9 October 2017
EMA/CHMP/733748/2015
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on the draft 'Questions and answers on sodium laurilsulfate' (EMA/CHMP/606830/2014)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	PAINT-Consult
2	Reckitt Benckiser Healthcare (UK) Limited
3	AESGP
4	Medicines Evaluation Board in the Netherlands
5	EFPIA
6	SciencePharma

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	The excipients labelling statement must be clear, precise, and brief and without difficult terms in order to achieve the highest benefit for patients. We at PAINT-Consult are a provider of readability tests of package leaflets and a researcher of this important patient information, with several published studies involving more than 10000 participants. See http://www.paint-consult.com/en/publikationen/publikationen/. The suggestions provided in "2. Specific comments on text" consider the findings of our extensive practical knowledge with package leaflets.	Noted.
2	It is proposed that information is to be added to the Package Leaflet. Will a proposal also be considered for the Summary of Product Characteristics?	SmPC information should be consistent in both the package leaflet and the SmPC, no matters whether it is specifies in the Q&A or not, but the SmPC is a matter for the SmPC guideline and is out of scope of this guideline.
3	Whilst a recommended threshold for sodium laurilsulfate (SLS) in topical products is difficult to establish, given the range of confounding factors, we feel that a 0% threshold is inappropriate and unnecessary. Low levels of SLS can be added to raw materials as process aid. As it is not stated as a general exclusion in the excipient guideline, the 0% threshold would require Marketing Authorisation Holders to establish from their raw material suppliers whether SLS was present as an additive. Given that trace amounts of SLS are unlikely to result in skin irritation, even in the presence of other known irritants, it may be better in the long-term to establish a non-zero threshold.	An excipient is an inert ingredient deliberately used to either aid the manufacture or stability of the dosage form or to use its properties to enhance the functioning of the dosage form in vivo. Trace amounts carried over from starting materials is not the subject of this exercise and is covered by other regulations.

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3	The proposed text for the package leaflet should not be added retrospectively on labels of topical products where it has been demonstrated through post-marketing safety data that the incidence levels of SLS associated adverse events is low.	As there is a tremendous under-reporting rate for adverse drug reactions by healthcare professionals, patients and marketing authorisation holders alike, one cannot say that existing products containing SLS are not able to cause ADRs. Therefore, the labelling must apply to (existing) authorised products and new applications going forwards.
4	The MEB highly supports the revision of the Excipients guideline and the immediate provision of information through question and answer documents. The MEB is of the opinion that the SmPC should include a warning as well. Any information considered relevant for health care professionals should be included in the SmPC, and hence reference to the SmPC should be included in the Q&A document. The MEB proposes the following warning for the SmPC: 'Sodium laurilsulfate may cause local skin irritation with redness and symptoms such as burning, stinging and itching.'	See above.
5	EFPIA welcomes the opportunity to comment on this draft questions and answers on sodium laurilsulfate in the context of the revision of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use'. We concur with the suggestion at line 65 that the skin irritancy associated with sodium laurilsulfate (SLS) is likely to be due to its surfactant properties. This is a common effect associated with sodium soaps. It is mild, reversible, and well understood after centuries of use in the domestic setting. The Registry of Toxic Effects of Chemical Substances (RTECS) lists 30 eye and skin irritation studies conducted with SLS in a variety of mammalian species including human. Mild skin irritation is the predominant finding. The	The cosmetics industry uses SLS as a positive control but there is no fixed concentration at which this is used. Academic literature reports that concentrations as low as 0.25% have been used and have resulted in skin damage. Other publications report even lower concentrations can cause biochemical changes in skin, thus the threshold of 0% is still supported. As regards the 'one widely marketed topical cream product', please see comment above. Confusion and confounding is due to many issues and given the lack of studies, the precautionary principle applies of using the 0% threshold.

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	European Chemicals Agency (ECHA) database of registered substances lists one key and 10 supporting studies. Again, mild irritation is the predominant finding. The conclusion of sensitising studies is that SLS is not a sensitiser. However, we would like to express our concerns with the proposed guidance. First, we concur with the point at line 89 that a threshold for irritant effects is difficult to determine. However, it should be noted that all the studies reported on the ECHA website relate to concentrations of 1% up to 100% SLS in the test formulation, the majority of studies being at 20% or greater. Empirical experience of the behaviour of soaps indicates that irritancy effects must be thresholded, and the fact that the cosmetics industry uses SLS as a positive control is not, in itself, sufficient rationale to conclude that a zero threshold is appropriate. The only evidence cited, at line 71, concerns products with SLS at 0.9%. By way of example, for one widely marketed topical cream product, containing SLS at 0.25% w/w, the MAH has examined the pharmacovigilance data set for the product, which has been authorised for several decades, and finds no evidence of reports of an irritant effect above the expected background level. Labelling this product with a new warning is not warranted as a result of a comprehensive examination of directly relevant human pharmacovigilance data specific to this product, and would introduce significantly confusing issues for the patient and prescriber given that the indications for this product manifest with itching, irritation and sensitivity. Overall, whilst a recommended threshold for SLS in topical products is difficult to establish, given the range of confounding factors, we feel that a 0% threshold is inappropriate and unnecessary. Low	Patients with skin disorders such as eczema are advised to try a range of medicated creams and emollients by healthcare professionals and thus the provision of the information proposed can enable patients to manage their condition better whilst providing much needed data at which threshold point skin irritation can be induced.

