by David C. Steinberg

European Union and US OTC Drug Updates

The European Union (EU) issued the latest Adaptations to Technical Progress (ATP) on April 17, 2007. This ATP prohibited several ingredients and severely restricted an important preservative. The Scientific Committee on Consumer Products (SCCP) also issued many new opinions on butoxyethanol and other ingredients, in addition to requesting data for the use of verbena as a fragrance component in cosmetics.

Latest ATP Decisions

The ATPs most recently issued will have significant effects on cosmetic formulations. This ATP prohibits the use of sodium iodate as a preservative and Orange 10/Orange 11 (CI 45425) as a color. These ingredients are of little interest since no formulations in the United States use them. The major change of this ATP is the new restrictions on iodopropynyl butylcarbamate (IPBC).

Previously IPBC was allowed at 0.05% (500 ppm) with the required warning: "Contains iodine"—if used on leave-on products above 0.02% (200 ppm). The new regulations will go into effect April 19, 2009, and restrict IPBC to 0.02% (200 ppm) in rinse-off products with the required warning: "Not to be used for children under three years of age," and will restrict leave-on products to 0.01% (100 ppm) except for deodorants and antiperspirants, where it is restricted to 0.0075% (75 ppm) with the same mandated warning. Further limitations include:

1. not to be used in oral hygiene and lip care products;
2. not to be used in preparations for children under three years of age, except in bath products/shower gels and shampoos; and
3. not to be used in body lotion and body cream or products intended for application on a large part of the body.

> The ruling on IPBC is a major problem for all. IPBC was one of the most effective antifungal preservatives available for cosmetic use.

Removing the "*"

In a June 2007 column, the removal of the "*" from many preservatives was briefly addressed.[1] Preservatives were listed on Annex VI (the preservative permitted list), and many had a "*" sign to indicate that they could be used in higher amounts for nonpreservation purposes. The ATP clarified many of these ideas; however it remains controversial why a chemical was safe at a low level for preservation and safe at a higher level for any other use. It is either safe or not.

Preservatives affected by this change include: benzoic acid, propionic acid, sorbic acid, *o*-phenylphenol, parabens, formic acid, undecylenic acid and their salts; hexetidine; 2-bromo-2-nitropropane-1,3-diol; dichlorobenzyl alcohol; triclocarban; *p*-chloro-*m*-cresol; triclosan; chloroxylenol; imidazolidinyl urea; polyaminopropyl biguanide; phenoxyethanol; methenamine; climbazole; DMDM hydantoin; piroctone olamine; bromochlorophene; and chlorhexidine and hexamidine and their salts.

While the above preservatives will lose their "*", formaldehyde (and) paraformaldehyde and phenoxypropanol will still have this designation. The previous preservatives are changed in the List of Preservatives Which Cosmetic Products May Contain (**Table 1**).

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Table 1. Changes to preservatives per Annex VI

Reference	Preservative	Maximum Concentrations	Limitations
1	Benzoic acid and its sodium salt	Rinse-off products except oral care products: 2.5% as acid Oral care products: 1.7% as acid Leave-on products: 0.5% as acid	---
1a	Salts of benzoic acid other than listed as 1 and esters	0.5% as acid	---
8	Zinc pyrithione	Hair products 1.0% Other products 0.5%	Rinse-off products only No use in products for oral hygiene

Conclusions

The ATP removing the "*" from preservatives is final recognition of reality. The "*" meant that a chemical had two levels of safety depending on its function, and by removing it, the EU is stating that it is either safe or not. The chemical could have a variety of functions, including being a preservative, a solvent or a moisturizer. These functions are determined by the user and not inherent in the chemical itself.

The loss of sodium iodate and Oranges 10 and 11 (CI 45425) will have little effect since they generally are not used. Perhaps the EU should list these as "not supported" rather than as prohibited or banned. By stating they are prohibited or banned, the implication is that there were safety problems as opposed to a lack of industry use and concurrent unwillingness to pay for more testing of the chemicals. The nongovernmental organizations (NGOs) claim that the EU is ahead of the curve in "banning" unsafe ingredients, when it could be that these chemicals are simply not supported, which is not to say they are unsafe.

> Either a chemical is safe at some level or it is not.

