PRESERVATION OF PHARMACEUTICAL PRODUCTS

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Preservatives

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

Preservatives

Preservatives are substances added to various pharmaceutical dosage forms and cosmetic preparations to prevent or inhibit microbial growth.

An ideal preservative would be effective at low concentrations against all possible micro-organism, be nontoxic and compatible with other constituent of the preparation and be stable for the shelf-life of the preparation.

Ideal Properties of Preservatives

- It should not be irritant.
- It should not be toxic.
- It should be physically and chemically stable.
- It should be compatible with other ingredients used in formulation.
- It should be act as good antimicrobial agent and should exert wide spectrum of activity.
- It should act in small concentration i.e. it must be potent.
- It should maintain activity throughout product manufacturing, shelf life and usage.

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

➢ Microbiostatic

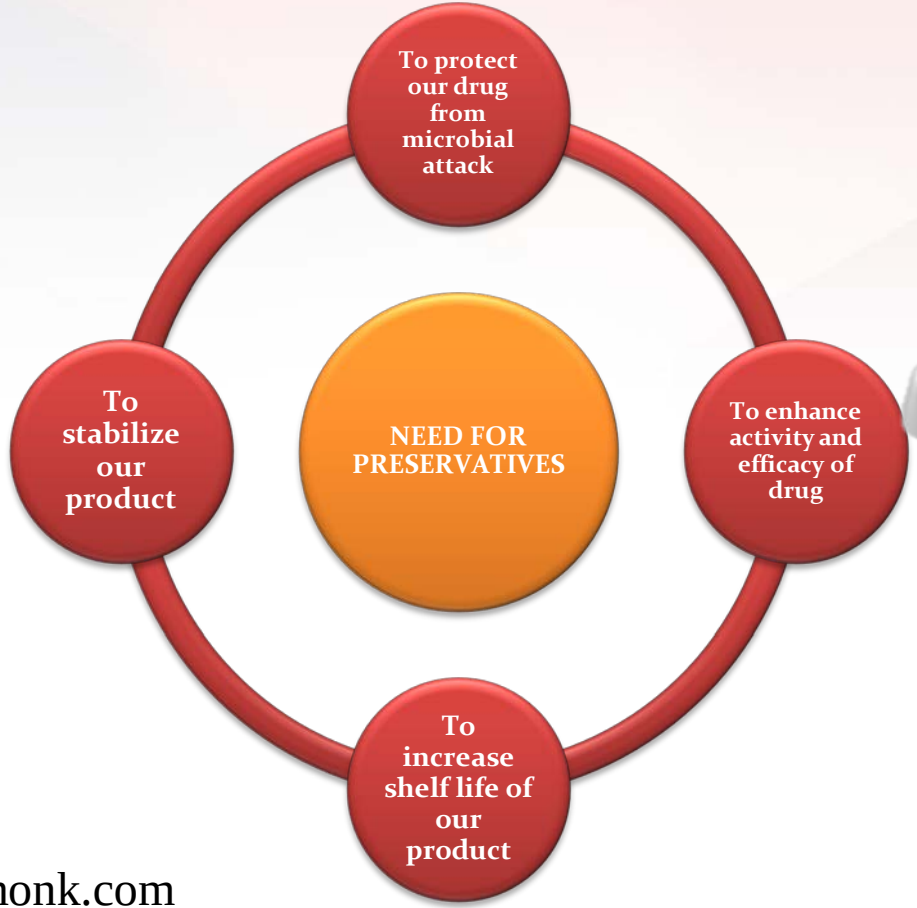
➢ Microbiocidal in nature

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

➢ Benzalkonium chloride

➢ Organo mercurial, cetrimide, chlorhexidine and 3- cresol are combined

NEED FOR PRESERVATIVES



PERFORMANCE REQUIREMENTS

Antimicrobial Activity	• Active Against Microbes at Low Concentration
Aqueous Solubility	• Should Be Soluble To Reach Minimum Inhibitory Concentration
Stability Properties	• Stable During and at The End of Manufacturing
Partitioning behaviour	• Remain in continuous phase in multiphase products
Organoleptic properties	• Odour and acceptable taste during administration of the product

SIGNIFICANCE OF CONCENTRATION AND TEMPERATURE

Concentration

- Change in conc. will change the efficacy
- Performs best on lower concentration
- Ex. Phenol
  Chlorhexidine

Temperature

- Activity changes With temperature, according to Q10
- Ex. Phenol
  Ethanol

CLASSIFICATION OF PRESERVATIVES

Preservatives are classified on variety of the basis and some of these are as follows

A. CLASSIFICATION BASED ON MECHANISM OF ACTION

1. Antioxidants:

The agent which prevent oxidation of Active pharmaceutical ingredient which otherwise undergo degradation due to oxidation as they are sensitive to oxygen.
Ex. Vitamin E, Vitamin C, Butylated hydroxy anisole (BHA), Butylated hydroxy toluene (BHT).

