**Upstream process** : refers to the production of bio-product in the raw form. In biochemical engineering, this part is divided into some steps which include growing microbes for culturing process (inoculum development), media development, improvement of inoculum (by genetic engineering process), and optimization of growth kenetics so that product development can be improved significantly.

 **Downstream process** refers to cell purification, a purification section, recovery of product and a polishing section. If it is in bio-separation process, the upstream refers to the first steps of separation which are removal of insolubles and product isolation. Removal of insolubles can be done by filtration (sometimes microfiltration is used), centrifugation, and cell disruption. Meanwhile product isolation can be done by extraction or adsorption.

 **Basis of separation in bioseparation processes**

Biological products are separated based on one or more of the following factors:

1. Size: e.g. filtration, membrane separation, centrifugation

2. Density: e.g. centrifugation, sedimentation, floatation

3. Diffusivity: e.g. membrane separation

4. Shape: e.g. centrifugation, filtration, sedimentation

5. Polarity: e.g. extraction, chromatography, adsorption

6. Solubility: e.g. extraction, precipitation, crystallization

7. Electrostatic charge: e.g. adsorption, membrane separation, electrophoresis

8. Volatility: e.g. distillation, membrane distillation, pervaporation

 The downstream part of a bioprocess refers to the part where the cell mass from the upstream are processed to meet purity and quality requirements. Downstream processing is usually divided into three main sections: **cell disruption**, a **purification section** and a **polishing section**. The volatile products can be separated by distillation of the harvested culture without pre-treatment.

 Distillation is done at reduced pressure at continuous stills. At reduced pressure distillation of product directly from fermentor may be possible. The steps of downstream processing are:

1. **Separation of biomass**: separating the biomass (microbial cells) generally carried out by centrifugation or ultra-centrifugation. If the product is biomass, then it is recovered for processing and spent medium is discarded. If the product is extra cellular the biomass will be discarded. Ultra filtration is an alternative to the centrifugation.
2. **Cell disruption**: If the desired product is intra cellular the cell biomass can be disrupted so that the product should be released. The solid-liquid is separated by centrifugation or filtration and cell debris is discarded.
3. **Concentration of broth**: The spent medium is concentrated if the product is extracellular.
4. **Initial purification of metabolites**: According to the physico-chemical nature of the product molecule several methods for recovery of product from the clarified fermented broth were used (precipitation, etc.)
5. **De-watering**: If low amount of product is found in very large volume of spent medium, the volume is reduced by removing water to concentrate the product. It is done by vacuum drying or reverse osmosis.
6. **Polishing of metabolites**: this is the final step of making the product 98 to 100% pure. The purified product is mixed with several inert ingredients called excipients. The formulated product is packed and sent to the market for the consumers.