than for single chemical entities.

Classical techniques for quality control include:

- *Activity related to single constituents or the combination of constituents.*
- *Thin-layer chromatography*
- *HPLC or gaschromatography/mass spectrometry for quantitative data.*
- *Spectroscopic techniques*
- *Nuclear magnetic resonance spectroscopy*
- *Immunoassays*
- *DNA methods*

The production system includes harvesting of plant material, drying and size reduction of the dried material, extraction of active constituents and then extract concentration.