W. Siegert

Microbiological Quality Management for the Production of Cosmetics and Detergents
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The Target

Cosmetic products are not expected to be aseptic; however, they must be completely free of high-virulence microbial pathogens and the total number of aerobic microorganisms per gram must be low (4). Skin and mucous membranes are protected from microbial attack by a natural mechanical barrier and various defence mechanisms (1). However, these defences may be damaged and a slight trauma may be caused by the action of some cosmetics. This may increase the chance of a microbial infection. Such infections are of particular concern in certain situations such as; when cosmetics are used around the eyes, on mucous membranes, on damaged skin, on children under 3 years, on the elderly and with people showing compromised immune responses (1). Pathogens or opportunistic pathogens whose incidence are of particular concern, especially in eye-area cosmetic products, include Staphylococcus aureus, Streptococcus pyogenes, Pseudomonas aeruginosa and other Pseudomonas species also Klebsiella pneumoniae (4). Pseudomonas

Introduction

Producing microbiological faultless detergents and cosmetics requires an integrated quality management system. This consists of good raw material quality, hygienic design of production facilities, good production hygiene and a validated preservative system. The sustainable use of preservatives is optimised by the antimicrobial stabilisation of detergents and cosmetics by utilisation of synergistic effects. Hazard analysis critical control point (HACCP) is a systematic preventive approach to safeguard microbiological faultless quality of products. The requirements of ISO 22716 (Cosmetics – Good Manufacturing Practices (GMP) – Guidelines on Good Manufacturing Practices) are demonstrated for the production of aqueous products. Examples of proper hygienic design and adequate hygiene measures are given, as well as a raw material and finished product assessment according to ISO 29621 (Cosmetics – Microbiology – Guidelines for the risk assessment and identification of microbiologically low-risk products).

<table>
<thead>
<tr>
<th></th>
<th>Cosmetics Europe (2)</th>
<th>PCPC (1)</th>
<th>SCCS (3)</th>
<th>US FDA (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Products specifically intended for children under 3 years (Category 1)</td>
<td>$5 \times 10^2$</td>
<td>$5 \times 10^2$</td>
<td>$5 \times 10^2$</td>
<td>$5 \times 10^2$</td>
</tr>
<tr>
<td>Products to be used in the eye area and on mucous membranes (Category 1)</td>
<td>$5 \times 10^2$</td>
<td>$5 \times 10^2$</td>
<td>$5 \times 10^2$</td>
<td>$1 \times 10^3$</td>
</tr>
<tr>
<td>All other products (Category 2)</td>
<td>$5 \times 10^3$</td>
<td>$5 \times 10^3$</td>
<td>$5 \times 10^3$</td>
<td>$1 \times 10^3$</td>
</tr>
</tbody>
</table>

Table 1 Limits for the total viable count for aerobic mesophilic microorganisms in cosmetics [cfu/ml]
**COSMETICS**

**Preservatives**

*Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Candida albicans* are considered the main potential pathogens in cosmetic products. These specific potential pathogens must not be detectable in 0.5 g or 0.5 ml of a cosmetic product of Category 1 and in 0.1 g or 0.1 ml of a cosmetic product of Category 2 (1).

Table 1 shows the recommended limits for the total viable count of aerobic mesophilic microorganisms (1-4) from different guidelines.

For household cleaning products «fit for use» is the main demand, there is no legal demand for microbial cleanliness. Nevertheless, in household products microbial growth will negatively affect the product quality. Beside the health hazard of malodour there is potential clouding or viscosity decrease (biodegradation of thickener) of the product. Bellying (gas formation e.g. by yeast growth) or contraction (oxygen consumption by aerobic growth) of the bottle could also be seen. Therefore following the same microbial limits for household products as for cosmetics is advisable.

### Basic Conditions

Humidity, which means water, is available in most products. It is the most important factor for the multiplication of microorganisms. Starting microbial cultures are always available from raw materials through a range of sources such as the used water, the production facilities and even from the air. Cosmetic products contain enough nutrients and their storage at ambient temperature is nearly ideal for the growth of microorganisms.

To produce microbial faultless products, an integrated microbiological quality management (MQM) is necessary. This includes securing the microbiological purity of the raw materials used, a validated product formulation including the preservation system, hygienic design and good production hygiene.

