# A Closer Look at Product Quality and the Role of Preservation and Preservative Testing

Pharmaceutical and cosmetic manufacturers are required to do extensive testing to ensure their products are safe for consumers. One such test is the Preservative Effectiveness Test (also known as the Antimicrobial Effectiveness Test) which is used to demonstrate the capability of preservatives that are incorporated into drugs, cosmetics and various household products to ascertain product quality for the life of the product. Microbiologics asked Dr. Phil Geis, a 30-year veteran of the pharmaceutical microbiology industry and founder of Geis Microbiological Services, to share his knowledge on the important topic of preservation and preservative testing and the role they play in product quality.

Dr. Geis earned a PhD in microbiology and mycology from the University of Texas. His career in microbiology began at a clinical lab in the US Army, moving to commercial media production, and in 1981 to The Proctor & Gamble Company (P&G). Through almost three decades with P&G microbiology, Phil managed preservative and disinfectant development and studies of household and skin microbial ecologies and hygienic manufacturing. He was the first recipient of P&G's namesake award – Dr. Philip Geis Microbiology Quality Award. Dr. Geis brings unique global expertise and experience in diverse regulatory, manufacturing, product quality and consumer realities for a broad range of products from OTC drugs to fabric softeners to dog food.

In this article, Dr. Geis discusses the importance of preservatives for maintaining product quality, the different types of preservatives used in the pharmaceutical and cosmetic industry, and the preservative effectiveness test.

**The Importance of Preservation in Product Quality**

An effective preservative capability is a central element of drug, cosmetic and household and institutional product microbiological risk assessment and quality. Such a capability can mitigate both incidental low-level contamination from a controlled manufacturing system, as well as introduction of contamination through typical, expected product use; establishing appropriate product quality for the life of the product. Whereas some products do not require frank preservation by design (e.g. aseptic production/single use), formulation (e.g. high ethanol contact, extremes of pH and anhydrous) or constraining dynamics of use (e.g. near term expiration dates, refrigeration), chemical preservation and preservative qualification remain a primary element of quality for the majority of products (1).

**Table 1: Frequency of Preservative use. Courtesy of David Steinberg.**

| Preservative | 2007 | 2010 |
|---|---|---|
| **Methylparaben** | 11609 | 13434 |
| **Propylparaben** | 9329 | 10421 |
| **Phenoxyethanol** | 5132 | 8878 |
| **Butylparaben** | 4447 | 5289 |
| **Ethylparaben** | 3789 | 4869 |
| **Isobutylparaben** | 1684 | 2693 |
| **MI** | 1409 | 2408 |
| **MCI/MI** | 1392 | 2235 |
| **DMDMH** | 1665 | 2035 |
| **Im. Urea** | 2266 | 2007 |
| **Benzyl Alcohol** | 1125 | 1991 |
| **Caprylyl Glycol** | 591 | 1712 |
| **Di. Urea** | 1299 | 1644 |
| **Sorbic Acid** | 1259 | 1456 |
| **Benzoic Acid** | 1153 | 1334 |
| **Chlorphenesin** | 441 | 1065 |
| **DHA** | 866 | 948 |
| **IPBC** | 429 | 834 |

**Antimicrobials and Preservatives**

A large number of chemicals are available in the drug, cosmetic, and household and industrial product categories. These preservatives or, as is more frequently encountered, preservative combinations, differ significantly from antimicrobials formulated to establish in-use benefits. By mitigating factors such as limited solubility and narrow spectrum of efficacy, antimicrobials are

typically not effective preservatives. Though there is some overlap, each product category relies on a unique set of preservative chemicals and only for cosmetic is the frequency of preservatives readily available (see Table 1).

**Types of Preservatives**

Via the Food and Drug Administration's voluntary ingredient reporting system, the cosmetics industry has established an ongoing record of its preservative use. Despite largely unwarranted concerns for some chemicals, this record reports a consistency of use that may be surprising to those not familiar with the critical need for the few effective preservatives available to this industry.

In the most recent report (2), and as has been the case for the over a decade, parabens (esters of p-hydroxy benzoic acid) remain the most frequently-used preservatives; followed by so-called formaldehyde releasers, isothiazolinones and a general application including organic acids and alcohols (Table 1). These preservatives are most often used in combinations, information of which can be found in literature (3), as well as by examination of ingredient labels of marketed products. This frequency of use has remained consistent despite technically-unwarranted public relation concerns for this category of chemicals, and the introduction of "natural" preservatives and dual-functional ingredients. The reasons are simple – 1) no new preservatives have been introduced in decades, 2) these molecules are safe in the context of use, 3) they readily establish effective preservation which is so important to product quality and ultimately consumer heath, a result not so easily established with alternative systems.

**Preservative Effectiveness Testing**

The preservatives mentioned above have been, and are used, to establish a remarkable record of microbiological quality for cosmetics, however their simple incorporation in this product category, or preservatives in any application, does not necessary assure efficacy. This capability is demonstrated using preservative effectiveness testing that, as with preservatives themselves, is product category specific with USP <51> indicated for drugs, the AOAC protocol developed by the Personal Care Products Council for cosmetics (4), and compendial (ASTM, ISO, EN) and in-house methods (e.g. 5,6) for household and institutional products.

These tests are relatively similar in that each exposes the product to an exaggerated microbial challenge: for USP $1x10^3$ to $1x10^6$cfu/ml depending on drug product category and for AOAC cosmetic methodology, $1x10^6$ cfu/gram for bacteria and $1x10^5$ cfu/gram for fungi. Microbial survival is determined through a 4 week period and a pass/fail determination is made –based

comparison of microbial reduction observations to established criteria. The primary differences between category methods are the microbes employed, kill-rate criteria establishing successful preservation, and probably most importantly, the domain or risk the capability proposes to address.

**Drugs**

As drug products are made under conditions of stringent hygiene, the relevant USP <51> with its small number of clinical isolates and relatively modest kill rate expectations, is more aligned to potential low-level contamination in use than to microbiological risks in manufacturing.

**Cosmetics**

In contrast, the AOAC and similar methods for cosmetics use many of the same clinical microbial strains of the USP, but also include microbial isolates that have been recovered from environmental sampling (environmental isolates), as well as manufacturing contaminants (objectionable organisms). Protecting consumer health is the first objective of in-use preservative efficacy for cosmetic products. The preservation test design also anticipates some level of efficacy to address contamination with low levels of microbes that may be encountered in a GMP-controlled manufacturing system.

**Household and Institutional Products**

As household and institutional products are rarely produced on manufacturing systems that establish effective microbiological control, the primary microbial component of challenge testing are manufacturing isolates. Clinical isolates are less relevant to these products as their basic formulation, packaging and intended use militate against contamination in use. Contrast this with manufacturing where continuous challenge in absence of GMP's that allows adaptation under relatively harsh conditions of microbes some might see as extremophiles (7,8).

**Conclusion**

It is clear that a successful risk assessment of any product requires consideration of manufacturing risk, preservation and intended product use. Heavily preserved products, even those with disinfectant levels of antibacterial ingredients, are subject to contamination if manufactured under sufficiently unsanitary conditions (9,10). Similarly, preservation and packaging must anticipate and be evaluated in context of ultimate product use (11,12). Systems developed in absence of a clear understanding of use and anticipated misuse may well suffer substantial and surprising contamination (13,14).

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