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WHEN PRESERVATIVE FREE MATTERS®



# “PRESERVATIVE FREE” – THE SKIN MICROBIOME’S CLOSE FRIEND

In this article, Marie-Christine Klein, PhD, Head of Development & Regulatory Affairs, Andreas Bilstein, PhD, General Manager, and Julia Krüger, Head of Business Development & Sales, all at URSATEC, discuss the effects of preservatives on the skin microbiome and consider new technologies that minimise the percentage of preserving agents used in cosmetic formulations.

## THE SKIN MICROBIOME

The skin, which is the largest organ of the human body, has an enormous surface that provides a habitat for diverse micro-organisms of different domains of life: bacteria, archaea and fungi, but viruses are also present. The common theme in biology – striving for a balanced equilibrium or homeostasis – is key to health. By implication, impairments of this homeostasis result in pathologies. And what homeostasis or, more precisely, eubiosis means in the case of the skin microbiome depends on many factors and is not a one-solution-fits-all situation.

Diversity is the main characteristic of the skin microbiome. The composition of infants’ skin microbiome is defined by the delivery mode at birth. Over time, the diversity of the microbiota extends because of environmental influences. This need for resistance against environmental factors triggers an evolution of strategies for bacteria to survive.

For example, the body’s skin has different ecosystems within which the microbial composition significantly varies. There are sebaceous sites, like the forehead, behind the ear or the back, which are dominated by lipophilic *Propionibacterium* species and, in general, have low bacterial

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diversity. Moist subset areas of the human body, such as the inner elbow or the sole of the foot, host mainly *Staphylococcus* and *Corynebacterium* species. Moreover, there are dry areas of the skin, such as the forearm or various parts of the hand, which are characterised by diversity, where Actinobacteria, Proteobacteria, Firmicutes and Bacteroidetes can be found (Figure 1).<sup>1</sup> Furthermore, not only location but also age, body temperature and the immune system, as well as extrinsic factors like the climate and the use of antibiotics, determine the composition and characteristics of the microbiome and make it very individual. Astonishingly, when studying the forearms of six healthy adults, only a few well-represented genera could be found, and the main finding was a low-level interpersonal consensus.<sup>2</sup>

## THE SKIN BARRIER

The term skin barrier unites different strategies that are used by nature to protect our bodies from external influences of various origins, which is a crucial task to fulfil. An



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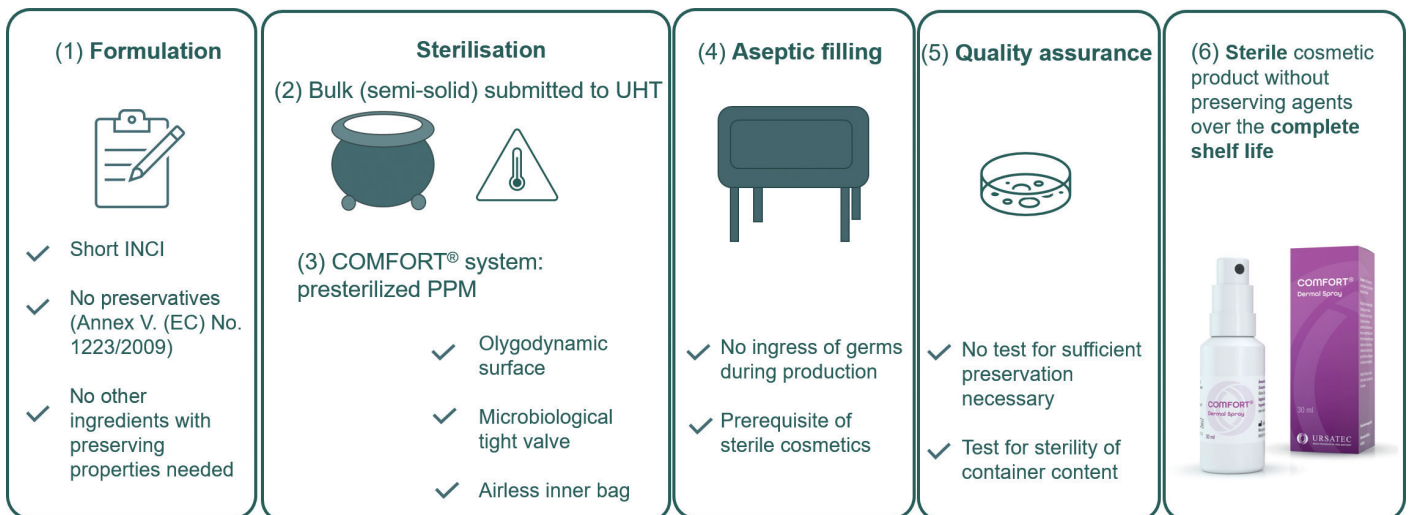


Figure 1: The process flow of creating a preservative-free cosmetic product. (1) Preservative-free formulation concepts have the advantage of short INCI lists because no preservatives have to be harmonised according to their physicochemical properties. Both the bulk product (2) and the primary packaging (3) of the product need to be presterilised. In the case of semi-solid formulations, UHT technology is a gentle mechanism for bulk sterilisation when sterile filtration is not possible. The COMFORT® system combines airless technology with bacteriostatic surfaces and is delivered sterile. (4) Filling of bulk in the primary packing occurs under sterile conditions in a controlled environment. (5) Instead of tests for preservative effectiveness, the sterility of the product is tested for release. (6) The content of the cosmetic product stays sterile for the complete shelf life.

