Preservatives

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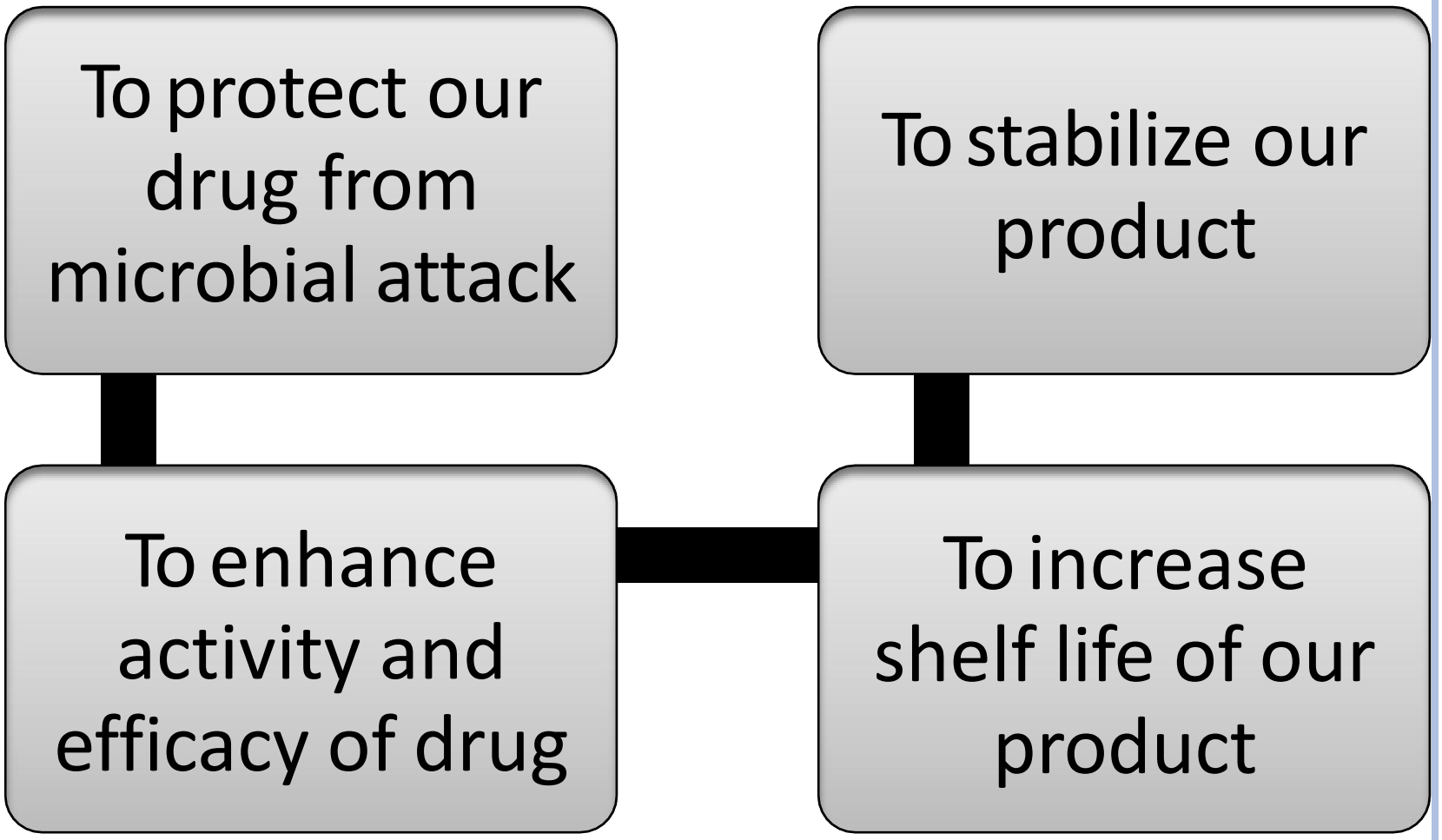
Definition

- A chemical substance used to preserve organic
  - substance from decay or spoilage by preventing microbial attack

