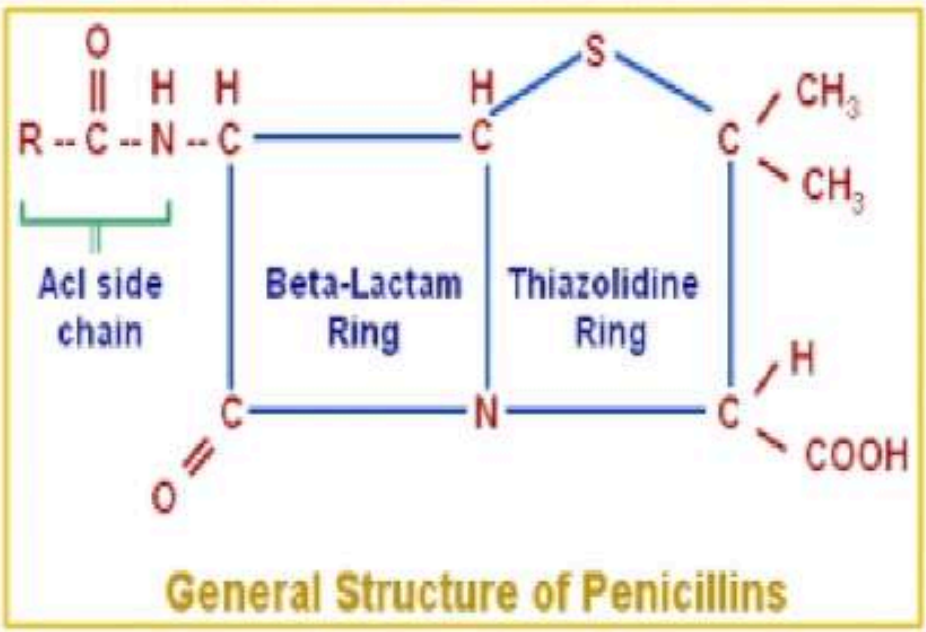
Antibiotics

Production of penicillin

INTRODUCTION

- **Penicillin** is a group of antibiotics.
- It is derived from common moulds known as Penicillium moulds; which includes penicillin G (intravenous use), penicillin V (use by mouth), procaine penicillin, and benzathine penicillin (intramuscular use).
- Penicillin antibiotics were the first medications to be effective against many bacterial infections caused by staphylococci and streptococci.
- They are still widely used today against many types of bacteria.
- Penicillin was discovered in 1928 by Scottish scientist Alexander Fleming. People began using it to treat infections in 1942.
- "Penicillin" is used as a antibiotics that contain the beta lactam ring.



General Structure of Penicillins

- Penicillin inhibits activity of enzymes that are needed for the cross linking of peptidoglycans in bacterial cell walls.
- Penicillin cause the cell wall weaken and death of bacterial cell.
- Some bacteria produce enzymes that break down the beta-lactam ring, called beta-lactamases, which make the bacteria resistant to penicillin.
- The *Penicillium* cells are grown using a technique called fed-batch culture, in which the cells are constantly subject to stress, which is required for induction of penicillin production.
- The carbon sources are also important: glucose inhibits penicillin production, whereas lactose does not. The pH and the levels of nitrogen, lysine, phosphate, and oxygen of the batches must be carefully controlled.

A 1957 fermentor (bioreactor) used to grow *Penicillium* mould.

- Penicillin is a secondary metabolite of certain species of *Penicillium*.
- It is produced when growth of the fungus is inhibited by stress.
- It is not produced during active growth.
- Production is also limited by feedback in the synthesis pathway of penicillin.

α-ketoglutarate + AcCoA → homocitrate → L-α-aminoadipic acid → L-lysine + β-lactam