2. Antimicrobial agents:

The agent which active against gram positive & gram negative microorganism which causes degradation of pharmaceutical preparation which are active in small inclusion level.
Ex. Benzoates , Sodium benzoate, Sorbates

3. Chelating agents:

The agents which form the complex with pharmaceutical ingredient and prevent the degradation of pharmaceutical formulation.
Ex. Disodium ethylenediamine tetraacetic acid (EDTA), Polyphosphates , Citric acid

B. CLASSIFICATION BASED ON SOURCE

1. Natural Preservatives:

These preservatives are obtained by natural sources that are plant, mineral and animal sources etc.

Ex. Neem Oil, Salt (sodium chloride), Lemon, Honey.

2. Artificial Preservatives:

These preservative are man made by chemical synthesis and active against various microorganisms in small concentration.

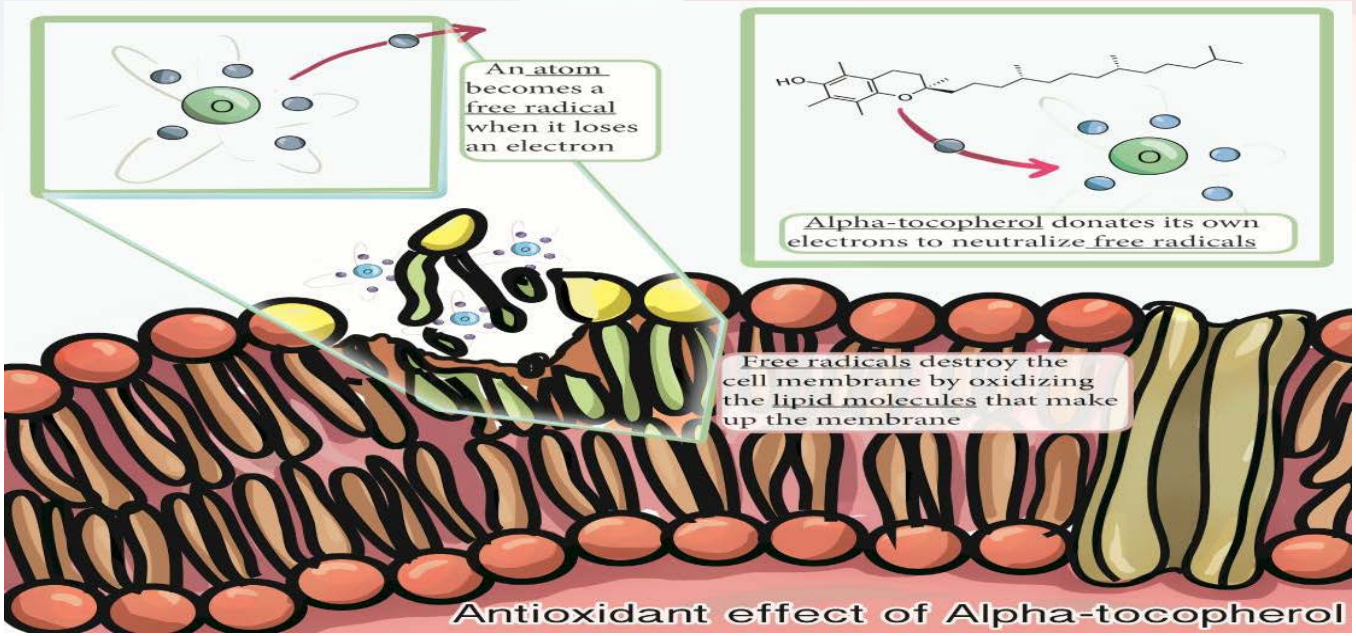
Ex. Benzoates, Sodium benzoate, Sorbates, propionets, nitrites.

MECHANISM OF ACTION:

- Natural substances such as salt, sugar, vinegar, and diatomaceous earth are also used as traditional preservatives.
- Certain processes such as freezing, pickling, smoking and salting can also be used to preserve food.
- Another group of preservatives targets enzymes in pharmaceutical products that continue to metabolize.