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obvious way to separate two distinct environments is by building a wall. This wall, as the first barricade against pathogenic micro-organisms, consists of multiple fine layers of epidermal keratinocytes. These are cells that are terminally differentiated and create a nearly impenetrable protective layer. Interestingly, this physical barrier is safeguarded by skin microbiota that secrete components that stabilise the lipid structure.

This leads us to chemical components that contribute to the skin barrier. Both the epidermis built by the host and the skin microbiome release lipids and acids as protective shields against intrusion. Another good example is chemicals released – especially by bacterial inhabitants of sebaceous regions – to produce free fatty acids that are responsible for the characteristic low pH value of the skin. Fatty acids inhibit the growth of pathogenic micro-organisms and enhance skin immunity. Again, balanced homeostasis leads to selective inhibition of pathogenic *Staphylococcus aureus*, whereas commensal species of *Staphylococcus* and *Corynebacterium* keep growing under these conditions. Although there is more awareness of the gut microbiome, the skin microbiome also stimulates immune responses to protect against cutaneous and systemic infections, and this adds another layer of complexity to the skin barrier function. And, last but not least, the skin microbiome itself can also defend against pathogens, for example, by disrupting their communication system or inhibiting their growth in a biofilm manner, as in the case of *Staphylococcus aureus* that is tackled by *Staphylococcus epidermidis*.<sup>3</sup> This competitive relationship between the skin microbiome and pathogenic micro-organisms is important for maintaining homeostasis.

## PATHOLOGIES ASSOCIATED WITH THE SKIN BARRIER

A well-balanced and functioning skin barrier is key to a healthier life. Therefore, perturbations in the skin barrier are associated with several pathologies. An example of a connection between pathology and an unbalanced skin microbiome is acne. In acne patients, the loss of diversity of different *Cutibacterium acnes* phylotypes is associated with the pathogenesis of the disease. Strains that trigger the innate immune system and skin inflammation are over-represented in those kinds of patients.<sup>3</sup>

Moreover, a well-researched disease in the context of microbiome dysbiosis is atopic dermatitis (AD). Between 1% and 10% of adults suffer from AD, and 15%–20% of children have a widespread chronic multifactorial inflammatory skin pathogenesis characterised by dysfunction of the skin barrier. AD lesions display an increased abundance of *Staphylococcus aureus* next to a generally decreased microbiological diversity.

The extent of *Staphylococcus aureus* and its secreted chemicals can disrupt the tightly balanced homeostasis so that the pathogen can reach deeper layers of the *stratum corneum* and interfere with the host’s immune system, which contributes to the pathogenic phenotype.<sup>3</sup> In fact, AD patients display an almost two-fold increase in skin absorption of different chemicals, including irritants and contact allergens.<sup>4</sup> Among these, contact allergens, preservatives beneath fragrances, emulsifiers, vehicle components and sunscreen agents contribute to contact hypersensitivity. About 6% of Europeans display hypersensitivity to preservatives, which is significant, given the fact that many personal care products contain preservatives and their widespread use.<sup>4</sup>

## PRESERVATIVES AND THEIR INFLUENCE ON THE SKIN MICROBIOME

Preservatives are being used to protect the cosmetic preparation against microbiological contamination throughout the shelf life of a cosmetic product. Contamination can originate from air germs during bulk production and filling of the product, and/or after the cosmetic is opened and the contents are exposed to air or come into contact with skin.

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As long as the formulation has nutritive properties, which holds true for most cosmetic formulations with water activity, the microorganisms benefit from the nutritive properties and start growing and metabolising. This culminates in the cosmetic product losing its claimed properties and causing health-threatening consequences to the product user.