### Optimising the Preservation

The use of biocides has enabled a shift towards products with greater biodegradability. It could be argued, the value of biocides to the quality of our lives is beyond price. Their function is primarily preventative, minimising waste of natural and limited resources while reducing exposure hazards of people to harmful microorganisms (5).

To achieve a sustainable preservative use it is important to utilise synergistic effects that minimise the biocidal actives concentration used. An optimised dosage concept offers additional benefits. The following products and application recommendations illustrate this principle.

#### Detergents and cleansers

Microbial contamination of detergent can occur during its manufacture. The majority of the contaminants are present in the source of water and raw materials but also in equipment vessels and plumbing lines (tanks and pipes). The addition of a fast-acting preservative with long term protection at the beginning of the production process to sanitise the water used for bulk production is a solution to this problem. The killing of bacteria by such a preservative must occur within a few minutes, the very best situation would be adding it before other ingredients (6). The principle of adding the full amount of biocide during the first water addition to the vessel is shown in Fig. 1.

From extensive research work, Bis(3-aminopropyl)dodecylamine (BDA) was recognised as an excellent enhancer for today's standard 'soft' preservatives based on methylisothiazolinone (MIT) in combination with benzisothiazolinone (BIT). This combination of actives is able to markedly reduce the contact time necessary to sanitise the water within the normal production process to a few minutes (Fig. 2), without enlarged holding times.

#### Cosmetics

To minimise the amount of preservative actives in cosmetics different approaches are used in the market:

- Combinations of preservative actives
- Addition of multifunctional actives to boost the antimicrobial effect
- Addition of chelating agents
- Combination of multifunctional actives to achieve self-preserving systems

By combining phenoxyethanol with the multifunctional cosmetic additive ethyl-
hexylglycerin an enhanced efficacy is achieved (7). The combination of 90% phenoxyethanol and 10% ethylhexylglycerin (euxyl® PE 9010) is a common replacement for the standard phenoxyethanol / paraben mixtures (8). Fig. 3 shows the boosting effect of ethylhexylglycerin.

Further improvement is achievable by adding chelating agents (9). Fig. 4 shows the boosting effect of the tetrasodium dicarboxymethyl glutamate (GLDA) on euxyl® PE 9010. GLDA in combination with citric acid gives a noticeably better effect, including an improved effectiveness against fungi, than can be achieved with EDTA.

The boosting effect of GLDA is also utilisable for self-preserving systems. Fig. 5 displays an example of a self preserving wet wipe liquid.

**Good Manufacturing Practices (GMP)**

Why more than adding a preservative is necessary?
The preservative must be able to control the types of microorganisms most commonly present in the intended application.

Preservatives are used for the protection of consumers and the prevention of product spoilage during the intended and foreseeable use. However, they should not replace good production hygiene. Contamination by microorganisms during production has to be avoided by recognising and eliminating its sources.

**ISO 22716**

In November 2007 the new guidance for Good Manufacturing Practices (GMP) for the cosmetics manufacturing industry ISO 22716 was published (10). It describes the basic principles of how to apply GMP in a facility that produces finished cosmetic products.

Since 1977 cosmetic products and their ingredients must be produced by cosmetic GMP rules. This is demanded in the sixth amendment (1993) of the Council Directive 76/768/EEC (11); but there were no detailed legal guidelines about cosmetic GMP. Some associations published guidelines:

- IKW (German Cosmetic, Toiletry, Perfumery and Detergent Association): Cosmetic GMP – guidelines for the production of cosmetic products (updated several times – last update 1997)
- Council of Europe: Guidelines for Good Manufacturing Practice of Cosmetic Products (1995)

The European Cosmetic Regulation 1223/2009 (12) was published on 30 Novem-
ber 2009 and came into force on 10 January 2010. From 11 July 2013 most of the provisions will be applicable, as the regulations are effective 42 months after coming into force. Article 8 of this regulation requires:

- The manufacture of cosmetic products shall comply with Good Manufacturing Practice with a view to ensuring the objectives of Article 1
- Compliance with Good Manufacturing Practice shall be presumed where the manufacture is in accordance with the relevant harmonised standards, the references of which have been published in the Official Journal of the European Union.

The reference to the harmonised standard ISO 22716 was published on 21.4.2011 in the Official Journal of the European Union (13).

