In the European Pharmacopoeia and, hence, in the Dutch Pharmacopoeia (8th Ed) standards of microbiological purity of pharmaceutical preparations have been set. These standards depend on the type of preparation and they vary from sterility for parenterals, to a maximum of 1000 c.f.u./g or ml for oral preparations. The more stringent demands made upon the microbial purity of preparations have consequences for the preservative capacities of these preparations. These capacities can be influenced by pH, water activity (a_w), redox potential, temperature of storage and added auxiliary substances such as preservatives. The pharmacopoeia allows the addition of preservatives to certain pharmaceutical preparations if the latter do not possess adequate antimicrobial activity (Table 1). The pharmacopoeia also mentions some substances as suitable preservatives for injections and eyedrops (Table 2).

The use of preservatives in Dutch pharmacy is best illustrated by the Formulary of the Dutch Pharmacists (F.N.A.). In this formulary standardized formulations are given. Table 3 shows the preservatives used in several F.N.A.-preparations.

Seventy percent of the eyedrops is preserved with benzalkonium chloride (BAC), 0.1 g/l, in combination with disodium edetate (EDTA), 1 g/l, and 28% is preserved with phenylmercuric borate (PMB), 0.04 g/l. The combination of PMB and phenylethanol (PEA), 6 g/l, has temporarily been abandoned because of irritation to the eye. All nasal drops are preserved with BAC + EDTA. The use of chlorbutol has been abandoned almost completely. Most of the syrups and several other oral liquids are preserved with methyl hydroxybenzoate (MHB), 1–2 g/l. In the oil-in-water creams this preservative has been replaced by sorbic acid (SA), 1.5 g/l.

Since the ideal preservative does not exist, problems in preserving a pharmaceutical preparation can be expected. Two examples are given:

Recently, a survey of the microbial quality of Lanette cream F.N.A. preserved with MHB 2 g/l, has been carried out (van Klinger et al., 1980). In 58% of the creams examined microorganisms could be detected. They all contained more than 100 c.f.u./g, which is the pharmacopoeial limit for this type of preparation. In 24% of the creams enterobacteria were found (Enterobacter aerogenes, E. agglomerans, E. cloacae, Klebsiella pneumoniae). Pseudomonas spp. were found in 20% and yeasts in 16% of the creams.

Examination of the microbial quality of an antacid liquid (Suspensio antacida F.N.A.), preserved with 2.1 g MHB per liter, showed that this suspension could be heavily contaminated (Tromp, personal communication). Microorganisms could be detected in 41% of the suspensions, and 28% contained more than 1000 c.f.u./ml, the pharmacopoeial limit for oral preparations. Enterobacteria were present in 10%, Pseudomonas spp. in 4% of the suspensions. Furthermore, gram-positive cocci
and rods, and fungi were present. The number of c.f.u./ml was negatively correlated with the concentration of undecomposed MHB. Hence, MHB appeared to be ineffective in both the cream and the suspension.

The inactivation of a preservative can be caused by direct or indirect interaction with the preparation in which it is incorporated.

Direct interaction occurs when the net concentration of preservative available for reaction with microbial cells is changed as a result of some type of binding with one of the other constituents of the preparation. Examples of direct interaction are: adsorption to solid materials, solubilization and binding by emulsifiers, partitioning between oil and water phase, or change in dissociation of the preservative due to a change in pH.

Indirect interaction implies an influence of one of the components of a pharmaceutical preparation on microbial cells by which the susceptibility of the cells towards a given concentration of the preservative is changed. This has been shown for e.g. EDTA and PEA (van Doorne, 1979).

The inefficacy of MHB in the Lanette cream was caused by partitioning of MHB between oil and water phase and by binding to the emulsifier sodium laurylsulphate. A better preserving capacity of the cream was obtained by addition of 1.5 g of sorbic acid per liter (van Doorne and Dubois, 1980); thus, the F.N.A. formulation was changed.

The high pH (8-9) of the antacid suspension is the cause of the inactivation of MHB (pKₐ = 8.25, concentration exponent n = 4.5). A better preservative for this suspension could not be found. Therefore, it was tried to lower the initial level of contamination of the preparation by heating some components with water to 100°C. A second survey of the microbial quality of the suspension demonstrated that the quality of the preparation was improved (Tromp, personal communication). Only 12% of the suspensions examined contained more than 1000 c.f.u./ml. No gram-negative microorganisms were found. Here, too, the F.N.A. formulation was changed.

Inactivation of preservatives can also be caused by containers and closures. Sorption of pre-