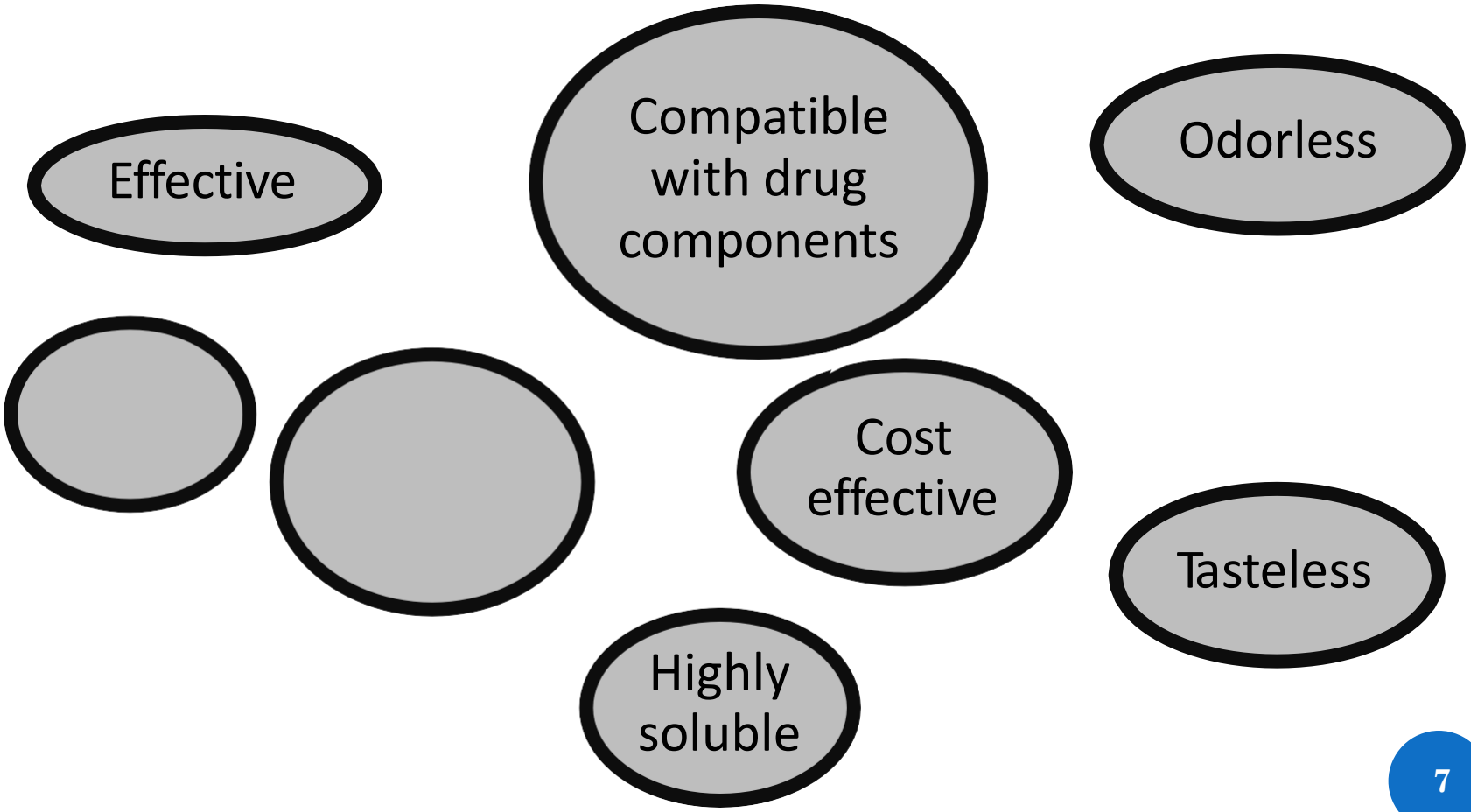
PHARMACEUTICAL PRESERVATIVES

Preservatives are the chemical substances used to improve or amplify shelf life of drugs by decreasing or lowering the oxidation of active and Excipients and by reducing microbial production

NEED FOR PRESERVATIVES



IDEAL PRESERVATIVE:



PRESERVATIVES

It must decrease the percentage of the microbes and prevent any re-growth They can be:

- –Microbiostatic
- –Microbiocidal in nature

Some preservatives are ineffective with some microbe strains and should be combined with others to be effective. Such as

- –Benzalkonium chloride
- –Organo mercurial, cetrimide, chlorhexidine and 3-cresol are combined

PERFORMANCE REQUIREMENTS

Antimicrobial Activity	• Active Against Microbes At Low Concentration
Aquous Solubility	• Should Be Soluble To Reach Minimum Inhibitory Concentration
Stability Properties	• Stable During And At The End Of Manufacturing

PERFORMANCE REQUIREMENTS

Partitioning behavior	• Remain in continuous phase in multiphase products
Organoleptic properties	• Odor and acceptable taste during administration of product

RELATIONSHIP BETWEEN:

- Concentration
  - Change in conc. will change the efficacy
  - Performs best on lower concentration
    - E.G. Phenol
      Chlorhexidine
- Temperature
  - Activity changes with temperature, according to Q10
    - E.G. Phenol
      Ethanol

RECOMMENDED PRESERVATIVE CONCENTRATION

Name	Recommended Concentration
Benzyl Alcohol	0.5 to 10%
Benzalkonium Chloride	0.01%
Chlorobutanol	0.25 to 0.5%
Methyl Paraben	0.01 to 0.5%
Phenol	0.065 to 0.02%

Preservative Concentration for Liquid Oral Preparation

Sr. No.	Name	Recommended Concentration
1.	Benzoic Acid	0.1 to 0.2%
2.	Sorbic Acid	0.1 to 0.2%
3.	Methyl Paraben	0.25%
4.	Propyl Paraben	0.5 to 0.25%
5.	Sodium Benzonate	0.1 to 0.2%
6.	Bronidol	0.001 to 0.05%

PRESERVATIVE CAPACITY

"Preservative capacity" is a term used to describe the cumulative level of contamination that a preserved formulation can tolerate before becoming so depleted as to become ineffective

FACTORS AFFECTING AVAILABILITY OF PRESERVATIVES

Preservative may interact with:

- Active ingredient
- Excipient
- Other components

As a result small amount is remain to show action

EFFECT OF PRODUCT pH:

Activity of weekly acidic preservatives is associated with unionized molecules so they work best when ionization is low

Benzoic and sorbic acids have limited preservative usefulness Above pH 5

Quaternary ammonium and chlorhexidine probably are effective in products of neutral pH.

EFFICIENCY IN MULTIPHASE SYSTEMS

Preservative interact with

- Oil phase
- Surfactant micelles
- Polymeric suspending agents
- Water phase
- Formulation ingredients

So a result small unbound proportion in bulk aqueous medium is available for activity