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	levels of SLS can be added to raw materials as process aid. As it's not stated as a general exclusion in the excipient guideline, the 0% threshold would require MA Holders to establish from their raw material suppliers whether SLS was present as an additive. Given that trace amounts of SLS are unlikely to result in skin irritation, even in the presence of other known irritants, it may be better in the long-term to establish a non-zero threshold. Second, the guidance appears significantly precautionary in its approach. As line 68 makes clear, the association of SLS with irritancy in formulated medicinal products is not well understood. We feel a precautionary approach is warranted where the effects are severe, or non-reversible, or difficult to control using standard techniques. None of those criteria apply here, and an evidence based approach would be more appropriate, since precautionary labelling inevitably carries a cost of reducing patient access to potentially very beneficial products which may have decades of use supporting an acceptable risk benefit profile. Given that the hazard, if there is one associated with formulated medicinal products, is mild, reversible, and easily managed using conventional approaches, the applicant urges that more consideration be given to the implications of labelling change, before elaborating an evidence- based guidance. We believe that this is strongly preferable to elaborating guidance now which relies on a precautionary approach justified by several speculative elements including read across from a different sector using SLS for different purposes and at different concentrations.	
5	We advocate that the proposed text for the package leaflet should not be added retrospectively on labels of topical products where it has been demonstrated through post-marketing safety data that the	See comment above.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	incidence levels of SLS associated adverse events is low.	
5	The current Questions and Answers document provides standard text for inclusion the package leaflet; we propose that corresponding standard text for inclusion in the prescriber information (SmPC), also be provided.	See comment above.
6	Although sodium laurilsulfate (SLS) is commonly used as a synonym for sodium dodecyl sulfate (SDS) it must be noted that it is not exactly the same substance. SDS is a pure compound of specific molecular structure and formula. SDS is key, but not the sole, ingredient of SLS. On the contrary E487 is indeed a synonym of SLS. According to some scientific findings, skin irritation effect is related to C12 carbon chain present only in SDS, thus extension of skin adverse effects to SLS or E487 is not fully justified. Furthermore it is not clear weather proposal for new information in the package leaflet corresponds only to SLS and E487 or to SDS as well. In conclusion, it is proposed to change the nomenclature used in the proposal for new information in the package leaflet and use the name sodium dodecyl sulfate instead of sodium laurilsulfate. Literature: Kligman AM, Wooding WM. A method for the measurement and evaluation of irritants on human skin. J Invest Dermatol 1967; 49:78–94 Stillman MA, Maibach HI, Shalita AR. Relative irritancy of free fatty acids of different chain length. Contact Dermatitis 1975; 1:65–69 Wilhelm KP, Cua AB, Wolf HH, Maibach HI. Surfactantinduced stratum corneum hydration in vivo: prediction of the irritation potential of anionic surfactants. J Invest Dermatol 1993; 101:310–	As SDS is the predominate component of SLS/E487 and SLS is commonly used name, it is proposed to use the INN of sodium laurilsulfate. SDS is not commonly used name in pharmaceutical preparations and is more reserved in biochemical studies e.g. in polyacrylamide gel electrophoresis. The Ph Eur states that sodium lauryl sulfate should contain not less than 85% of sodium alkyl sulfates calculated as the C_{12} chain.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	315	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 91-92	3	**Comments:** "...It is, therefore, proposed to have a threshold of 0% for SLS in topical medicinal products for all age groups..." A 0% threshold would be burdensome in practice. It would necessitate drug product manufacturers and, more significantly, excipient suppliers to confirm whether or not SLS was present as an additive in their product. The removal of SLS may cause difficulties in the manufacture of raw materials and or finished product. The labelling requirement should only apply if SLS has been intentionally added as a component of the formulation for new products without established safety profile.	Not accepted. An excipient is an inert ingredient deliberately used to either aid the manufacture or stability of the dosage form or to use its properties to enhance the functioning of the dosage form *in vivo*. Trace amounts carried over from starting materials is not the subject of this exercise and is covered by other regulations.
Line 91-92	5	**Comments:** "...It is, therefore, proposed to have a threshold of 0% for SLS in topical medicinal products for all age groups..." As discussed under the general comments, a 0% threshold may be inappropriate and would be burdensome in practice. It would necessitate drug product manufacturers and, more significantly, excipient suppliers to confirm whether or not SLS was present as an additive in their product. The removal of SLS may cause difficulties in the manufacture of raw materials and or finished product. **Proposed change:** We propose a reassessment and amendment of the 0%	Not accepted. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		threshold proposed.	
93 column "Name"	1	**Comments:** Please also include the other common name of "sodium dodecyl sulfate", as many people are only familiar with this name for the substance as opposed to "Sodium laurilsulfate or E487". **Proposed change:** Sodium laurilsulfate or sodium dodecyl sulfate or E487	Not accepted. SDS is not the excipient term but is used in the R&D / laboratory when it is used as a reagent. Additionally, SDS is not as pure compared to SLS which must meet Ph. Eur. Requirements.
93 column "Informati on of the package leaflet"	1	**Comments:** The sentence "This product contains sodium laurilsulfate x% w/w." contained in the proposal dated 23 July 2015, must be deleted. It is a repetition of the QRD template heading "X contains sodium laurilsulfate". Furthermore, the abbreviation "w/w" is unfamiliar for most people and difficult terms must be avoided according to the readability guideline. Last but not least, what is most important is the information that this excipient is contained; therefore, information relating to the concentration "x% w/w" is unnecessary and not helpful for patients, particularly as lines 84 ff. state: "Skin sensitivity to SLS varies according to the concentration of SLS, contact time, patient population and experimental approaches... Recommending a threshold for SLS in topical products is difficult to establish... It is, therefore, proposed to have a threshold of	Partly accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		0% for SLS in topical medicinal products for all age groups." The examples of skin reactions provided in the text bracket "(such as stinging or burning sensation)" should be deleted as - according to lines 72 and 73 - many further symptoms, such as itching or redness, may occur. In addition, it is impossible and unnecessary to provide all possible symptoms. Research experience with package leaflets informs us that mentioning "local skin reactions" is absolutely sufficient. Examples are not required as patients have an idea of what constitutes local skin reactions. The beginning of the last sentence should be shortened, with a stronger connection to the preceding sentence as suggested below. **Proposed change:** Sodium laurilsulfate may cause local skin reactions**,** ~~(such as stinging or burning sensation)~~ in particular if you have sensitive skin. **This** ~~M~~**m**ay increase ~~local reactions caused by~~**if** other medicines ~~when~~ **are** applied to the skin in the same area.	
93	2	**Comments:** The proposed wording is lengthy and may be difficult to implement on package leaflets with limited space. In the interest of brevity it is proposed that the following changes are made, which does not impair intent, readability or comprehension. The rearrangement of text also clarifies that patients with sensitive skin may also be at increased	Partly accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		risk of potentiation of skin irritation caused by concomitant application with other medicines. **Proposed change:** ~~This product c~~**C**ontains sodium laurilsulfate x% w/w. ~~Sodium laurilsulfate m~~**M**ay cause local skin reactions (such as stinging or burning sensation) **or increase reactions caused by other medicines when applied in the same area,** ~~in~~ particular**ly** if you have sensitive skin. ~~May increase local reactions caused by other medicines when applied to the skin in the same area.~~ Clean version: Contains sodium laurilsulfate x% w/w. May cause local skin reactions (such as stinging or burning sensation) or increase reactions caused by other medicines when applied in the same area, particularly if you have sensitive skin.	
Line 93 column "Informati on of the package leaflet"	3	**Comments:** "...This product contains sodium laurilsulfate x% w/w..." Change the above statement to the one proposed below, thus focussing on formulation quantity rather than any potential trace additive **Proposed change:** This product**'s formulation** contains sodium laurilsulfate x% w/w."	Not accepted.
93	4	**Comments:** Since the threshold for a warning regarding SLS in the	Not accepted. Stakeholder has misunderstood what is meant by the 0%

