Russell, Hugo & Ayliffe's

Principles and Practice of Disinfection, Preservation & Sterilization

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Principles and Practice of Disinfection, Preservation & Sterilization

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Chapter 14

Preservation of medicines and cosmetics

Sarah J Hiom

1 The nature of medicines and cosmetics

Medicines are formulated to assist in the administration of drugs to treat or prevent diseases or to alleviate symptoms in patients. Medicines can be delivered by a wide variety of routes, from relatively non-invasive topical applications to highly invasive injections. Cosmetics, however, are designed to deliver agents that enhance personal appearance, modify body odour or assist in body cleansing. Application is largely restricted to the skin, although such products as toothpaste or those for 'feminine hygiene' may come into contact with mucous membranes. Eye-area cosmetics may also come into secondary contact with the cornea and conjunctiva.

Although the intended outcomes for medicines and cosmetics are fundamentally different, there are many similarities in the nature of the formulations created and the uses (and abuses) to which both can be subjected, including common microbiological problems. In order to create elegant products that are also efficacious, stable and safe to use throughout their intended shelf life, it is often necessary to include several other ingredients in addition to the specific therapeutic agent or that producing the cosmetic effect. While a few formulations may be simple aqueous solutions or dry powders, many are extremely complex, both in the number of ingredients used and in their physicochemical complexity. Some indications of this variation and complexity of medicinal and cosmetic formulations can be obtained from the reviews of Friberg (1984), Eccleston (1990), Frick (1992), Pena *et al.* (1993) and Lund (1994).

The possibility that microorganisms might contaminate medicines and cosmetics during manufacture, storage or use must be addressed to ensure the continued stability and safety of the product. The complex chemical and physicochemical nature of many formulations is often found to be conducive to the survival and even multiplication of such contaminants, unless specific precautions are taken to prevent it. Such survival, and even growth, may result in appreciable damage to the product and/or the user. The consequences of this damage will increasingly be reflected in loss of remuneration and prestige for the manufacturer as strict product-liability legislation continues to come into operation. Good manufacturing practices should provide adequate control of contamination from raw materials and processing activities (see Chapter 21; Clegg & Perry, 1996; Anon., 1997a; Beaney, 2001). One procedure adopted to limit the establishment of microbial contamination after manufacture is to include antimicrobial preservatives in the formulations, although other protective techniques can be used instead of, or in combination with, these agents. Selection of a preservative system is a complex issue. It is essential to understand and fully evaluate the preservative needs and problems of individual products and to be aware of how potential antimicrobial agents may behave in that formula.

The ideal properties required of a preservative have been described (Beveridge, 1998) together with monographs of available agents (Steinberg, 1996; Kibbe, 2000; BP, 2001). Very few preservatives are able to meet all the required criteria and it is often a case of 'best choice under current circumstances'. However, the selection process will include consideration to the properties of the formulation, preservative and likely challenge microbes, together with an evaluation of the intended use of the product and the associated contamination risks.

2 The consequences of microbial contamination

Micro-organisms possess diverse metabolic activities and are likely to present a variety of hazards (eg. infection, toxicity and degradation of the formulation) both to the user and to the stability of the products, if allowed to persist. The *British Pharmacopoeia* (BP, 2001) sets limits for the presence of microorganisms in medicines, which vary depending on the product and its intended use. However, microbial contamination over and above these pharmacopoeial levels is still reported in distributed UK medicines (Baird, 1988, Bloomfield, 1990), although stricter regulatory controls have improved the situation compared with that of the pre-1970 period (Beveridge, 1975). Other indications that the risk of microbial contamination is still a problem include reports that 20% of the UK drug alerts since October 2001 were due to an inability to provide microbial assurance to the required level (Defective Medicines Report Centre) and that 7.1% of Medicines Control Agency (MCA) inspection deficiency reports (1998–99) were associated with the potential for microbial contamination (Taylor *et al.*, 2000). In-use contamination hazards also continue to be a problem, particularly for multidose eye-drops (Geyer *et al.*, 1995; Brudieu *et al.*, 1999; Tasli & Cosar, 2001) and multidose injections (McHugh & Roper, 1995). In the USA, concern currently centres around the microbial hazards that accumulate during the use of cosmetics (Anon., 1992a; Tran & Hitchins, 1994). Few recent published data have been found for cosmetic contamination in the UK, although anecdotal evidence suggests a similar situation to that in the USA.

The most commonly reported microbial hazards found in liquid medicines and cosmetics are pseudomonads and their related Gram-negative rods, with spores (bacterial and fungal) predominating in dry tablets, capsules and cosmetic powders. Shared-use cosmetics accumulate human microflora, such as *Staphylococcus epidermidis*, *Staphylococcus aureus* and corynebacteria, as well as pathogenic fungi, yeasts and bacterial spores. Those which contain water or become wet during use reveal pseudomonads and related bacteria. The clinical and pharmaceutical significance of such contamination of medicines has been reviewed by Ringertz & Ringertz (1982), Martone *et al.* (1987) and Denyer (1988) and for cosmetics by Sharpell & Manowitz (1991). The implications for product spoilage of both have been discussed by Spooner (1996) and Beveridge (1998).

The risk (likelihood of harm actually occurring) associated with delivery of contaminated products is less clearly determined. It will depend upon the type of microorganism present, the infective dose (dependant on the ability of the formulation to encourage microbial survival and the level of preservative protection built into it), the route of administration of the product and the hosts resistance to infection (including immune status or degree of tissue damage at site of application). Prior to the 1960s, incidents of infection attributed to contaminated products seemed to be regarded as unfortunate but isolated occurrences, these included severe eye infections from contaminated ophthalmic solutions (Theodore & Feinstein, 1952) and tetanus infection of newborn children from contaminated talc dusting powders (Tremewan, 1946). During the 1960s, a number of key investigations demonstrated the existence of a much wider problem. Ayliffe *et al.* (1966) reported on an extensive UK outbreak of severe eye infections, traced to traditional but wholly inadequate official guidelines for the preservation and manufacture of ophthalmic solutions. The 'Evans Medical disaster', in which contaminated infusion fluids caused serious injury and contributed to some deaths, precipitated public awareness and led to an official inquiry (Clothier, 1972). In Sweden, Kallings *et al.* (1966)

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