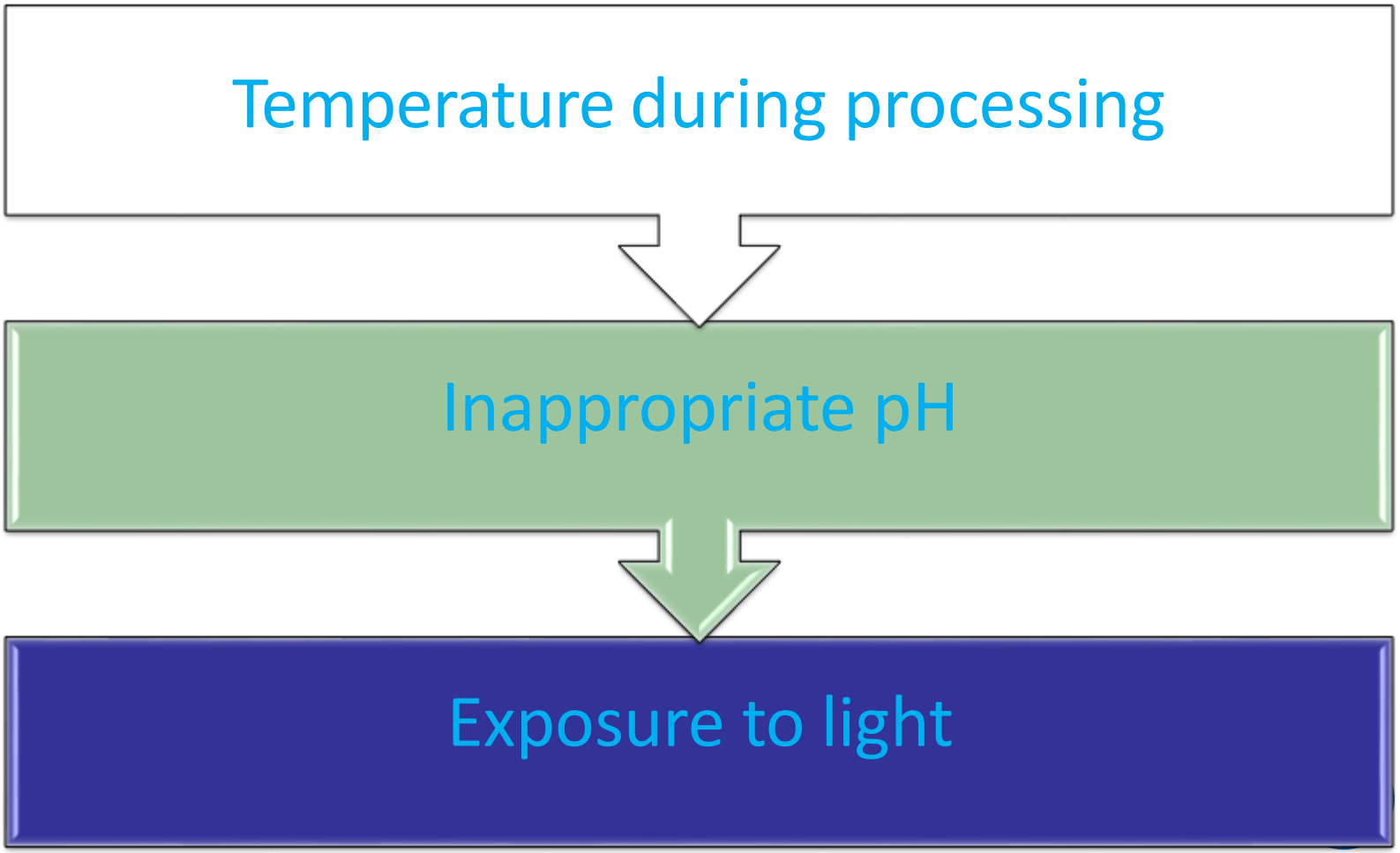
EFFECT OF CONTAINER OR PACKAGING

Preservative availability reduced by interaction with packaging materials.

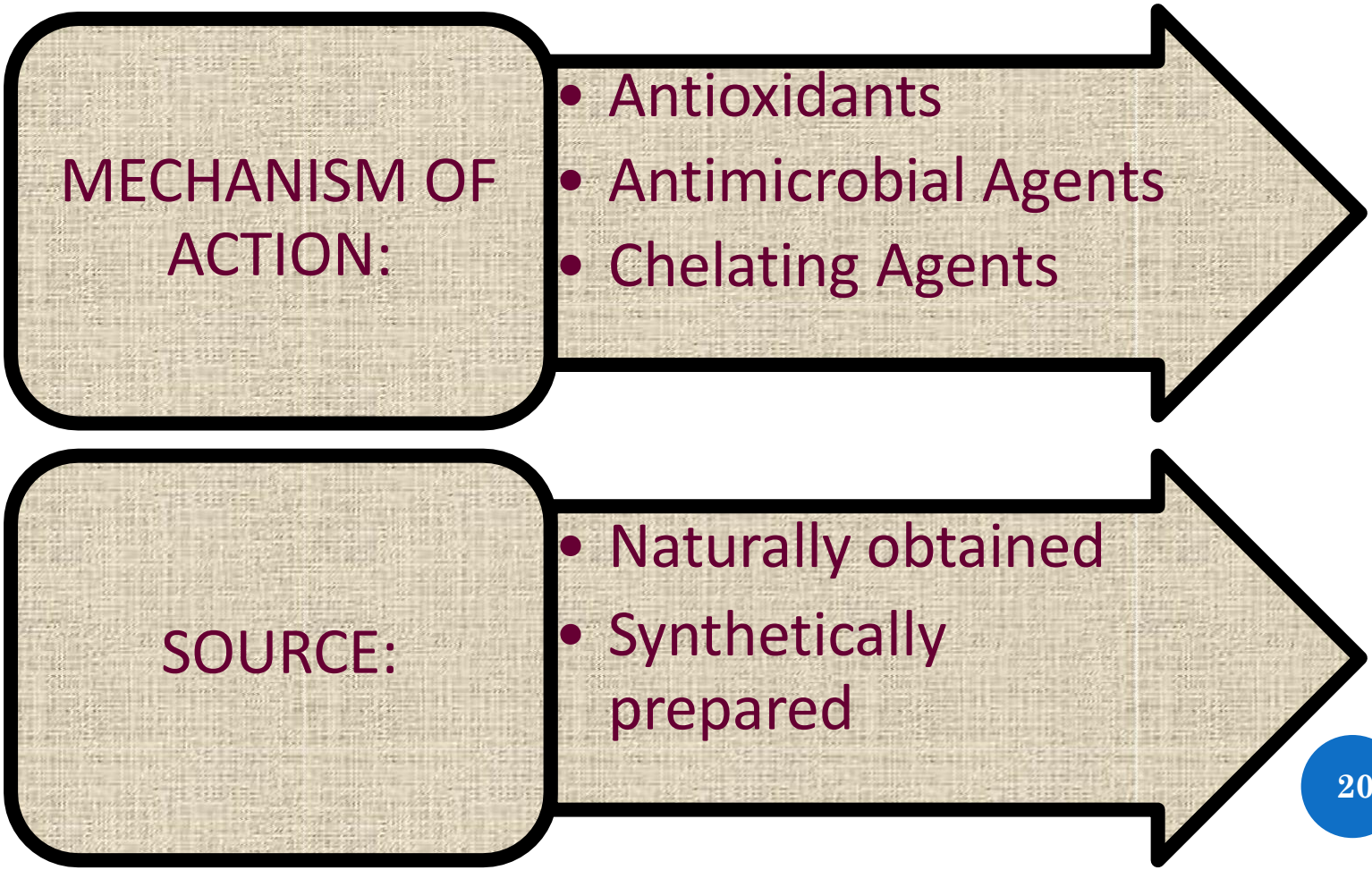
Phenolics will permeate the rubber wads and teats of multi-dose injection containers