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



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

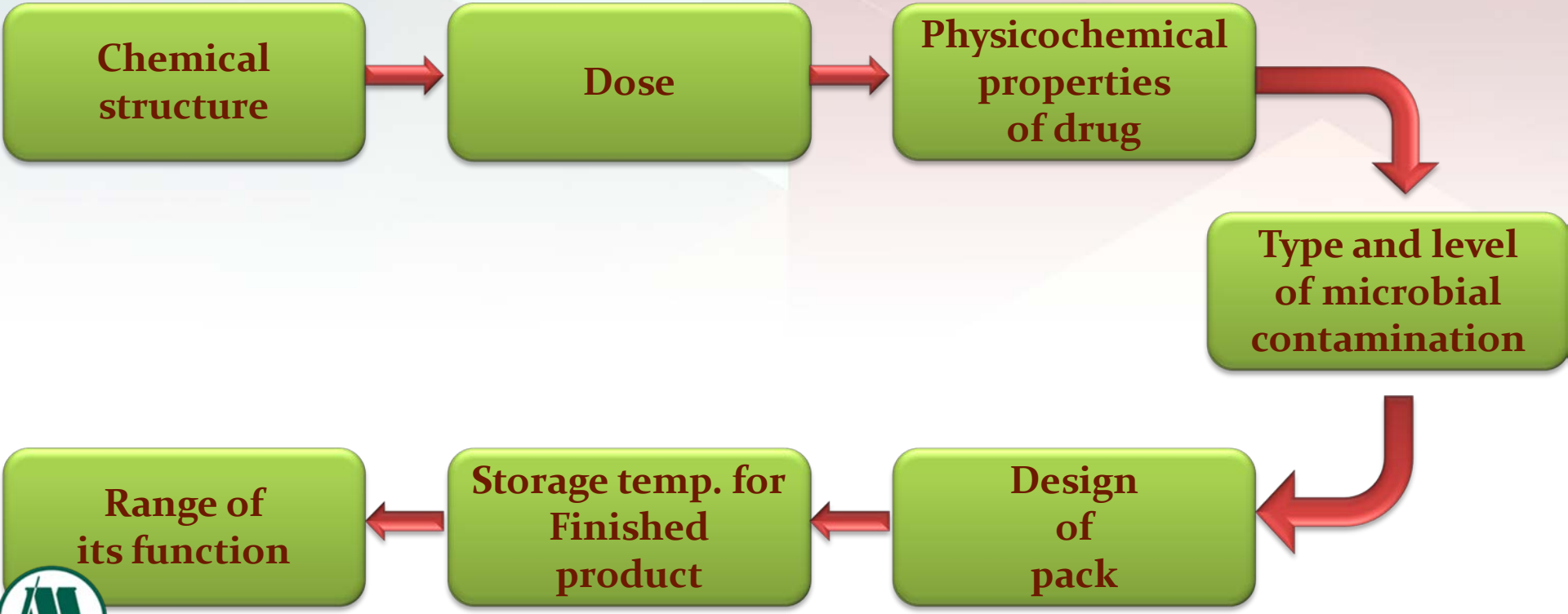
- These agents mainly work by inhibiting the cell wall, cell membrane growth or other bacterial organelles which may attack our product.

PREPARATIONS REQUIRED ANTIMICROBIAL 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.

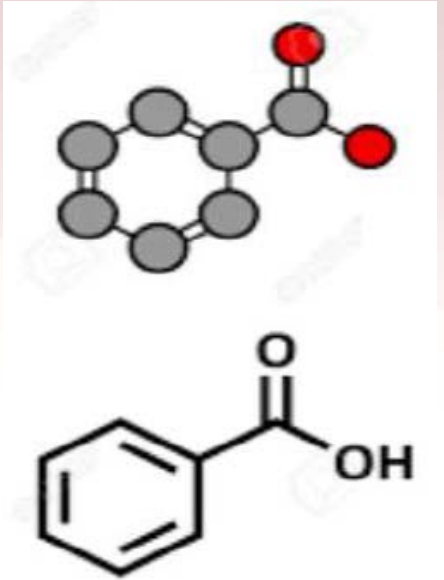
Factors Affecting Efficacy of Antimicrobial Preservatives



