PILOT CHEMICAL COMPANY

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Technical Bulletin:

PRESERVATIVES

What is a preservative?

A preservative is a chemical which, when added to a product, inhibits the growth of microscopic or sub-microscopic organisms such as bacteria and fungi.

Note: preservatives are specifically designed to inhibit growth. The use levels prescribed by the manufacturer are, therefore, recommended with only this use in mind. Thus, preservatives should not be used to destroy such organisms pre-existing in a product as this usage would probably require significantly higher concentrations than those recommended.

What products require a preservative?

Generally, any product which contains organic material and > 60 wt.% water can become contaminated with bacteria or fungi and will require a preservative. Thus, in Pilot's case, Calfoam® SLS-30 requires a preservative; Calsoft® L-60 does not.

How do you test for contamination?

The simplest microbiological test to check for contamination is an Aerobic Plate Count (APC). In an APC, a (usually diluted) sample of the product under test is spread onto an agar plate. After an incubation period, usually 48 to 72 hours at 32 to 37°C for bacteria, 25 to 30°C for fungi, the number of colony forming units (CFU's) are counted. This count multiplied by the dilution factor gives the number of viable organisms per gram of sample. Counts range from less than 10 CFU's up to approximately 300 CFU's above which the value is reported as Too Numerous to Count (TNTC).

How do you test that a preservative is working?

This APC test is also used when evaluating a preservative by challenge testing. In a challenge test, a sample of the preserved product is inoculated with a known number of organisms. Usually 10^6 organisms per gram of sample is the level used. Small portions of this sample are plated, incubated and counted immediately and regularly over a period of time, usually four weeks. Reduction of the initial counts to less than 10 CFU's in one week indicates an acceptable level of preservation.

How does contamination arise?

There are three main sources for contamination: unsanitary working conditions and/or equipment, the water used in manufacture of the product, or, in the case of formulations, outside raw materials. All of these sources can be monitored. (Note: only basics are mentioned here).

- Work areas and equipment need to be cleaned and sanitized on a regular basis. Special care should be taken to clean areas such as pipe dead ends, cracks and interstices (e.g. at flange gaskets) where biofilms can build up.
- Organism levels in water must be monitored; process water should meet the EPA potable water quality standards of 4 CFU's max. per 100 ml.
- Specifications for outside raw materials can include microbiological information.

How are preservatives regulated?

In the U.S., preservatives for the personal care industry are regulated by the Food and Drug Administration (FDA). The FDA does not approve preservatives, it can only restrict or ban them - this is called a negative list. Ingredients currently on this list include: hexachlorophene, mercury compounds, bithionol and halogenated salicylanilides.

Additionally a group known as the Cosmetic Ingredient Review (CIR) lists the preservatives below as unsafe or "insufficient data to be declared safe." This designation may lead to FDA regulations in the future: benzylparaben, chloroacetamide, glutaral for leave-on products, bronopol in combination with secondary amines, formaldehyde in aerosols.

Both the European Union (EU) and Japan approve preservatives. These are positive lists and only materials on these lists can be used in that area.

What preservatives are on the market?

For the purposes of this review, the available preservatives will be separated into a number of classes. Special emphasis is given to those materials used by Pilot.

1. **Phenolic types:** this category includes the parabens, esters of ρ-hydroxybenzoic acid. Not used by Pilot because of limited water solubility. Parabens are most active against fungi. They are deactivated by strongly hydrogen-bonding materials such as ethoxylated compounds. Parabens are universally permitted. Also in this group: phenoxyethanol - often used as a solvent for parabens; ρ-chloroxylenol (PCMX) - used in some anti-bacterial soaps; dichloroxylenol is popular in Europe.

2. **Products which react positive to the Hantzsch test:** The Hantzsch test is a colorimetric method for the detection of formaldehyde (HCHO). Unfortunately, the test does not differentiate between HCHO itself and compounds which break down under the rigorous test conditions to give HCHO or other aldehydes.