Quaternary ammonium adsorbed onto the surfaces of plastic and glass containers.

DEGRADATION OF PRESERVATIVES

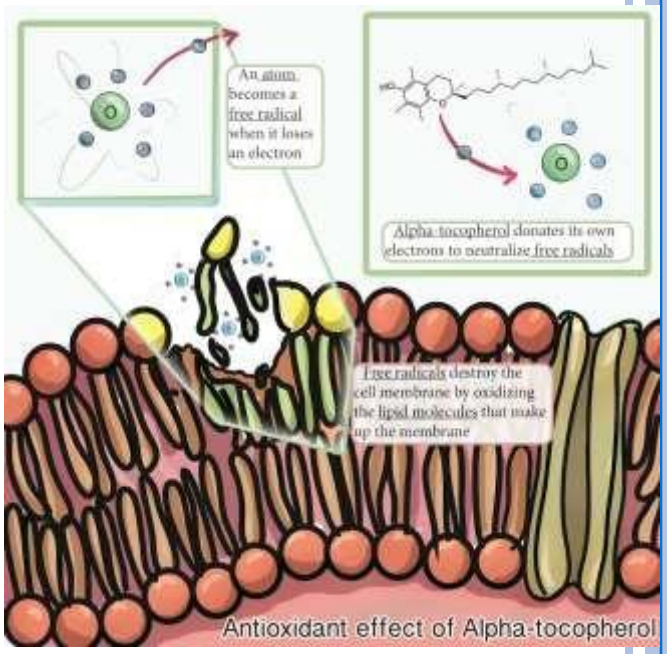


CLASSIFICATION OF PRESERVATIVES



ANTI-OXIDANTS:

Anti oxidants are used to reduced the oxidation of active compound and excipients due to formation of free radicals by using their self reducing activity in finished product

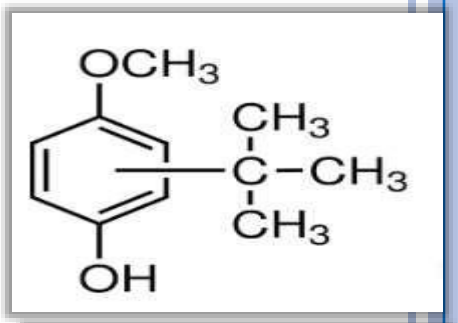


TYPES OF ANTI-OXIDANTS:

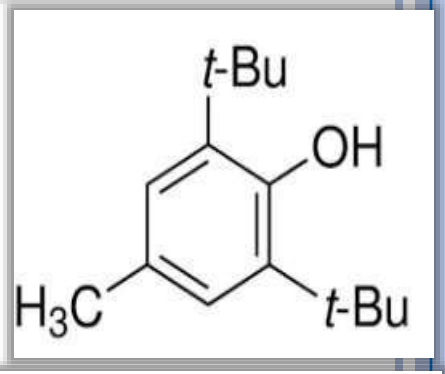
Type	Definition	Example
True antioxidants	These are thought to block chain reactions by reacting with free radicals	Butylated hydroxytoluene (BHT)
Reducing agents	These have a lower redox potential than the drug or excipient they are protecting	Ascorbic acid
Antioxidants synergists	These enhance the effects of antioxidants	Sodium edetate

EXAMPLES OF ANTI-OXIDANTS:

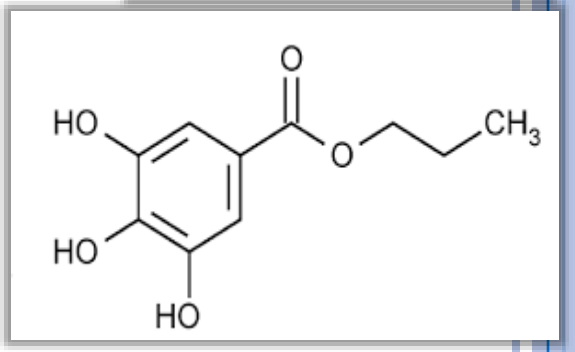
BHA (butylatedhydroxyanisole)



BHT (Butylatedhydroxytoulene)



Propyl gallate:



ANTI-MICROBIAL PRESERVATIVES:

- It is added in product to minimize risk of spoilage and to kill low levels of contaminants introduced during storage or repeated use of a multi-dose container