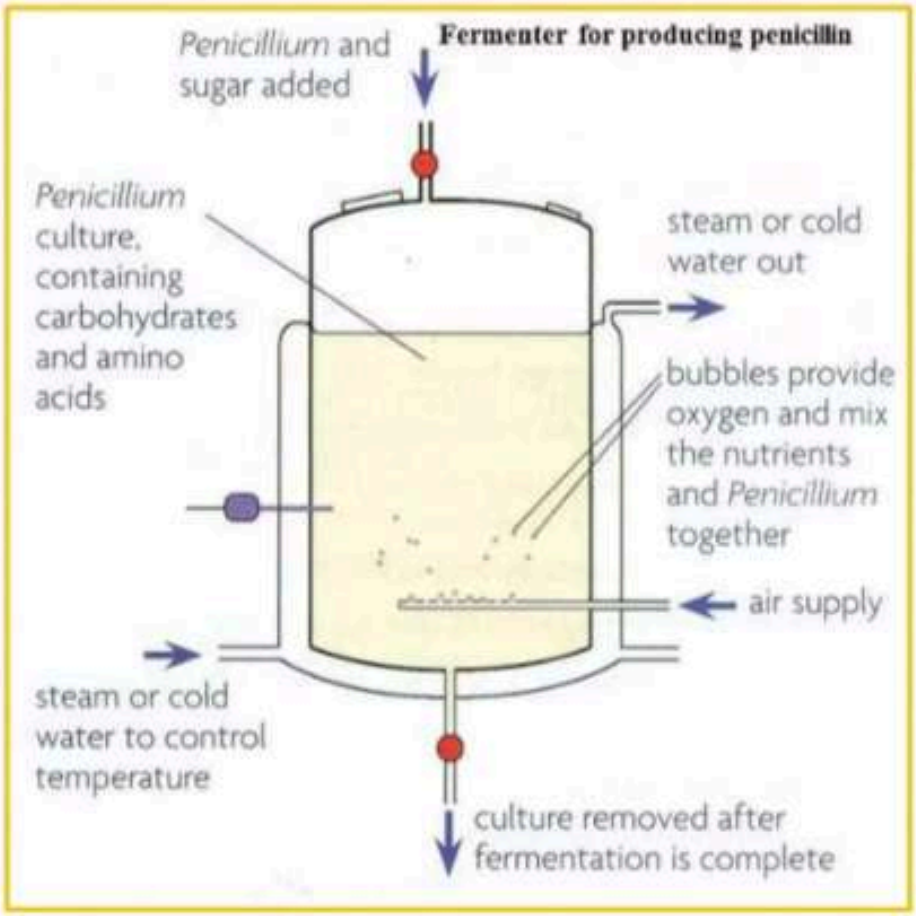
- The by-product, L-lysine, inhibits the production of homocitrate, so the presence of exogenous lysine should be avoided in penicillin production.

- The industrial production of penicillin was generally classified into two processes:

  upstream processing

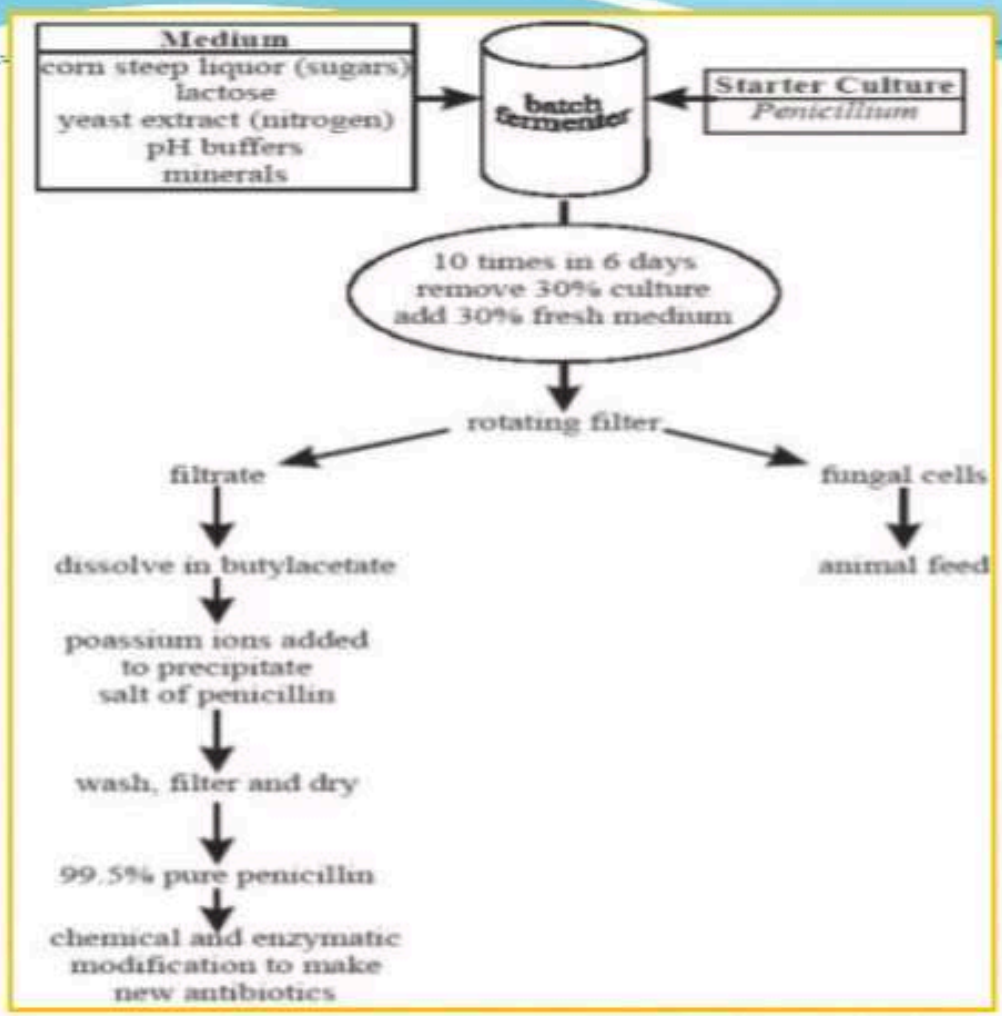
  downstream processing

- **Upstream processing:** Technology that leads to the synthesis of a product and includes the development and production.
- **Downstream processing:** The extraction and purification of a biotechnological product from fermentation process.


