SUNSCREEN PRODUCTS - DRUG OR COSMETICS? A COMPARISON OF THE LEGAL REQUIREMENTS FOR SUNSCREEN PRODUCTS IN EUROPE, AUSTRALIA AND UNITED STATES

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Mein Dank gilt meinem Mann Peter

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List of Abbreviations

AAN	Australian Approved Name
ACCC	Australian Competition and Consumer Commission
ADME	Absorption, Distribution, Metabolism and Excretion
ANPR	Advance Notice of Proposed Rulemaking
ARTG	Australian Register of Therapeutic Goods
AICS	Australian Inventory of Chemical Substances
BCC	Basal Cell Carcinoma
CAS	Chemical Abstract Service number
CDER	Center for Drug Evaluation and Research
CIR	Cosmetic Ingredient Review
COLIPA	European Cosmetic Toiletry and Perfumery Association
CMM	Cutaneous malignant melanoma
CMR	Carcinogenic, Mutagenic or toxic for Reproduction
CPNP	Cosmetic Products Notification Portal
CTFA	Cosmetic, Toiletry and Fragrance Association
DEA	Drug Enforcement Administration
D-U-N-S®	Data Universal Numbering System
EC	European Community
ELF	Electronic Listing Facility
EPA	Environmental Protection Agency
EU	European Union
FTC	Federal Trade Commission
GMP	Good Manufacturing Practice
GRASE	Generally Recognized as Safe and Effective
HRIPT	Human Repeat Insult Patch Test
IND	Investigational New Drug
INN	Non-proprietary Name
ICATM	International Cooperation on Alternative Test Methods
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ISO	International Organisation for Standardisation procedure
JCIA	Japan Cosmetic Industry Association
MED	Minimal Erythema Dose
NDC	National Drug Code
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
OECD	Organisation for Economic Co-operation and Development

OTC	Over-The-Counter
PDP	Principal Display Panel
PLD	Private Label Distributor
PMMA	Polymethylmethacrylate
RH	Relative Humidity
SCC	Squamous Cell Carcinoma
SCCS	Scientific Committee on Consumer Safety
SPF	Sun Protecting Factor
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TGA	Therapeutic Goods Administration
TSE	Transmissible Spongiform Encephalopathy
UNII	Unique Ingredient Identifiers
USA	United States of America
UV	Ultraviolet
UVA	Ultraviolet A
UVB	Ultraviolet B
UVC	Ultraviolet C
WHO	World Health Organisation

1 INTRODUCTION

1.1 History of sunscreen products

In former times, the Egyptians used sunscreens, which were a mixture of inorganic clay and mineral powders. Especially for people with high social rank, it was important to have light skin. Ancient Greeks used a mixture of oil and sand to protect their skin from sun exposure during their training for the Olympic Games. In 1801, Johann Wilhelm Ritter detected ultraviolet rays.

Norman Paul discovered the correlation between sun exposure and the development of skin cancer already in 1918. A few years later, Karl Eilham Hausser and Wilhelm Vahle found that ultraviolet rays between 280 nm and 315 nm cause sunburn and concluded that the human skin could be protected by filtering out of those wavelengths. This influenced research concerning new organic sunscreen products with the aim to avoid the UVB effects on the human skin. Nonetheless, UVA rays were considered as harmless for a longer time. In 1936, Eugene Schueller, the founder of “L'Oréal”, invented the first sunscreen, marketing one of his first formulations as “Ambre Solair”. Two years later, Franz Greiter created the glacier crème (“Gletscher Crème”), after having been sunburnt while climbing in the Alps. This was the beginning of the sunscreen product “Piz Buin”.

In 1940, Benjamin Green developed a petroleum-based red jelly (“Red-Vet-Pet”), which was used by soldiers during World War II. He improved his formulation and so the “Coppertone suntan cream” arose in 1944. Later in 1962, Franz Greiter established the concept of sun protection factor (SPF). He created a method for measuring the effectiveness of a sunscreen product in terms of preventing sunburn.
In 1977, Isaac Willis detected that UVA exposure causes ultrastructural changes of the skin, which leads to skin ageing. This better understanding of the effects of UVA and UVB rays, as well as changing consumer behavior, led to a change in the composition of UV filters in sunscreen products. In 1980, “Coppertone” was distributed as the first UVA/UVB sunscreen product.
Subsequently, the relationship between UV light and skin ageing as well as skin cancer was investigated in more detail; for instance, through the development of a photoageing concept by Albert Kligman in 1986, or the relationship between tanning and development of skin cancer reported by the WHO in 2007 [1].