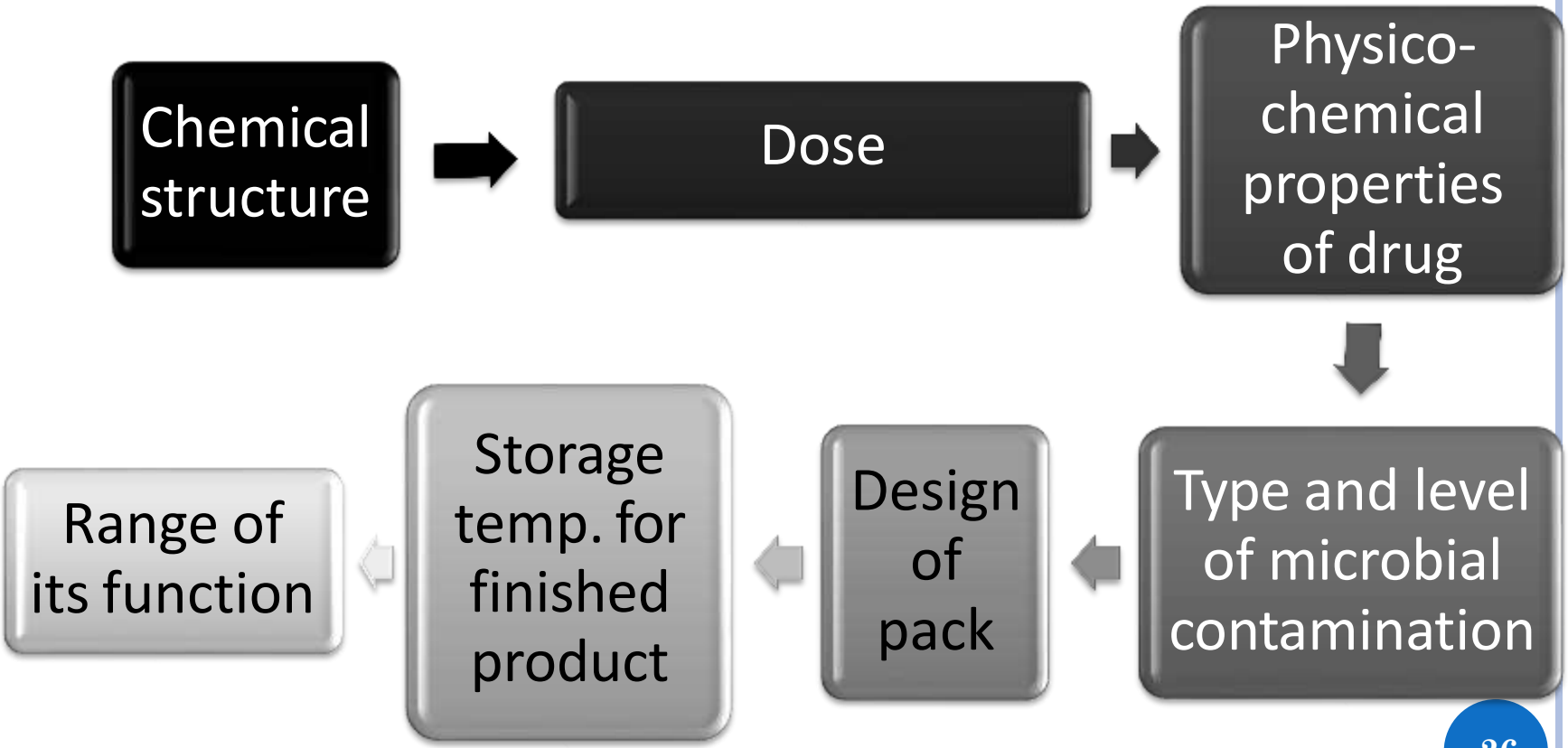
- These agents mainly work by inhibiting the cell wall, cell membrane growth or other bacterial organelles which may attack our product.

PREPARATIONS REQUIRED ANTI- MICROBIAL PRESERVATIVES:

Preparations which contain water are at risk of microbial spoilage such as:

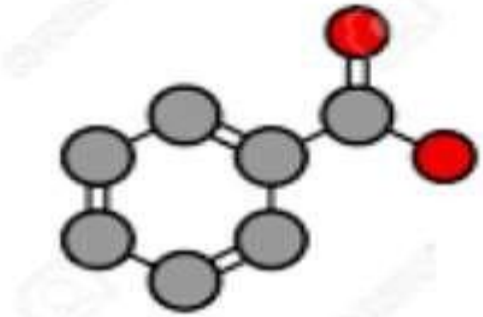
- ✓Solutions
- ✓Suspensions
- ✓Emulsions
- ✓Topical preparation e.g creams
- ✓Injectable
- ✓Eye drops etc

Factors Affecting Efficacy Of Antimicrobial Preservatives



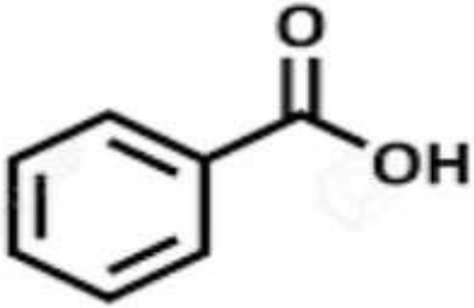
EXAMPLES:

BENZOIC ACID



It is used as a food preservative

It inhibits the growth of microbes including mould, yeast and some bacteria.

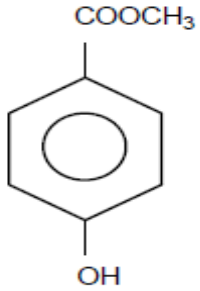


Used as antiseptic also

METHYLPARABENS

It is a white crystalline powder, characteristic odor, freely soluble in water and alcohol

It is used as antiseptic and preservative in various pharmaceutical preparations.

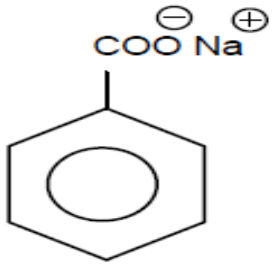


It is also used in cosmetic preparations susceptible to decomposition.