Basic requirements
ISO 22716 gives guidelines for the production, control, storage, and shipment of cosmetic products. Related to microbial quality the main requirements are:

- Cosmetic GMP regulations must be followed in all areas of production, for all cosmetic products and for all businesses (large or small)
- Ensure adequate professional qualifications of the person who is responsible for the production
- Provision of suitable premises
- Sufficient staff with appropriate training
- Documentation of the activities and inspections during production

Requirements for a good production hygiene
Personnel hygiene
§ 3.5.1 of ISO 22716 describes the demands for personnel hygiene. Hygiene programmes should be established and adapted to the needs of the plant. These requirements should be understood and followed by every person whose activities take them into production, control and storage areas. Additionally the training document ISO/TR 24475 (15) states

![Graph showing log germ count reduction](image)

**Fig. 4** Boosting effect of the tetrasodium dicarboxymethyl glutamate (GLDA) on euyxyl® PE 9010

![Graph showing log germ count reduction](image)

**Fig. 5** Self preserving wet wipe liquid

<table>
<thead>
<tr>
<th>INCI Name</th>
<th>Trade Name</th>
<th>Function</th>
<th>A %</th>
<th>B %</th>
<th>C %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water (Aqua)</td>
<td>Deionised Water</td>
<td></td>
<td>ad 100.0</td>
<td>ad 100.0</td>
<td>ad 100.0</td>
</tr>
<tr>
<td>Propylene Glycol</td>
<td>Humectant</td>
<td></td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Caprylyl/Caprylic Triglycerides</td>
<td>Tegosoft CT</td>
<td>Emollient</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>PEG-35 Hydrogenated Castor Oil</td>
<td>Jecem CAH-25</td>
<td>Emulsifying</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Polysorbate 20</td>
<td>Tween 20</td>
<td>Emulsifying</td>
<td>1.2</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Caprylyl Glycol / Ethylhexylglycerin</td>
<td>sensitive® OC 10</td>
<td>Emollient</td>
<td>1.0</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Tetrasodium Dicarboxymethyl Glutamate (47.4 %)</td>
<td>Dissolvine GL 47-6</td>
<td>Chelating</td>
<td>0.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Procedure:** Combine ingredients in order listed, while slowly mixing. Mix at 20-30°C for 15 minutes or until uniform. Adjust final pH to 5.0 with citric acid or sodium citrate.

*Developed by Unsworth Consulting Laboratories, UK*
The personnel represent a permanent source of potential errors and contaminations and therefore need to have undergone appropriate training in accordance with their level of responsibility. Hands are an often underestimated risk of transmission of microorganisms. Fig. 6 shows a typical contamination of a hand. If direct contact with products, raw materials, production equipment, or packaging material occurs, a hand sanitising is recommended, preferably with an alcoholic rub in.

Cleaning and sanitisation of premises and equipment

For cleaning and disinfection the following items have to be taken into account:

- Premises used for the production should be maintained in a clean condition
- Cleaning and, if necessary, sanitisation should be carried out to achieve the objective of protecting each product
- Cleaning and, if necessary, sanitising agents to be used should be specified and effective
- There should be cleaning and, if necessary, sanitisation programmes corresponding to specific needs of each area
- All equipment should be subject to an appropriate cleaning and, if necessary, sanitisation programme
- Cleaning and sanitising agents should be specified and effective

<table>
<thead>
<tr>
<th>Application area</th>
<th>Product</th>
<th>Use level</th>
<th>Frequency</th>
<th>Use advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production vessels</td>
<td>grotonol 3025</td>
<td>0.5 % solution</td>
<td>After every use - at least weekly</td>
<td>Add the biocide to the last rinsing water</td>
</tr>
<tr>
<td></td>
<td>grotonol SR 1</td>
<td>1.0 % solution</td>
<td>Once or twice a year</td>
<td></td>
</tr>
<tr>
<td>Inlets / outlets</td>
<td>grotonol 3025</td>
<td>0.5 % solution</td>
<td>After every use</td>
<td>Thorough cleaning of residues first</td>
</tr>
<tr>
<td></td>
<td>grotonol SR 1</td>
<td>1.0 % solution</td>
<td>Once or twice a year</td>
<td></td>
</tr>
<tr>
<td>Storage tanks</td>
<td>grotonol 3025</td>
<td>0.5 % solution</td>
<td>Every 3 month</td>
<td>Spray on all surfaces</td>
</tr>
<tr>
<td></td>
<td>grotonol SR 1</td>
<td>1.0 % solution</td>
<td>Once or twice a year</td>
<td></td>
</tr>
<tr>
<td>Pipes / Pumps</td>
<td>grotonol 3025</td>
<td>0.5 % solution</td>
<td>Every 3 month</td>
<td>Clean tools first before keeping in disinfectant solution</td>
</tr>
<tr>
<td></td>
<td>grotonol SR 1</td>
<td>1.0 % solution</td>
<td>Once or twice a year</td>
<td></td>
</tr>
<tr>
<td>Working tools</td>
<td>grotonol 3025</td>
<td>1.0 % solution</td>
<td>Permanently</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 6 Contact slides from a hand show the importance of hand disinfection