1.2 UV radiation and skin cancer

1.2.1 Skin cancer types and incidence rates

Our skin is sensitive to UV radiation, which can cause skin damage and skin cancer in the long term. Uncontrolled cell division is the reason for the development of all cancers types, whereby the cell growth can be divided into benign or malignant. The characteristic feature of malignant cells is that they are able to form metastasis, while benign cells are unable to form metastasis [2].

Cutaneous malignant melanoma (CMM) and non-melanoma skin cancer (NMSC) are the most common cancer types. Non-melanoma skin cancer has two known subtypes: basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Non-melanoma skin cancer is less fatal in comparison to malignant melanoma [3].
The incidence of skin cancer is generally increasing, but fortunately mortality is stable or decreasing all over the world. Non-melanoma skin cancer has an incidence rate around 18 - 20 times higher than for malignant melanoma. [4].
In Europe, the incidence rate for melanoma is about 60.000 new cases every year, compared to around 12.500 new cases every year in Australia [5]. Melanoma rates have doubled over a twenty-year period from 1986 to 2006 [6]. Skin cancer is also the most common type of all cancers in the United States. For 2014, the number of melanoma is estimated at more than 76.000 new cases [7].

1.2.2 Risk factors of skin cancer and preventive measures

The most important risk factor of skin cancer is exposure to sunlight, although other factors can also promote its development, including sunburns, tanning, personal or family history of skin cancer, skin type, common moles or dysplastic nevus, intake of medicine (hormones, antibiotics, antidepressants) or organ transplantation (immunosuppression).
Preventive measures include avoiding sun exposure during midday (shadow, indoor), wearing of clothes, sunglasses and headgears and the proper use of sunscreen products [2].

1.3 Scope of thesis

As described in the previous chapter, sunscreen products have a protective effect against sunburn, skin ageing and skin cancer. Sunscreen products have a particular purpose for consumers, although this is evaluated differently by the authorities. In the following thesis, the different regulatory framework of sunscreen products in Europe, Australia and the United States will be discussed, including their commonalities and differences.

2 SUNSCREEN PRODUCTS - DRUG OR COSMETICS? A COMPARISON OF THE LEGAL REQUIREMENTS FOR SUNSCREEN PRODUCTS IN EUROPE, AUSTRALIA AND UNITED STATES.

2.1 Sunscreen products in Europe

In Europe sunscreen products are regulated as "cosmetic products" and they belong to the category of "sunbathing products". Sunscreen products do not fall under the scope of "medicinal products". Cosmetic products and medicinal products show a different intended purpose. The intended purpose of a sunscreen product is to protect human skin against UV exposure and the intended purpose of a medicinal product is to prevent or to treat a disease. A cosmetic product cannot be a medicinal product at the same time or vice versa. In particular, UV-filters and nanoparticles are essential ingredients for sunscreen products. Cosmetic products and medicinal products have a different definition [8], [58], [60].

Cosmetic products: "*any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition or correcting body odours*" [8].

Medicinal products: "*any substance or combination of substances presented as having properties for treating or preventing disease in human beings or any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis*" [58], [60].

The differentiation between medical product and cosmetic product is not always explicit clear. There are two main criteria that should be analyzed in order to determine, if it is a cosmetic product or a medicinal product. Is the mainly intended purpose in treating or preventing of a disease together with a pharmacological, immunological and metabolic mode of action then it indicates a medicinal product. The mainly intended purpose of a cosmetic product is to protect or to keep the body in a good condition [59]. A cosmetic products can also have a medically purpose, but the cosmetic purpose is always prevalent. Cosmetic products are allowed to use claims that are related to an illness. However, the use of misleading claims or problems with differentiation in regard to medicinal products should be avoided [67].

2.1.1 Directive 76/768/EEC

The first regulatory framework for cosmetic products was determined in the Directive 76/768/EEC, which came into force in 1976 and contains all details for the composition,

labelling and packaging of finished cosmetics products. The Directive has been amended several times during recent decades to introduce important requirements into the law [9].