EXAMPLES

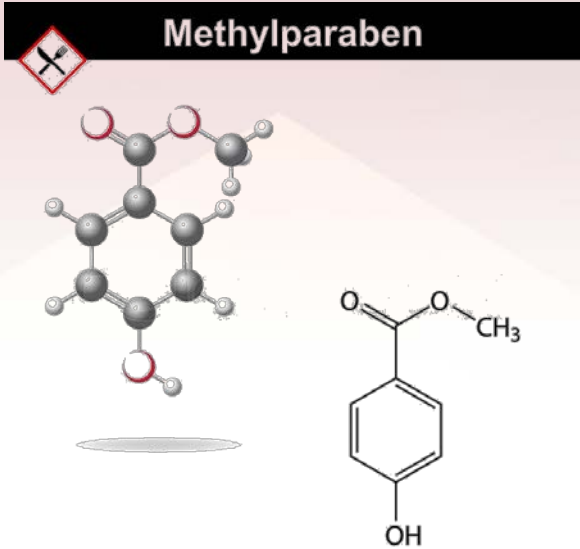
BENZOIC ACID

- It is used as a food preservative.
- It inhibits the growth of microbes including mould, yeast and some bacteria.
- Used as antiseptic also

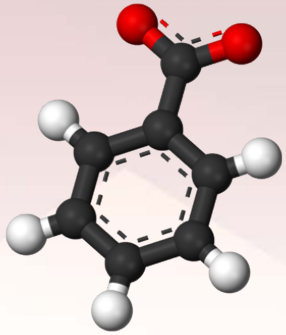


METHYLPARABENS

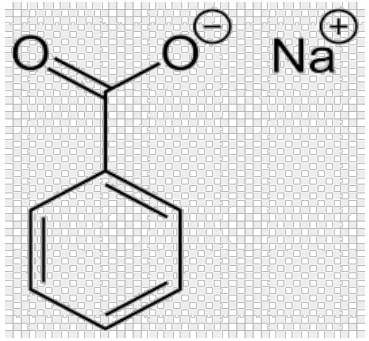
- It is a white crystalline powder, characteristic odor, freely soluble in water and alcohol.
- It is used as antiseptic and preservative in various pharmaceutical preparations.
- It is also used in cosmetic preparations susceptible to decomposition.



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 bacteriostatic agent along with fungistatic activity.

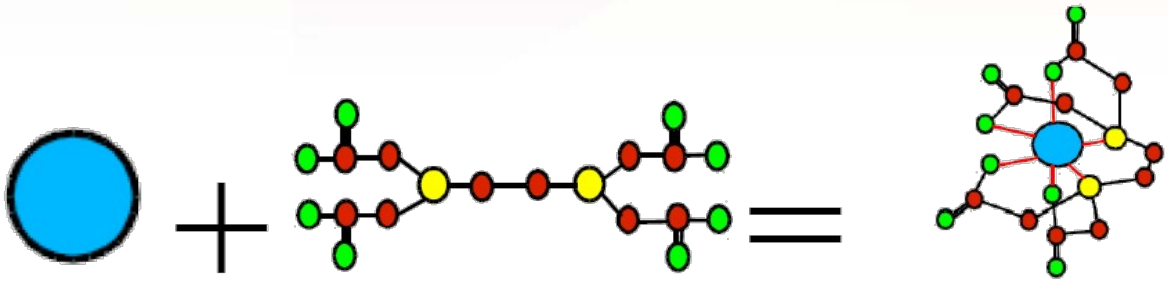


CHELATING AGENTS

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

Examples include:

- EDTA
- Citric acid etc.



FACTORS AFFECTING PRESERVATIVE EFFICACY

1. Interaction with formulation components
2. Properties of preservatives
3. Effect of containers
4. Types of micro-organisms
5. Influence of pH

1. Interaction with formulation components

- Hydrocollids such as **methylcellulose, alginates, tragacanth** can interacts with preservatives and **diminish** their activity.
- Many emulgents are used in pharmaceutical preparations to produce elegant applications. Interaction may occur between **preservatives and emulsified oil phase and with emulgent molecules**.
- Nature of oil, oil water ratio, type of concentration of emulgent, influence the concentration of preservatives needed to protect the system.
- Many **tablet additives** cause problems in tablet preservations due to their **interaction with added preservatives.**

2. Properties of preservatives

- The distribution of preservative must be **homogeneous** and **more solubility** in the bulk phase is preferable in multi phase system.

- Some chemicals such as **chlorobutol may hydrolyse on storage** if the pH is unfavourable.

- Preservatives may **react with substances leached from the container** and lose its antimicrobial activity.