Fig. 7: Example of an individual hygiene plan
Where equipment is assigned to continuous production or production of successive batches of the same product, equipment should be cleaned and, if necessary, sanitised at appropriate intervals.

For the production of aqueous products like shampoo, lotions, gels etc. sanitisation is necessary because these products allow the proliferation of microorganism.

Hygiene plan
The sanitisation procedures including the sanitising agents should be described in an individual hygiene plan (Fig. 7).

Hygienic design
The ISO 22716 requires the principle: »Equipment should be suitable for the intended purpose and capable of being cleaned and, if necessary, sanitised and maintained«. ISO/TR 24475 states: »If there are ridges or unreachable corners, there is a risk of contamination of the previous manufacturing run mixing with the current batch«. Hygienic design principles ensure that the machines can be cleaned quickly and safely. The following standards help to specify the demands:

- ISO 14159; Safety of machinery - Hygiene requirements for the design of machinery (16).
- DIN EN 1672-2; Food processing machinery - Basic concepts - Part 2: Hygiene requirements (17).

Fig. 8 shows an example from ISO 14159 about the design of tanks or container.

Availability of relevant documents (ISO 22716)
An essential demand of GMP is the documentation. Relevant documentation should be available at each stage of manufacturing operations. Manufacturing operations should be carried out according to manufacturing documentation, including detailed manufacturing operations for each stage, such as addition of raw materials, temperatures, speeds, mixing times, sampling, cleaning and sanitising of equipment, and bulk product transfer.

Before starting any manufacturing operations, it should be ensured that:

- All documentation relevant to the manufacturing operations is available
- All raw materials are available and released
- Suitable equipment is available for use, in working order, cleaned and sanitised
- Clearance of the area has been performed to avoid mixing with materials from previous operations

- Highly concentrated material is less critical
- Water-free but water soluble compounds are normally considered to be safe
- Water insoluble compounds may be accompanied by a small water phase e.g. from condensing water
- Even white oil or natural oil can be contaminated if proper hygiene is not ensured (regular draining)

As guideline ISO 29621 »Guidelines for the risk assessment and identification of microbiologically low-risk products« (14) is helpful. The rules for finished products can be also applied to raw materials. Fig. 9 shows some examples of microbiologically low-risk products from ISO 29621.

Critical raw materials
All water and water-containing raw materials may be microbi ally polluted. The risk can be assessed as follows:

The total amount of preservative
The total amount of preservative is the sum of:

- The preservative added to the water phase
- The preservative added to the oil phase
The preservative added to the finished product

The preservative added to a premix

The preservative in the raw materials

The producer should know which and how much preservative is in the raw materials. If the preservative in the raw material changes the preservation of the finished product may fail.

How to make sure the preservative is really added?

From our experience one of the main reasons of the failure of a preservative in a cosmetic product which has passed the preservative test is just to forget to add it. A manual dosing should be performed on the basis of the «four-eye principle». To guarantee this it is recommend that one person is weighing the small compounds and provide a set of these raw materials for each batch. In the production another person should control and dose them to the batch. For automatic dosing mass flow-meters are recommended. Volumetric systems are less safe and dependent on the temperature. For these at least an alarm for an empty dosage system is necessary because these systems will also measure air.

Critical process

A hot process e.g. at 80 °C will eliminate most contamination from the water and raw materials. In contrast to this a cold process cannot eliminate this risk which means that the raw material quality will be a more critical factor. Also highly viscous systems are more difficult to cope with. Often a preservative cannot be added at the end of the process which limits the possible selection of preservatives. Furthermore the material may be filled at a higher temperature which leads to an increased formation of condensing water. A preservative which provides head space protection becomes more important.