2.1.2 Regulation 1223/2009/EC

The Regulation 1223/2009 came into force in January 2010 and has been fully valid for all member states since July 2013. The particular feature of this Regulation is that the legal framework of cosmetic products should be recasted as one single document, in order to ensure greater clarity. The main points of the Regulation are product safety, the designation of a responsible person, notification of cosmetic products, additional claims, reporting of serious adverse events and requirements for the use of nanomaterials [8].

2.1.3 The European Cosmetic, Toiletry and Perfumery Association (COLIPA)

COLIPA is an association within the cosmetic industry that voluntarily initiates the harmonisation of labelling and product testing activities for sunscreen products. It is mostly responsible for the dialog between the industry and the authorities and has influenced the legal framework to use tested efficacy claims and harmonised consumer information.
It is worth mentioning that labelling and product testing have always been outside of the scope of the Directive 76/768/EEC. Milestones of COLIPA include the development of a standardised SPF testing, the introduction of a standardised test protocol for the SPF, water resistant and photostability testing and the development of a method for UVA protection measurement [10].

2.1.4 Essential requirements of sunscreen products

2.1.4.1 Responsible person

As responsible person acts a legal or natural person, who will be designated within the European Union. This person can be the manufacturer, importer or distributor. The manufacturer is responsible for the manufacturing according to GMP, while the distributor has to monitor the correct labelling and shelf life of the product. Each of them has to take care that the legal requirements are fulfilled. If a sunscreen product does not comply with the legal requirements, then the product has to be recalled or withdrawn from the market. However, if a sunscreen product implies a risk to human health, then the responsible person has to inform the competent authorities of all member states in which the product is available about the risk details and correcting measures. The responsible person has to provide all detailed information or documents upon request of the authorities [8].

2.1.4.2 Notification of a sunscreen product

A sunscreen product has to be notified via the Cosmetic Products Notification Portal (CPNP) before it can be put on the market [11].

The following information is required for such notification:

- Name of the sunscreen product and its category

- Address details of the responsible person (access to production information file)
- Name of the country
- Name of all member states where the sunscreen product will be marketed
- Contact details
- Information about nanomaterials (if applicable)
- Name and classification of substances (INN, CAS-and EC-number)
- Medical treatment in case of emergency

After the sunscreen product is put on the market, the responsible person must indicate the current labelling and packaging to the Commission. This information contains the class of the sunscreen product and all the names of the member states in which the product is available. Moreover, contact details of the responsible person are also required. The Commission makes the information available to all competent authorities under the scope of market surveillance and analysis, evaluation and consumer information [8].

2.1.4.3 General labelling claims

A sunscreen product needs a special labelling of packaging and container before the product can be distributed, including the following:

- Contact details of the responsible person
- Country of origin (imported products)
- Content (volume, weight)
- Date of minimum durability or time period after opening (if applicable)
- Protective measures for use
- Function of the sunscreen product
- Catalogue of all substances
- Small-sized products or products without packaging [8]

The Commission has constituted an additional guideline to the Regulation No 655/2013 to determine common criteria for the use of claims for cosmetic products in the European Union. These common criteria are legal compliance, truthfulness, evidential support, honesty, fairness and informed decision making.
The labelling, image and advertising of the cosmetic product have to be in accordance with the characteristics of the product. It is prohibited to claim special properties without proof of evidence [12].

2.1.4.4 SPF testing and claims

The Commission Recommendation 2006/647/EC determines that a sunscreen product has to assure a minimum efficacy to provide adequate protection against both UV rays. While the level of protection should be quantified with standardised testing methods, in-vitro testing methods should be favoured and photo-degradation should also be taken into consideration. For the testing, the international SPF test method is used, reflecting an international cooperation between Europe (COLIPA), Japan (JCIA), South Africa (CTFA –SA) and

Cosmetic, Toiletry and Fragrance Association (CTFA). The minimum erythemal dose (MED) on unprotected and protected skin will be measured. The sun protecting factor is "*the ratio of minimum erythemal dose (quantity of erythema-effective energy) on skin protected by a sunscreen product to the minimum erythemal dose on the same unprotected skin"*. For the calculation of the SPF, 10 to 20 valid results are sufficient, whereby the valid results have to be within the 95% confidential interval [13].
The efficacy of sunscreen products depends on the correct application and reapplication on the skin, as well as the quantity of sunscreen itself (about 36 grams). The level of protection will be reduced if a lesser quantity of sunscreen product is applied on the skin, which should be clearly stated on the labelling. It is forbidden to use claims about 100% UV-protection ("*sun blocker*") or that it is not necessary to reapply. Babies and young children should be protected from sunlight. The categories for the labelling are low, medium, high and very high [14].