Finally, the ruling on IPBC is a major problem for all. IPBC was one of the most effective antifungal preservatives available for cosmetic use. Typical use levels are 150–175 ppm—equivalent to its solubility in water. With the restriction to 100 ppm and the ban on its use in most emulsions, formulators have lost the chance for a global formulation. This comes shortly after Japan approved IPBC for all uses up to 200 ppm, except in products that come into contact with the mucous membrane. Since IPBC was generally formulated as a "preservative cocktail," removing its use will mean total reformulation. Was this decision made because one or two EU countries were concerned about possible exposure to iodine?

If the industry turns its back on antifungal agents, such as IPBC and parabens, and ignores the science that shows they are safe, then this author sees the only other alternative as growing mold in products.

SCCP Opinions

The SCCP has continued to issue more of its opinions on the safety of hair dye components and other ingredients (see **Table 2**), as well as opinions on a UV filter, a preservative, a solvent and a fragrance ingredient.

Table 2. SCCP opinions on hair dye components and other ingredients

Chemical	Colipa No.	Maximum Amount	Conclusion	Use in United States
1,5-Naphthalenediol	A18	1.00%	Insufficient data	30
2,7-Naphthalenediol	A19	1.00%	Insufficient data	0
3-Amino-2,4-dichlorophenol HCl	A43	1.50%	Does not pose a risk	0
4-Nitro-o-phenylenediamine	B24	0.50%	Does not pose a risk	24
4-Amino-3-nitrophenol	B51	3.00%	Insufficient data	21
N-Phenyl-P-phenylenediamine	A9	0.20%	Insufficient data	14
M-Aminophenol	A15	1.20%	Does not pose a risk	1,062
Phenyl methyl pyrazolone	A39	0.25%	Does not pose a risk	351
2,6-Dihydroxy-3,4-dimethylpyridine	A99	1.00%	Does not pose a risk	0
Hydroxypropyl bis (n-hydroxyethyl-p-phenylenediamine) HCL	A121	1.50%	Not safe	0
HC Blue No. 2	B37	2.80%	Does not pose a risk	138
3-Nitro-p-hydroethylaminophenol	B54	3.00%	Does not pose a risk	29

Butoxyethanol was found to pose no risk up to 4% in oxidative hair dyes and up to 2% in nonoxidative hair dyes. Homosalate posed no risk as a UV filter up to 10%; however, spray applications were not considered. This UV filter is allowed up to 15% by the US Food and Drug Administration (FDA).

Alkyl (C16, C18, C22) trimethylammonium chloride for uses other than as a preservative was determined to pose no risk in rinse-off products at these levels: sum total of cetrimonium and steartrimonium chloride (C16, 18) up to 0.5%; and the sum total of behentrimonium, cetrimonium and/or steartrimonium chloride (C16, 18, 22) up to 3.0%. Finally, insufficient data was available on the use of verbena in fragrances for cosmetics.

Request for Opinions

The SCCP has been asked by the European Union for its opinion on the following ingredients:

- *Indigofera tinctoria* up to 25% for hair dyes
- Acid Violet 43 up to 0.5% for hair dyes
- Basic Red 76 up to 2.0% for hair dyes
- Basic Orange 69 up to 2.0% for hair dyes
- 1,2,4-trihydroxybenzene up to 3% for hair dyes
- Acid Red 52 up to 1.5% for hair dyes
- 2-Chloro-*p*-phenylenediamine up to 4.6% for hair dyes
- 2,4-Diaminophenoxyethanol dihydrochloride and sulfate up to 2% for hair dyes
- 2,6-Diaminopyrdine up to 0.15% for hair dyes
- Oakmoss/Treemoss up to 0.1% for fragrances
- Phytonadione (Vitamin K1) in all cosmetics

Conclusions

This author believes that continuous reviews on hair dye ingredients and other ingredients seem to serve no purpose. This is because the idea that cosmetic companies cannot use certain ingredients or could be restricted in their use of ingredients by regulation directly opposes being self-regulated, as an industry. Cosmetics are required to be safe, period. If they are not safe, the product must be reformulated to be safe. The idea of all this control seems to waste time. The EU Cosmetic Directive essentially is saying that it believes in self-regulation but that it really does not trust the cosmetic manufacturer. It is odder still that the EU requires a safety assessment by a qualified safety assessor for each cosmetic put on the market; with such a stringent requirement in place, there should be no need for the SCCP to spend time reviewing these ingredients. Perhaps this process simply placates the NGOs.