HCHO is an excellent preservative, active against both fungi and bacteria. It is volatile (repeated opening of a container can deplete the HCHO level of the contents significantly). HCHO is banned in Japan and restricted to < 500 ppm in the EU.

The so-called "Formaldehyde Releasers or Donors" include such commonly used materials as DMDM Hydantoin (Dantoguard® from Lonza), Imidazolydinyl and Diazolidinyl Ureas (Germall® 115 and Germall® II, respectively from Sutton) and Bronopol (Myacide® BP from Angus). Generally these compounds are very active against bacteria but have little activity against fungi. All these materials test positive to the Hantzsch method for formaldehyde and thus suffer from a number of the same restrictions as HCHO itself. Additionally, Bronopol acts as a catalyst for the formation of nitrosamines from secondary amines and thus CIR has found it not safe in formulations using these materials.

Other common preservatives which give positive Hantzsch tests, but are not formaldehyde releasers include Quaternium-15 (Dowicil® 200 and Dowicil® 75 from Dow) and Glutaral (Ucarcide® from Union Carbide). Dowicil® has a broad spectrum of activity, however, it is more effective against bacteria than fungi. Glutaral reacts positive to the HCHO test because it is an aldehyde itself. It acts against both bacteria and fungi but can become deactivated in the presence of primary and secondary amines. CIR has found glutaral not safe in leave-on products due to sensitization concerns.

3. **Acids and their salts:** Only active in the undissociated form i.e. at low (<5) pH's. Not used by Pilot for this reason. Benzoic acid is used in pH <3 soft drinks.

4. **Halogenated Compounds:** by far the most common of these is Methylchloroiso-thiaolinone/ Methyliso-thiaolinone (MCI/MI), which is a 1.5% aqueous solution of a 3:1 mixture of MCI and its unchlorinated counterpart. The solution is stabilized with 23% magnesium sulfate. MCI/MI has excellent activity against all microorganisms. The efficacy of MCI/MI is increased by use of EDTA. It can be deactivated by extended periods at high (>50°C) temperatures, pH's >9, primary or secondary amines, and reducing and oxidizing agents such as bisulfite or peroxide. As supplied, the MCI/MI solution is corrosive and a sensitizer.

5. **Newcomers:** two materials bear mentioning in this category. Iodopropynyl butylcarbamate (IBCP) is very active against fungi but weak against bacteria. It is found as the adjunct fungicide to DMDM hydantoin (Glydant Plus® from Lonza) and Diazolidinyl Urea (Germall Plus® from Sutton). IBCP's main drawback is its very low solubility in water - 160 ppm. It is most active at saturation. There is a growing market for Methyldibromo-glutaronitrile (DBDCP) because of its popularity in the EU, especially Germany. Marketed as Merguard® by Calgon in the U.S. Inactivated by pH's > 8.5, or > 7 with heating.
6. **Blends:** blending two or more preservatives together in a package can give a broader spectrum of activity and improve the ease of incorporation. Examples would be the previously mentioned Glydant Plus® and Germall Plus® and Paragon II® from MacKintyre. One problem with blends is that they sometimes contain illogical compositions, for example, in a blend of compounds A and B, dilution to the efficacy level of A would result in B being present at a concentration above its solubility limit.

7. **"Natural Preservatives":** generally, so-called natural preservatives require such high use levels - 10% or more for Tea Tree Oil (compared to 15 ppm to 0.5% for most manufactured products), that they are prohibitively expensive. They are also only active against fungi.

What is an adjuvant?

An adjuvant is a compound which aids the efficacy of a second. For example, Pilot uses EDTA as an adjuvant when MCI/MI is used as a preservative. EDTA chemically removes iron from the organism's cell wall, weakening it and allowing the biocide easier access.

What preservatives are used by Pilot?

Pilot's default preservative for almost all products is formaldehyde. Pilot offers a special grade of some products preserved with MCI/MI. A few of Pilot's products are preserved with either Dowicil® 75 or Dowicil® 200.