Therefore, the need for microbiological-safe cosmetic products is the highest priority, which stimulated the career of preserving agents a long time ago. As already discussed, the drawback to using preservatives and preserving agents is the high potential for contact hypersensitivity. In this context, preservatives range second (58%) after fragrances for contents with allergic potential throughout the main cosmetic categories.<sup>5</sup> There is also a negative correlation between preservatives and commensal species of the skin microbiome, such as *S. epidermidis*, whose numbers are reduced following the usage of preservatives, such as phenoxyethanol, parabens and methylisothiazolinone.<sup>6,7</sup> This negative impact on the skin microbiome is exacerbated by the fact that, even after regular showering, personal care and hygiene products have been demonstrated to stay on the skin for weeks after their first use, which has an enormous impact on the bacterial ecosystem of the user.<sup>8</sup>

Taken together, the skin microbiome and its balance between opportunistic and commensal species are endangered by the use of preservatives, which should add a layer of consciousness for the cosmetic user and fuel the development of alternative solutions in the cosmetic industry.

## DISPENSER TECHNOLOGY

The development of airless dispensers was the first step in the right direction to realise new and innovative product concepts, minimising the percentage of preserving agents used in cosmetic formulations. We need to understand that all ingredients that inhibit the growth of germs are preserving agents and not only those that use this function primarily. Pentylene glycol, several types of alcohol

“Both a microbiologically tight closing valve and the bacteriostatic effect of the surfaces used in the nozzle guarantee perfectly protected contents.”

or even magnolia extract, for example, can be used in cosmetic products in Europe for preserving the formulation without the need to declare them accordingly (EC Regulation 1223/2009, Annex V). If those kinds of formulations are then filled in innovative airless packaging solutions, the consumer would understand the claim “preservative free” as being true, which is not the case, unfortunately. With most of the currently used packaging solutions and respective manufacturing processes, a claim of “100% free from preservatives” cannot be achieved.

New technologies are necessary to provide a true alternative for preserving ingredients in cosmetics. The combination of high-end technologies in dosage systems, such as the COMFORT® system, and innovative manufacturing conditions, such as the “ultra high temperature” (UHT) process, will become the gold standard for “real” preservative-free products in the cosmetic industry.

The COMFORT® system is an airless dosage system for dispensing very sensitive liquid or semi-solid formulations. It makes it possible to avoid any kind of preservatives, even after the product has been opened, as the special design of the system prevents contamination. Both a microbiologically tight closing valve and the bacteriostatic effect of the surfaces used in the nozzle guarantee perfectly protected contents. A microbiologically tight valve is technically very complex regarding the minimum permissible manufacturing tolerances of the individual components and, physically, requires a high opening pressure because the smoother the valve for the product outlet, the easier it is for germs to overcome the valve and enter the bottle.

The bacteriostatic effect is achieved by a silver-based additive. This prevents biofilm formation on the surface. Additionally, the flexible airless inner bag, which folds when the vacuum emerges due to pressing the pump, dispenses the contents without being in contact with any oxygen. This leads to proven perfect protection of the preservative-free contents. The innovative UHT technology used during the aseptic manufacturing process rounds off modern technology to provide products that are 100% free from preservatives. UHT sterilisation is the process of heating milk or cream to temperatures exceeding 275°F (135°C) for one or two seconds, then packaging it in a hermetically sealed container.

Eliminating dispensable ingredients like preservatives and, at the same time, guaranteeing safety against microbial contamination has a winning effect on the skin microbiome. Impairments in terms of species diversity, which directly correlate with the skin barrier, can be avoided. The same is true for a substantial proportion of substances prone to contact hypersensitivity. The term “less is more” could not be more applicable to this topic.

## ABOUT THE COMPANY

URSATEC was founded in 1993 to accomplish one mission: the establishment of preservative-free applications based on its proprietary packaging systems in different application areas, primarily nasal, dermal, buccal and otological fields. Having sold almost two billion units within the last 30 years, URSATEC systems are widely established. URSATEC is consistently expanding its business and

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offers a full development service, dosage systems, primary packaging materials, filling services for OTC and Rx applications to the healthcare industry, and also stands for sophisticated cosmetic products and food supplements that completely lack preserving ingredients.

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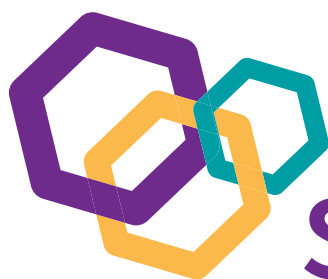
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## ABOUT THE AUTHORS

**Marie-Christine Klein**, PhD, is a biochemist by training and joined URSATEC in 2019. She is head of the development team, which is focusing on innovative developments in combination with URSATEC application technology, for example, in preservative-free cosmetics.

**Andreas Bilstein**, PhD, has been the Managing Director of URSATEC since August 2020. He is a biologist with more than 15 years of experience in developing preservative-free products for various applications.

**Julia Krüger**, a biotechnologist, combines her scientific background with excellent skills in B2B and B2C marketing and sales. She joined the OTC healthcare industry in 2005 and gave direction to the development and sales of substance-based medical devices and cosmetic portfolios. Ms Krüger has been part of URSATEC since December 2020, and is head of the business development and sales department.



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