SODIUM BENZOATE:

It is a white crystalline solid, soluble in water and alcohol

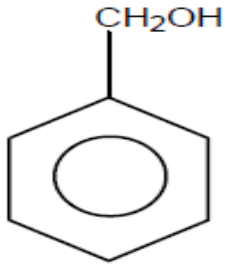
It is used extensively as food and pharmaceutical preservatives.



It is not a bactericidal, only a bacterio-static agent along with fungistatic activity

ALCOHOLS

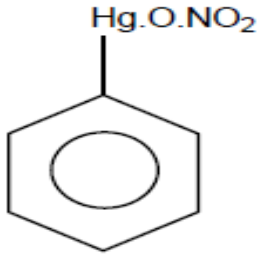
CHLORO BUTANOL:



It is used as preservative and bacterio-static agent.

MERCURIAL COMPOUNDS

PHENYLMERCURIC NITRATE:



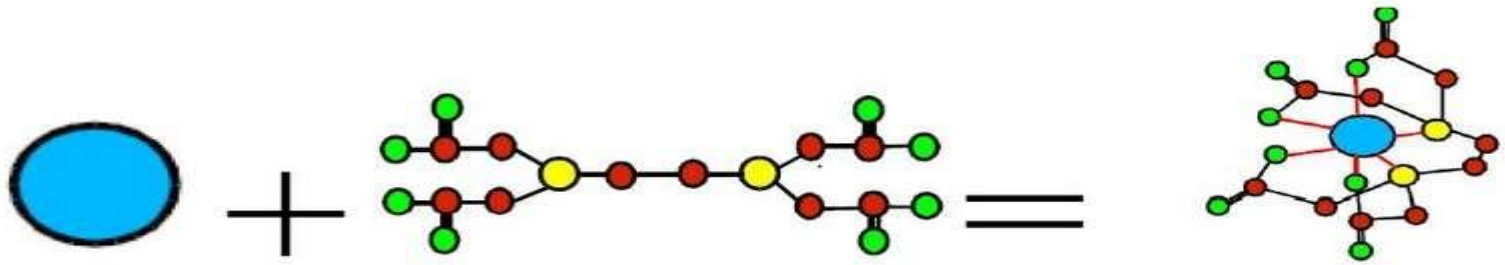
It is used as bacterial preservative in pharmaceutical preparation and also used as topical antiseptic.

CHELATING AGENTS:

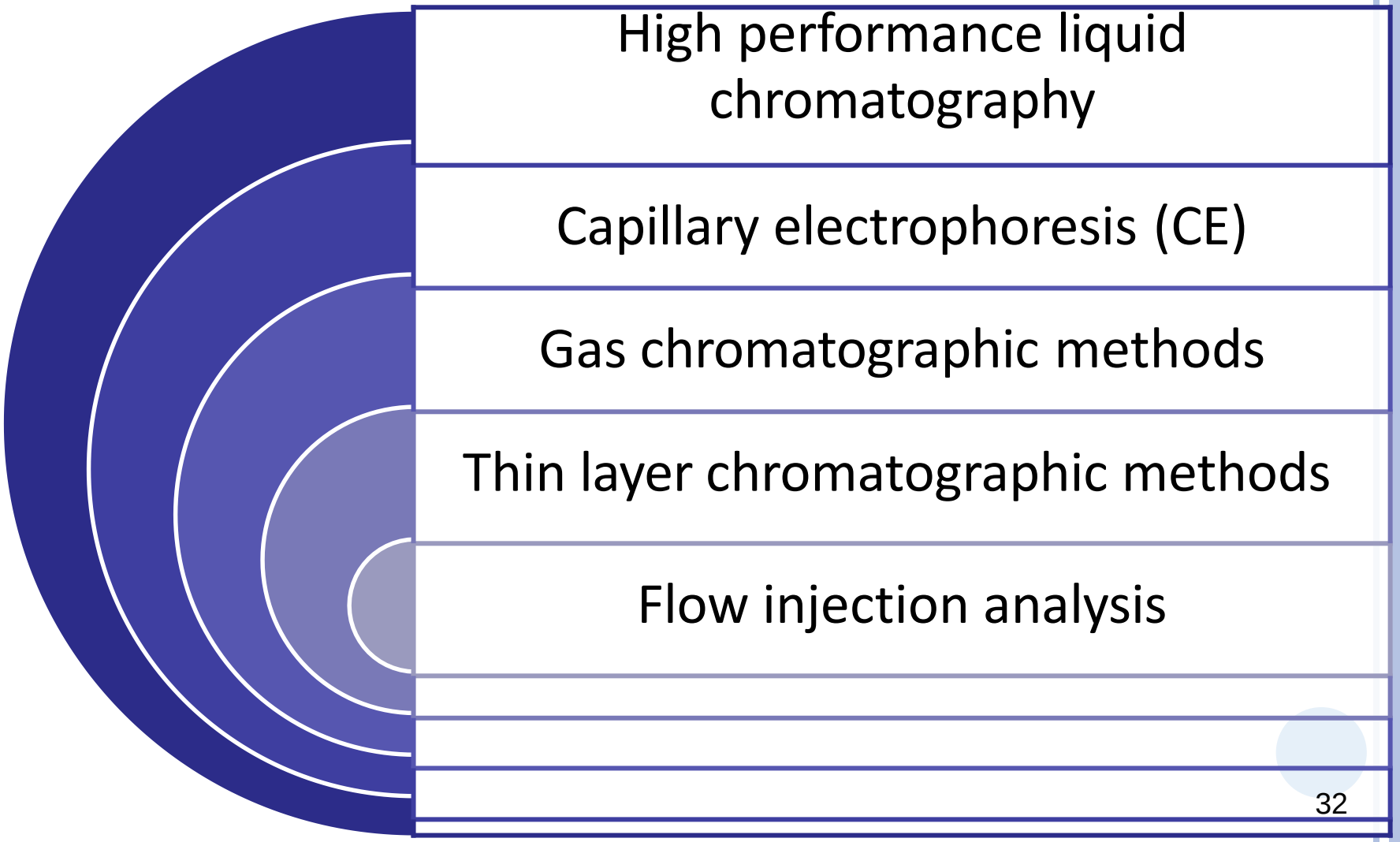
Chelating agents act as preservatives and protect product by forming complex with it preventing its deterioration

