

PHMB

Third party submission of information on potential candidates for substitution

NON-CONFIDENTIAL

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INTRODUCTION

Sauflon Pharmaceuticals Ltd is a global manufacturer of contact lenses and contact lens care solutions, with products sold in over fifty countries.

Sauflon have manufactured contact lens care solutions for thirty years and the majority of these solution formulations utilise PHMB as either disinfecting agent or preservative. Sauflon's competitors in the contact lens care solution market also use PHMB in their solution formulations. Contact Lens care solutions are regulated as medical devices in Europe and many other countries globally. In a few countries these products are regulated as pharmaceuticals.

Sauflon have significant experience in the disinfection and preservative efficacy, clinical safety and chemical stability of contact lens care formulations containing PHMB. .

PHMB is used in lens care solutions at levels of around 1-2 ppm which is sufficient to kill a broad range of microorganisms *in situ* in the contact lens case, but is still well below the sensitisation level for human cells ¹. Indeed, the biocompatibility index of PHMB is reported as being above a value of 1, therefore indicating it is an effective antimicrobial with relatively low cytotoxicity when compared to other antimicrobial agents ².

1. ALTERNATIVE IDENTITY AND PROPERTIES

There are a very limited number of commonly used alternative chemistries available.. The available chemistries are summarized below:

CHEMISTRY	PROPERTIES
HYDROGEN PEROXIDE	Broad spectrum activity Hard water tolerant Can be corrosive to soft metals aluminum, copper, brass, zinc, mild & galvanized steel High concentration has pungent odour, may cause chemical burns and can be explosive Limited storage stability & diluted solutions unstable Temperature sensitive No wetting properties Biocidal properties limited to acid - neutral pH-range Activity can be reduced by organic matter For eyecare applications, requires neutralisation prior to inserting lens in the eye. For this reason products which use Hydrogen Peroxide as the main disinfecting agent are less "user friendly" and less convenient to use.
QUATS	Broad spectrum activity, however efficacy varies across the available compounds. Poorer efficacy against moulds and yeasts. Combines biocidal activity with detergency / surface activity Not compatible with anionic surfactants Strong foaming

Each chemistry has a unique blend of properties which together with its activity spectrum makes it suited to certain applications but not to cover all user/patient or market requirements in the eye care, medical device or pharmaceutical industry.

PHMB has a number of strengths which are not found in the available alternatives and thus has a place in medical device and eye care applications and it cannot be easily replaced by other chemistries.

Reducing the already limited choice of chemistries may make it very difficult for manufacturers in the eye care and medical devices field to select a suitable chemistry for their application and places increased resistance development pressure on the remaining chemistries. Additionally there would be a negative impact on product choice and availability for the end user – the contact lens wearer

2. TECHNICAL FEASIBILITY

Commonly sought after properties for disinfectants in the medical device industry are:

<u>Microbiological</u>	<u>Chemical</u>
Broad-Spectrum Activity	Safe to Transport
Fast Acting	Long Shelf Life: Improper or prolonged storage of disinfectants may lead to growth of bacteria in them
Not Readily Neutralized in Organic or Inorganic Matter	Safe & Easy to Store: Improper storage of disinfectants may lead to explosions or fires
Resistance development unlikely	Non-Corrosive & Material Compatible: Using the wrong type or level of disinfectant may cause corrosion or other damage

PHMB has various attributes which makes it a key ingredient in the formulation of disinfecting solutions for medical device and pharmaceutical applications. The physical performance attributes of PHMB (not leaving streak marks on surfaces, ease of water rinsing from surfaces, it's low corrosiveness to construction materials, it's low-foaming activity) and the ability of PHMB to maintain effectiveness in use applications (effectiveness over a wide pH range, tolerance to organic load, relatively low toxicity) means PHMB delivers unique performance benefits for medical device and pharmaceutical applications.. Some of the key benefits are:

- Broad spectrum – bactericidal, fungicidal, amoebicidal and virucidal
- No known development of resistance
- Fast speed of kill
- Tolerant of organic matter
- Stable and effective over wide pH range
- No taste or smell
- Non-staining
- Non tainting to food
- Low corrosivity
- Low cytotoxicity

PHMB is one of the most effective biocides in use and has been proven over time in contact lens care solutions (more than 30 years safe history of use) to provide critical protection against key ocular pathogens such as *Pseudomonas aeruginosa*, *Staphylococcus* species, the highly resistant amoebal pathogen *Acanthamoeba* and a broad range of other bacteria, viruses, fungi and protozoa.

Other available chemistries do not offer the same blend of characteristics and therefore are not a good alternative for medical device applications.

3. HAZARDS AND RISKS OF THE ALTERNATIVE(S)

Alternative chemicals either require neutralisation prior to patients being able to insert the contact lenses in their eyes, potentially display lower biocompatibility indexes, or conversely do not display the broad range of antimicrobial efficacy to sufficient levels to cover the range of ocular related diseases.

Therefore a continued reduction in the number of available chemistries:

- Makes it more and more difficult for formulators to create products which meet the needs of contact lens wearers.
- Reduce the differentiation of products in the marketplace
- Make it very difficult for manufacturers to select a suitable product/chemistry for their application
- Place increased resistance development pressure on the remaining chemistries
- Reduces choices for the contact lens wearer

Decisions on active substance approval must be taken in the context of the need to achieve adequate microbiological control, the arsenal of tools/chemistries available and the potential costs of failure should control mechanisms breakdown.

A full analysis of the potential risks of an increase in microbiological contamination against the potential benefits of removing a disinfectant from the market should be commissioned before any decision is taken.

4. AVAILABILITY

PHMB is a proprietary material that will be extremely difficult for us to replace. Although there may be other similar chemicals available, their suitability as direct replacements is not validated.

The Lonza material we use is specifically named on various product licences and has limited manufacturing sites.

Lack of availability of such a critical material would be a major problem for Sauflon and the eye care industry as a whole.

5. CONCLUSION ON SUITABILITY AND AVAILABILITY OF THE ALTERNATIVE

- A decision on an individual active substance should not be taken in isolation.
- The context is the overriding need to achieve adequate microbiological control, the limited arsenal of chemistries available, their properties, and the potential costs of failure should microbiological control breakdown.
- A full analysis of the potential risks of an increase in microbiological contamination against the potential benefits of removing one more chemical from the market should be commissioned by the ECHA before any decision is taken.
- PHMB has a number of unique performance attributes which are not found in the available alternatives and thus cannot be readily substituted.
- PHMB has a proven track record of providing protection in the eye care, medical device and clinical environments.

6. OTHER COMMENTS

In summary PHMB has an outstanding safe history of use in the contact lens care industry and has been chosen by many companies as their disinfecting agent/preservative of choice when formulating contact lens care products.

REFERENCES

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