Fermenter for producing penicillin
Penicillium and sugar added
Penicillium culture, containing carbohydrates and amino acids
steam or cold water out
bubbles provide oxygen and mix the nutrients and *Penicillium* together
air supply
steam or cold water to control temperature
culture removed after fermentation is complete

The fermentation Process

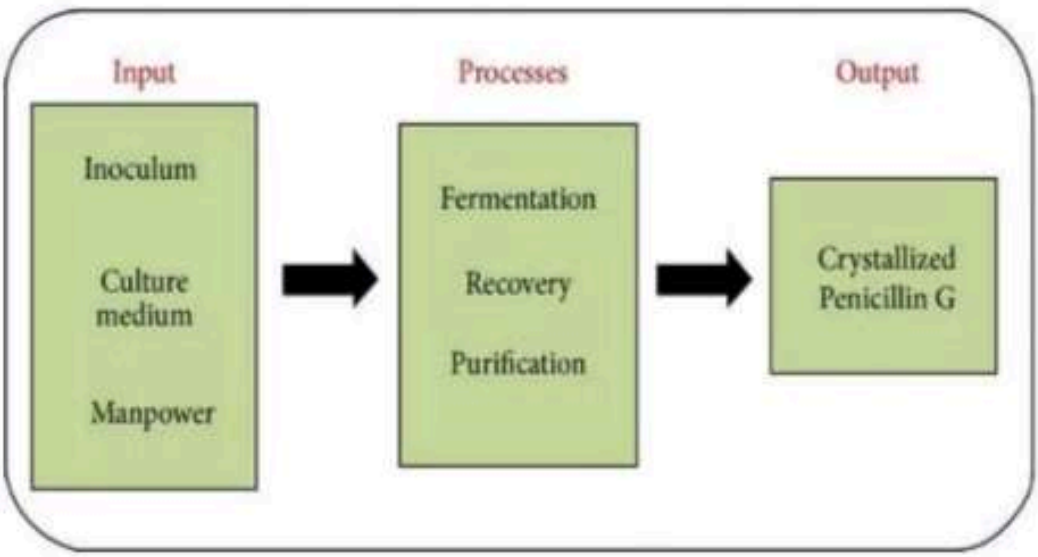
- Fermentation is the technique used for the commercial production of penicillin. It is a fed-batch process that is carried out aseptically in stainless steel tank reactors with a capacity of 30 to 100 thousand gallons.
- Various carbon sources have been adopted for this process – including glucose, sucrose and other crude sugars.
- Sugar is also used for the regulation of the pH value during active penicillin production phase.
- Penicillin is excreted into the medium and recovered at the end of fermentation.
- Whole broth extraction is best performed at acidic pH, with a 2-5% improvement in overall extraction efficiency.
- Solvent extraction of chilled acidified broth is carried out with amyl, butyl or isobutyl acetate.


Medium
corn steep liquor (sugars)
lactose
yeast extract (nitrogen)
pH buffers
minerals
batch fermenter
Starter Culture
Penicillium
10 times in 6 days
remove 30% culture
add 30% fresh medium
rotating filter
filtrate
fungal cells
dissolve in butylacetate
animal feed
poassium ions added
to precipitate
salt of penicillin
wash, filter and dry
99.5% pure penicillin
chemical and enzymatic
modification to make
new antibiotics

- Penicillin is actively produced by the species of ***P. chrysogenum* (mould).**
- Several strains of *P. chrysogenum* are being used for penicillin production at laboratory and commercial levels.
- To use cheap raw materials as substrate and to employ simple methods of cultivation for better penicillin production.
- Agro industrial waste used as raw material such as sugar cane bagasses (SCB), corn steep liquor (CSL), a waste product of starch (maize) industry.

There are various steps for production process:

- Strain Selection
- Strain improvement
- Media optimization
- Process optimization: agitation, aeration, pH control, temperature control etc.
- Inoculum preparation
- Production of product


Input
Processes
Output
Inoculum
Culture medium
Manpower
Fermentation
Recovery
Purification
Crystallized Penicillin G