Examples include:

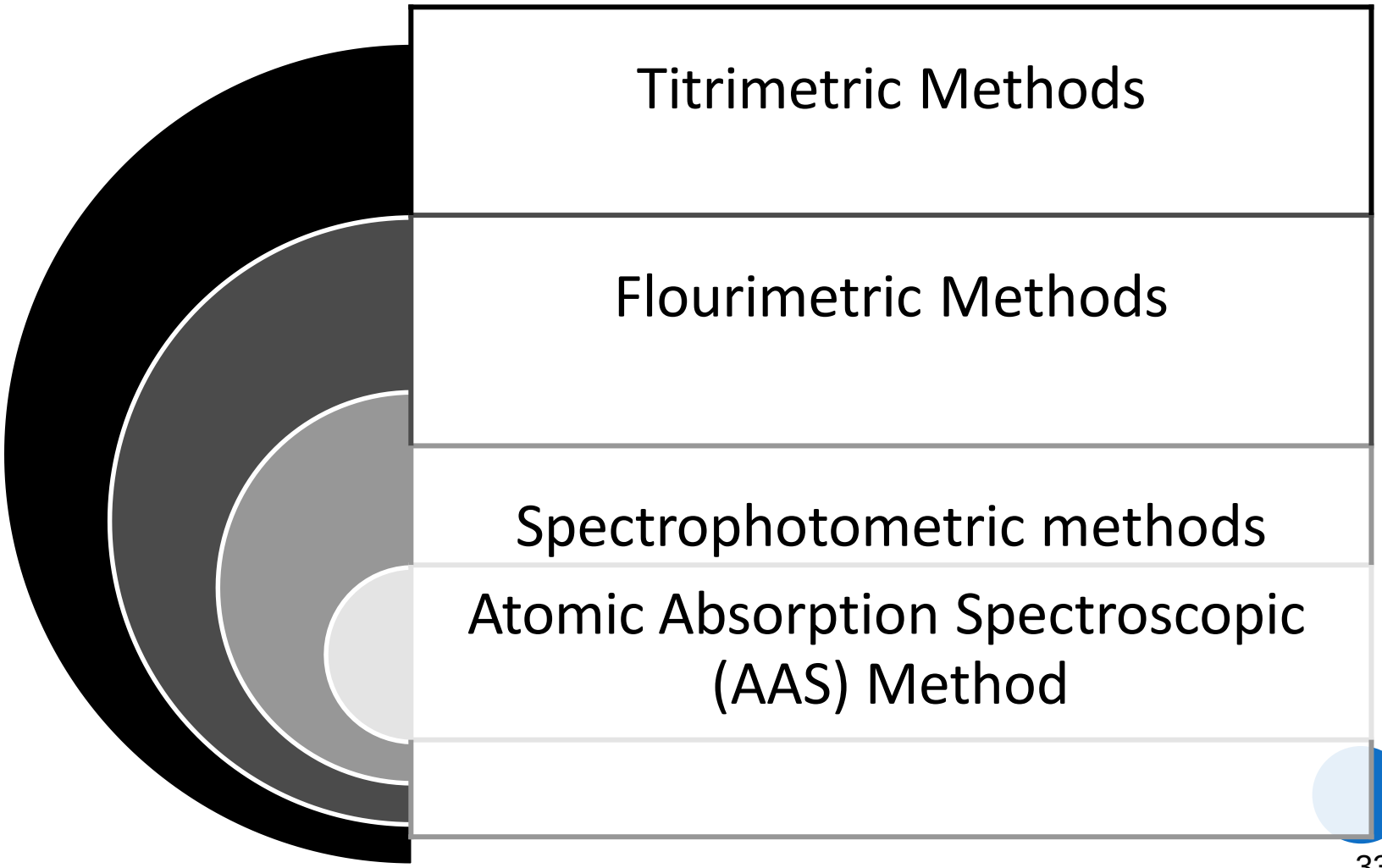
- EDTA
- Citric acid etc



ANALYSIS OF PRESERVATIVES IN PRODUCTS



ANALYSIS OF PRESERVATIVES IN PRODUCTS



SIDE EFFECTS

While choosing preservative for drug product consideration should be made about:

1. Concentration
2. Toxicity
3. Selectivity
4. Interaction with formulation etc

COMMON SIDE EFFECTS:

HYPERSENSITIVITY	ALLERGY	ASTHMA
HYPERACTIVITY	NEUROLOGICAL DAMAGE	CANCER

Preservative	Side effects
Paraben	Neurological damage in rats Potent irritants
Formaldehyde Diazolidinyl urea Imidazolidinyl urea	Skin irritants Eye irritants lung irritants
Benzyl alcohol	fatal toxic syndrome in low weight neonates
Cetyl alcohol Stearyl alcohol	Infrequent sensitizers

Preservatives	Side effects
2-Phenylethanol	Irritant to skin, eye and mucous membranes
Benzoic acid	Gastro-irritant
Chloroxylenol	Cross sensitivity
Chlorocresol	Irritant to skin, eyes and mucous membranes
Hexachlorophene	Neurotoxicity
EDTA	Dose-related broncho-constriction

EVALUATION OF PRESERVATIVES

The evaluation of preservatives has traditionally involved time-consuming tests :

Pharmacopoeial antimicrobial effectiveness tests (AET)

Preservative efficacy tests (PET).