Table 1 Labelling of sunscreen products [14]

Level of protection	Sun Protection Factor (Label)	UVA protection factor
Very high	SPF 50+	1/3 of labeled SPF
High	SPF 30, 50	
Medium	SPF 15, 20, 25	
Low	SPF 6, 10	

2.1.4.5 Water resistant testing and claims

The determination of a sunscreen product's water resistance should be executed according to the COLIPA Guidelines. The water resistant testing has two 20-minute or four 20-minutes water immersion periods. The measurement of the SPF takes place before and after water immersion. The testing has to be conducted in the same laboratory with the same number of subjects. Sunscreen products can be labeled with the claims "*water resistant*" or "*very water resistant*" [15].

2.1.4.6 Stability testing and claims

The manufacturer has to assure that a sunscreen product meets physical, chemical and microbiological quality standards. The storage conditions influence the shelf life of the product. The stability testing is executed in terms of real time or accelerated conditions on laboratory batches and batches of the marketed product. Thereby, the stability of the product under applicable conditions of use, storage and transport will be determined. Furthermore, the microbiological and chemical stability as well as the compatibility of the product and the container will be verified. It is also recommended to analyze the stability together with the package of the product. The package should be the same or similar to the package that will be marketed. If more package types and different sizes will be marketed, then it is important to test all different package types by using the smallest size. It is very common to conduct the prediction of the shelf life of a product with accelerated test conditions. Depending on the product category, the temperature and duration of the testing are selected based upon scientific evaluation. Accelerate tests are conducted for 1-3 months or longer at temperatures

of 37 °C, 40 °C or 45 °C. Apart from the accelerate testing, it is a general standard to also perform real-time monitoring to obtain realistic data about market stability. This kind of testing should be conducted in the final package under storage with an ambient temperature or under accelerate conditions with a controlled temperature [16].

On the basis of stability testing the labelling claims are performed. Two options are possible. First, the minimum durability of the finished product is less than or equal to 30 months. In this case the date of minimum durability has to be explicitly stated e.g. *"best used before the end of"* or use of a known symbol. Second, the minimum durability of the finish product is more than 30 months. In this case a date of minimum durability is not needed but it is recommended to indicate that the product can be used without any harm for certain "*period of time after opening*". For this purpose a known symbol has to be combined with a time period in months or years for instance "x M".(Month). For some products the period of time after opening is not important e.g. "single use products" [66].

Stability testing is also required for medicinal products. Accelerate and long-term testing will be performed, in order to receive relevant data about the shelf life and the storage conditions. Long-term testing will be performed by 25 °C and 60 % RH for 12 month and accelerate testing will be performed 40 °C and 75 % RH for 6 month. As a minimum three batches of the drug product have to be evaluated in order to receive sufficient data. On the label the expiration date and the storage condition will be claimed [68].

For multidose medicinal products an in-use stability testing is also required, in order to receive information about contamination, degradation etc.. For the evaluation of the in-use shelf life two batches have to be tested in order to analyze the microbiological, physical and chemical features as well as to collect information about changes during storage. Information about the in-use shelf life has to be added on the label. General information about the storage has to be put on the carton or has to added in the product information texts [69].

2.1.4.7 Product safety report and product information file

The use of sunscreen products under normal conditions should be harmless for human health. This means that the presentation has to be in accordance with the Directive 87/357/EEC. The responsible person has to take care that the labelling, instructions for use and disposal, as well as any other information or indications, are in line with the law. Before a sunscreen product can be put on the market, the product has to pass a safety assessment, which should be performed by a well-educated and experienced person. The conduction of non-clinical safety studies should be in compliance with the concept of good laboratory practice (GLP) and, if relevant, it should also be harmonised with other international standards. The responsible person has to ensure that a product safety report is compiled [8], [17].