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		package leaflet is zero, the amount of SLS in the product is not relevant for the user. The sentence "This product contains sodium laurilsulfate x% w/w." could lead to confusion and should be removed from the warning.	threshold.
93 column "Information of the package leaflet"	5	**Comments:** Information for the Package Leaflet: "This product contains sodium laurilsulfate x% w/w. Sodium laurilsulfate may cause local skin reactions (such as stinging or burning sensation) in particular if you have sensitive skin." Revised wording is proposed for improved readability and comprehension. For example, to explain that sodium laurilsulfate is soap, rather than just using the chemical name, which may mean nothing to a lay person. Also patients may not understand the term "local skin reactions". **Proposed change:** "This medicine ~~product~~ contains sodium laurilsulfate x% w/w, which is found in many household cleaning products such as soap. Sodium laurilsulfate may cause skin problems ~~local skin reactions (~~such as stinging or a burning sensation~~)~~, in particular if you have sensitive skin."	Partly accepted.
93 column	5	**Comments:** Information for the Package Leaflet:	Partly accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
"Information of the package leaflet"		"May increase local reactions caused by other medicines when applied to the skin in the same area." As the wording does not give any guidance to the patient, revised wording is proposed for improved clarity and readability, and so that the sentence is grammatically correct. **Proposed change:** "~~May increase local reactions caused by other medicines when applied to the skin in the same area.~~ If you apply this medicine to the same place as other medicines that irritate your skin, it might irritate your skin even more."	