These are required for the assessment of the antimicrobial preservation of multiple-use pharmaceutical products

PRESERVATIVE EFFICACY TESTING (PET)

Such tests involve challenging a product with a defined number of colony forming units (cfu) of a variety of test microorganisms (bacteria, yeasts and fungi), enumeration at time zero and then monitoring the kill / survival rate at defined time intervals up to 28-days.

CHALLENGING ORGANISMS USED FOR TEST

Test organisms that are recommended by all of the pharmacopoeias include:

- Staphylococcus aureus.
- Pseudomonas aeruginosa.
- Fungi / mould, Aspergillus niger.
- Yeast, Candida albicans.

PROCESS

The product is inoculated with specified number of each challenge organism.

The inoculated product is held at room temperature for 28 days.

It is examined by the duplicate plate count method.

All results are evaluated in accordance with the tabulated acceptance criteria test protocols.

Table 1. Compendial Product Categories

Category	Product Description
1	Injections, other parenterals including emulsions, otic products, sterile nasal products, and ophthalmic products made with aqueous bases or vehicles.
2	Topically used products made with aqueous bases or vehicles, nonsterile nasal products, and emulsions, including those applied to mucous membranes.
3	Oral products other than antacids, made with aqueous bases or vehicles.
4	Antacids made with an aqueous base.

CRITERIA FOR ANTIMICROBIAL EFFECTIVENESS

For category 1	
Bacteria	3.0 log reduction in 14 days, no increase upto 28 days
Yeast/Molds	No increase from initial count at 14 and 28 days
For category 2	
Bacteria	2.0 log reduction in 14 days, no increase upto 28 days
Yeast/Molds	No increase from initial count at 14 and 28 days

CRITERIA FOR ANTIMICROBIAL EFFECTIVENESS

For category 3	
Bacteria	1.0 log reduction in 14 days, no increase upto 28 days
Yeast/Molds	No increase from initial count at 14 and 28 days
For category 4	
Bacteria	No increase from initial count at 14 and 28 days
Yeast/Molds	No increase from initial count at 14 and 28 days

OTHER TECHNIQUES:

High sensitive analytical techniques are being investigated as possible replacements for the cumbersome and time-consuming pharmacopoeial tests.

These include methods such as:

ATP bioluminescence

Electrical impedance spectroscopy

Spectro-fluorimetry

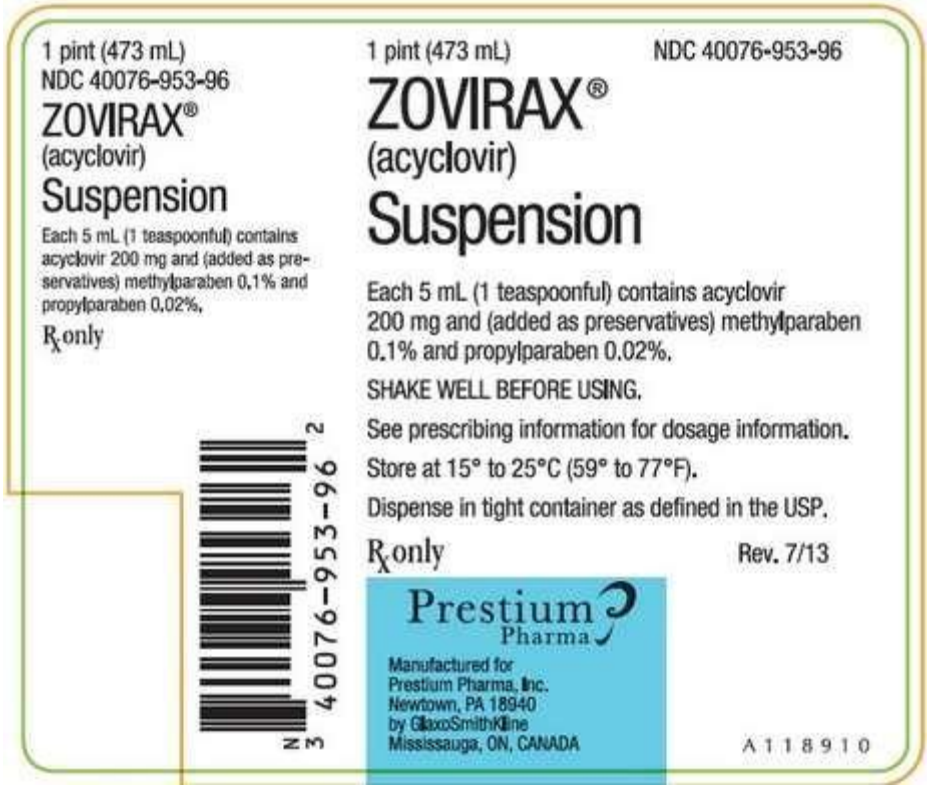
Chemiluminescence.

PRESERVATIVES FOR DIFFERENT DOSAGE FORM

Oral	Methyl, ethyl, propyl parabens, sodium benzoate, calcium lactate, sodium and potassium, sorbic acid
Dermal	Benzalkonium chloride, cetrimide, thiomersal, imidurea, chlorhexidine, chlorocresol, phenyl salicylate

EXAMPLES:

Oral dosage form:



PRESERVATIVES FOR DIFFERENT DOSAGE FORM

Dental	Sodium benzoate, benzoic acid, potassium sorbate, cetylpyridinium chloride, methyl and ethyl parabens
Ophthalmic	Benzalkonium chloride, EDTA, benzoic acid, thiomersal, imidurea, chlorhexidine, sodium perborate, boric acid

PRESERVATIVES FOR DIFFERENT DOSAGE FORM

Nasal	Benzalkonium chloride, phenylcarbinol, potassium sorbate, chlorobutanol, chlorocresol, EDTA
Rectal	Benzyl alcohol, benzoic acid, sodium benzoate, methyl hydroxybenzoate, chlorhexidine gluconate

- Topical/injectables dosage form