2.1.4.7.a Product Safety report

The main elements of the product safety report are:

Part 1: Safety data

- Composition (qualitative, quantitative)
- Properties (physical, chemical) and stability
- Quality aspects (microbiological)
- Contaminants (forbidden substances), properties of packaging material
- Standard conditions of use
- Risk potential of the product and its substances
- Toxicological analysis of the substances
- Data about all side effects
- Additional data

Part 2: Safety assessment

- Final outcome of the evaluation
- Criteria for labelling (warning notices, package instructions)
- Explanatory statement
- Acknowledgement of the assessor

2.1.4.7.b Product information file

The product information file contains the following details:

- Characterization and safety statement of the product
- Description of the production process and GMP statement
- Confirmation about the effects of the products (relevant for the claims)
- Animal testing information

The product information file is stored by the responsible person and the competent authority should have easily access to this data, if required. The file has to be preserved for a period of 10 years after the last batch was put on the market [8].

2.1.4.8 Ingredients (prohibited, restricted, allowed)

In Regulation 1223/2009/EC, all substances are listed that are forbidden for the use in cosmetic products or whose use is restricted in cosmetic products. There are also all colorants, preservatives and all UV-filters mentioned that are accepted for use in cosmetic products [8].

2.1.4.9 Nanoparticles

Nanoparticles have the same dimension as body cells (1 - 100 nanometers). Zinc oxide or titanium dioxide are nanoparticles used in sunscreen products. In order to ascertain whether there is an interaction between nanoparticles and body, it is necessary to conduct a safety assessment. The result of the safety evaluation is that nanoparticles are considered as safe for use in cosmetic sunscreen products, meaning that they do not penetrate the skin. Only the use

of nanoparticles in sprays are not considered as safe, because inflammation of the lung can occur due to small particles being breathed in the lungs [18].
Before a sunscreen product is put on the market, the nanoparticles have to be notified six months before the market launch. All nanoparticles that are used in a cosmetic product will be evaluated by the Scientific Committee on Consumer Safety (SCCS). The Commission is preparing a list with all nanoparticles [8].

The notification contains the following information:

- Nomenclature, name and description of the nanoparticles
- Particle size, specification and characteristics (physical, chemical)
- Yearly amount of nanoparticles in a cosmetic product placed on the market
- Safety and toxicological data of the nanoparticles
- Expected conditions of exposure [8].

2.1.4.10 Animal testing

The final aim of the European Union is the prevention of animal testing. While the “ban on animal testing” and the “marketing ban” were implemented in the past, the marketing ban has to be extended due to a lack of alternative tests for repeated-dose toxicity, reproductive toxicity and toxicokinetics. The aim of ban is to forbid the merchandising of cosmetic products where the ingredients were tested on animals for safety reasons. In the case of security concerns, the Commission can allow an exemption, which is only possible if a well-known substance cannot be substituted by another substance. On grounds of safety reasons, it is allowed to conduct animal tests based upon a study protocol, which will be evaluated by the Commission.
In recent years, it has been possible to find proper alternative methods for testing skin irritation, corrosion and skin penetration, as well as for phototoxicity. These tests are validated and adjusted as OECD testing rules. In the area of acute systemic toxicity and eye irritation, it was only possible to gain OECD confirmation for eye irritation. Alternative tests for in vitro genotoxicity are in the status of improvement. OECD is reviewing the alternative test methods for skin sensitisation and carcinogenicity. Finding alternative test methods is not always a one-to-one exchange. It may be the case that more tests are necessary to achieve sufficient results [8] ,[19].
The International Cooperation on Alternative Test Methods (ICATM) is a voluntary initiative in Europe, Canada, USA, Japan and South Korea that supports the coordination of the scientific evaluation and validation of alternative testing methods for in vitro toxicity testing. The principal aims of ICATM are the development of validation studies, peer review, giving advice on strengths and weaknesses of alternative methods, while the reduction of effort and the sparing of resources are also important, in order to encourage alternative methods being acknowledged as international standard [20].
ICATM is also interested in entering into a dialog with the cosmetic industry of Australia, Brazil, China, Korea and Saudi Arabia to discuss alternatives to animal testing, nanoparticles, allergens, etc. [21].
It is worth mentioning that in Germany a National Centre for Documentation and Evaluation of Alternatives to Animal Experiments (ZEBET) exists. It was founded 20 years ago and it is