3. Effect of containers

- Formulations packed in **glass containers can be expected to retain their preservative content** if closure is airtight.
- Preservatives may **penetrate through the plastic container and interacts with it.**
- **Rubber also reacts** with many preservatives but is still used for closures.
- Containers or closures may cause contamination of pathogens.
- Screw–capped containers and corks are the common source of mould spores.

4. Types of microorganisms

- **Plants products may contain pathogenic microorganisms from the soil.** Ex. Clostridium species, Bacillus anthracis. These soil microorganisms can cause spoilage of pharmaceutical products.
- Many **products prepared from animal sources may contain pathogens** like Salmonella typhi.
- Spores of tetanus and gas gangrene have been isolated from gelatin.

5. Influence of pH

- Adjustment of the pH of solution may affect the chemical stability and the activity of the preservative.

- The **majority of preservatives are less dependent upon pH**, although cationic active quaternary ammonium compounds (Benzalkonium chloride, Etilbencil chloride, Alkyl Dimethyl Ethyl Benzyl Ammonium and Dioctyl Dimethyl Ammonium Chloride) are more active at high pH values.

RECOMMENDED PRESERVATIVE CONCENTRATION

Preservative Concentration for Liquid Oral Preparations

Name	Recommended Concentration
Benzoic Acid	0.1 to 0.2%
Sorbic Acid	0.1 to 0.2%
Methyl Paraben	0.25%
Propyl Paraben	0.5 to 0.25%
Sodium Benzonate	0.1 to 0.2%
Bronidol	0.001 to 0.05%

Preservative Concentration for Other Preparations

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%

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

ANTIMICROBIAL EFFECTIVENESS TESTS (AET)

- ✓ This test is used to evaluate the effectiveness of preservative systems in multi dose dosage form.

- ✓ Originally designed to evaluate the performance of antimicrobials added to inhibit the growth of microorganisms that may be introduced in the product during or subsequent to the manufacturing process.

PROCESS

- ✓ Inoculating a measured amount of product with known amount of microorganisms.
- ✓ Whenever possible, the the original containers are also utilized for the test.
- ✓ The containers are protected from light and incubated at ambient temperature for 28 days.
- ✓ The death rate is measured over a 28 day period and compared to the acceptance criteria of compendial product list.

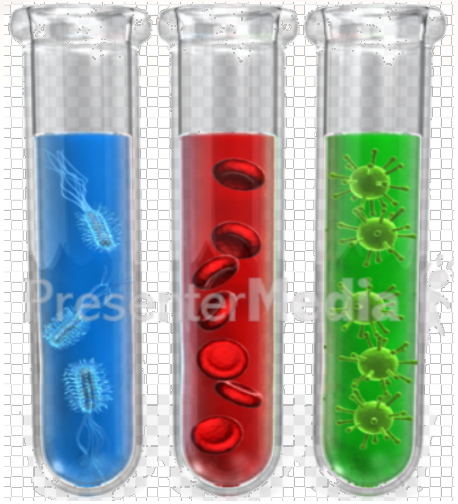
PRESERVATIVE EFFICACY TESTING (PET)

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.

COMPENDIAL PRODUCT CATEGORIES

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
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

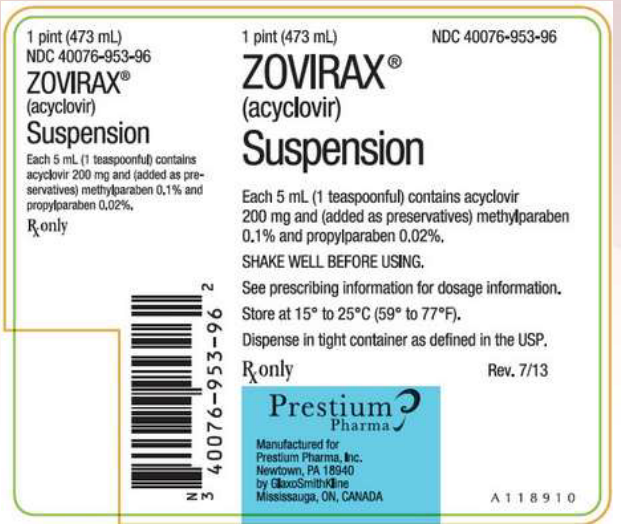
OTHER TECHNIQUES:

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

These include methods such as:

- ATP bioluminescence
- Electrical impedance spectroscopy
- Spectro-fluorimetry
- Chemiluminescence

EXAMPLES



THANK YOU