United States

Two recent changes have been made to over-the-counter (OTC) drug rules in the United States. The first has to do with all OTC labeling and reporting, and the second deals with convenience-sized packaging.

On Dec. 6, 2006, the US Congress passed a law called the *Dietary Supplement & Nonprescription Drug Consumer Protection Act* (S 3546). This law will take effect in December 2007. Within 270 days of the passage of this bill, however, the FDA must issue a guidance report explaining the data that should be included in a serious adverse event report. A *serious adverse event* is defined as resulting in death, a life-threatening experience, in-patient hospitalization, disability or incapacity, or birth defects. The report must also take into account situations in which medical or surgical intervention is required.

The law itself requires the company that puts the product on the market that caused the serious adverse event to notify the FDA within 15 business days of the event associated with the product. The report must include a copy of the product label. Of course, a clause was built into the bill stating that submission of this report in compliance with the law is not an admission that the drug or supplement caused or contributed to the adverse event.

The law requires the use of forms[a] for all nonprescription drugs and OTC drugs approved via a new drug application (NDA). The FDA is planning to develop separate forms for supplements and monographed OTC drugs. They have 270 days from the passage of the bill.

> The EU already requires a safety assessment ... and with such a requirement, there should be no need for an SCCP review.

The most important part of the law is that one year from the date of enactment, all OTC drugs and supplements must include a domestic address and/or contact phone number on their labels for a consumer to report an injury to or they will be deemed "misbranded." For domestic companies, this imposes a major difficulty; for foreign marketers, this represents another obstacle to conducting business in the United States. The injury phone lines should be manned 24/7 by a person who is well-trained on how to deal with serious injuries. Most companies require you to push numerous commands before you can reach a live person, which will certainly not be allowed by the FDA, as they will most likely require a live English speaker to answer the calls. Furthermore, all records must be kept for six years and be made available to the FDA upon request.

[a] *A Medwatch form (Form FDA 3500A) is a document of the FDA.*

The second ruling on OTC drugs was a newly proposed rule[2] for the exemption of convenience-sized drugs from a full *Drug Facts* label requirement. The FDA proposed that these products should have a newly modified format that will fit the smaller package size. This proposal limits convenience-sized packages to one or two doses. The personal care industry wanted relief for packages that contain less than two ounces, but the FDA felt that convenience-sizes packages were purchased and used immediately, usually outside of the user's place of residence in an airport or hotel. Warnings, directions, etc. are critical on any drug label and should be included on all personal care products regardless of size.

Continuous reviews on hair dye ingredients and other ingredients seem to serve no purpose.

Discussion

In both of the US proposals, the US Congress and the FDA continue to ignore any difference between OTC drugs for ingestion and treatment of chronic conditions and cosmetic-like drugs without dose restrictions.

The small package exemption for drugs sold for immediate use and with the restriction of one or two doses makes sense. Although the industry wanted relief for all OTC drugs of two ounces or less, most of these would not be of sufficient size to give a needed dose. Travel size cosmetic drugs are common, and the manufacturers have adjusted their Drug Facts labeling to accommodate these small sizes. The real impact of the small package exemption will be on samples such as a free packet of sunscreen that has a major use as a moisturizer. The amount is enough to allow consumers to try the product to see if they like it but not enough to give the labeled SPF. A possible solution would be to have the US Congress amend the Food Drug and Cosmetic Act, and move these sample-sized products without dose restrictions into the cosmetic category and away from drug regulations. This suggestion incites fear in some who do not believe that Congress does anything that simplifies the lives of personal care manufacturers.

If a poll was taken of the US Congress, most members would say that lip balms, skin protectants, antiperspirants, sunscreens and antidandruff shampoos were cosmetics. Although most of the world considers and regulates these products as cosmetics, the United States considers them and regulates them as drugs. The problem is that the United States has not updated the 1938 Food, Drug and Cosmetic Act, which required these products to be labeled with adequate directions for safe use.

The ruling that companies have to report adverse effects is really a nuisance for cosmetic drugs. It requires an address or phone number that likely will never be used since the number of serious adverse effects reported from sunscreens, dandruff shampoos, lip balms, etc. is low. This is a move by the US Congress to correct a problem with dietary supplements and ingested drugs, but in doing so, they are creating a problem for the personal care industry.

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Reference

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