Critical downtime

Long cold unpreserved phases (>3 h) should be prevented during the production process. The staff has to be trained that even during unplanned downtime this is guaranteed. We recommend installing special quality control checks if a longer period occurs by accident. A typical mistake which leads to longer unpreserved phases is to add the water to a vessel the day before production to be quicker at the start of next day in the first batch. If the water is preserved of course this can be done, but unpreserved storage should never happen.

Critical contamination – control of bacillus spec.

Bacteria spores are difficult to kill. Temperatures above 100 °C are needed to kill them. Chemically, high amounts of formaldehyde or glutaraldehyde can kill bacterial spores as well as oxidising agents like chlorine, hydrogen peroxide or peracetic acid. Preservatives control only the vegetative form of bacillus species, but do not kill their spores. To prevent bacillus contamination in a cosmetic product they should not be present in the raw materials. Especially critical are the raw materials derived from roots, leaves, or mud. Of course any multiplication of bacillus species in pre-solutions has to be prevented. This can be managed by the addition of normal preservatives. Bacillus spores should also not be brought in during the production process. That means no soil or dust should get into the product.

Change control

Any changes in the formulation, in the raw material quality, in the production process or in the batch size have to be analysed if they might have an influence on the microbial stability of the formulation.

Supposed minor changes can have severe influence on the susceptibility to microbial growth. For example a perfume composition can be a synergist to the preservative system. One glycol will reduce the active water value more than another. An extract can contain a biocidal compound which another will not contain.

The same INCI name does not necessarily mean the same compatibility. Impurities often lead to more incompatibilities then the chemical itself. For example the change from carbomer in powder form to a liquid form has shown dramatic effects. The liquid material contained sulphite impurities from the polymerisation process, which destroyed the isothiazolinones being used for the preservation of the end product. Also sulphonates based on the production process can contain high amounts of sulphite.

Different pH values of raw materials have to be adjusted in the finished product. Otherwise the stability can be influenced or pH value can get out of activity limits of the preservative actives.

The upgrading of a formulation to a bigger batch size is not only critical for the galenic properties of emulsions. The bigger batch size leads to a longer heating period which means a good sanitation of raw material contamination but a possible destruction of biocides. The longer cooling period can lead to growing conditions for microbes before the preservative is added but also to a better dis-

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**Examples of low-risk products ISO 29621**

<table>
<thead>
<tr>
<th>Physico-chemical factor</th>
<th>Limit</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>≤3,0</td>
<td>Skin peels (glycolic acid)</td>
</tr>
<tr>
<td>pH</td>
<td>≥10,0</td>
<td>Hair relaxers</td>
</tr>
<tr>
<td>Ethanol or other alcohol</td>
<td>≥20%</td>
<td>Hair sprays, tonics, perfumes</td>
</tr>
<tr>
<td>Filling temperature</td>
<td>≥65°C</td>
<td>Lip balms, lipsticks, cream blushes</td>
</tr>
<tr>
<td>Water activity($a_w$)</td>
<td>≤0,75</td>
<td>Solvent-based products Nail enamels</td>
</tr>
<tr>
<td>Oxidizing products</td>
<td></td>
<td>Hair dyes</td>
</tr>
<tr>
<td>Aluminium chlorohydrate</td>
<td>≥25%</td>
<td>Anti-perspirants</td>
</tr>
</tbody>
</table>

**Fig. 9 Examples of low-risk products**
tribution of the preservative in the water phase caused by the longer stirring time.

Normally a microbiological challenge test is done during the development of a formulation. A re-validation should be performed with the first production batch. Each change should be secured by a new microbiological test.

Summary

According to the EU rapid alert system for dangerous consumer products (RAPEX) contamination of cosmetics such as baby shampoo, cream, make-up, toothpaste or shower gel has increased in the past few years (18).

It must be the aim of all manufacturers to ensure that their products are safe in all respects under normal and reasonably foreseeable conditions of use. Contaminating microorganisms may be harmful to the consumer and may cause spoilation of the product. It is, therefore, necessary to limit them. This can be achieved by:

- Use of microbiologically satisfactory raw materials
- Use of good plant hygiene and manufacturing practices
- Hygienic design
- Use of a validated preservative system

A microbiological quality management (MOM) is legally requested at least for the production of cosmetics, but also strongly recommended for the production of cleaning products. The ISO 22716 guidelines provide guidance regarding Good Manufacturing Practices.

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