engaged in the developing and validation of alternative testing methods for cosmetic products. ZEBET works in line with European and German law. Moreover ZEBET has also established a AnimalALT-ZEBET database that offers plenty of information about alternative testing methods. ZEBET has an own laboratory and is responsible for the developing of alternative testing methods e.g. in the area of skin and eye irritation but also for the determination of embryotoxicity, cell and tissue culture methods etc.. The OECD and European committees have already accepted those alternative testing methods [61].
In 2007 the REACH Regulation 1907/2006/EC came into force, in order to improve the safety of human health and the environment. The use of alternative methods in order to assess hazards of substances are also included in this regulation. The key point of this regulation is to ensure that chemical substances that are placed on the market are really safe for the consumer and for the environment. All chemical substances that are used in a cosmetic product for instance sunscreen have to be registered. For this step all required data about physical, chemical, toxicological and eco-toxicological properties have to be provided. Some substances are excluded of the registration process and they are mentioned in the annex of the Regulation. This means that a lot of substances need to be re-assessed. At the same time the use of alternative testing methods are recommended, in order to avoid animal testing as good as possible. In this context a new procedure for the acceptance of new alternative testing methods was introduced by all EU member states and the OECD that should ensure a approval process within 5 months [62], [63].

2.1.4.11 Reporting of serious undesirable effects

A principal point of the Regulation 1223/2009 was to implement the serious adverse event reporting for cosmetic products in the law, given that the safety of cosmetic products is very important for public health. The outcome of this is that all serious adverse events have to be reported directly to the competent authority (e.g. Germany: competent authority for consumer protection) by the responsible person (manufacturer, importer) or the distributor, while health professionals or consumers are also asked to report such events. The report should mention all identified serious undesirable effects, the name of the product concerned and all the corrective measures that are taken into account. The competent authority, which receives the report about serious undesirable effects, has to inform the Commission and the competent authorities of all EU member states in which the product is marketed. Poison centers also have access to this information to help people in the case of an emergency [8].

2.1.4.12 Good manufacturing practice (GMP)

The production of cosmetic products should be carried out according to the GMP requirements. A cosmetic product has to be in compliance with the harmonised standard ISO 22716, which came into force in July 2013. This standard is obligatory for all cosmetic enterprises all over the world. Manufacturers, importers and exporters as well as distributors are responsible for the compliance, in order to guarantee high product quality and product safety [22].

The key aspects of ISO 22716 are:

- Quality management system and management of responsibilities

- Human resource management, training and equipment
- Documentation of procedure, storage and shipment
- Regular audits (control of laboratories)
- Control of the suppliers
- Management of the materials
- Control of hygiene, sanitary conditions and personal hygiene
- Control of labelling
- Handling of product complaints and recalls [22]

2.2 Sunscreen products in Australia

2.2.1 History of Sunscreen Standard for therapeutic sunscreen products

The Sunscreen Standard AS 2604:1983 was first published in Australia in 1983, whereby the SPF test procedure was described and the sun protection factor was limited to SPF 15+. In the revision of 1986, the testing of broad spectrum protection and water resistance were added. The third revision came in 1993, when New Zealand joined the Sunscreen Standard of Australia. By means of the fourth revision in 1997, the permitted SPF claims were upgraded from SPF 15+ to SPF 30+. The level of protection was described as low, moderate and high, while some criteria for the labelling were also adapted. In 1998, there was only a minor revision of the Sunscreen Standard, which did not lead to a change of the regulation. In 2012, the Sunscreen Standard was updated to comply with the current scientific standards. The new Sunscreen Standard allows the labelling of the product up to SPF 50+ instead of SPF 30+ according to the old Sunscreen Standard, if the product passes the relevant tests. Moreover, the numbering of the SPF claims that are labeled on the product have been changed. This change also provides a better overview of the level of protective factor [23].

Table 2 SPF values in the old and new Sunscreen Standard [23]

Level of protection	Sunscreen Standard 1998	Sunscreen Standard 2012
Very high	SPF 30+	SPF 50+
High	SPF 15 – 29	SPF 30, 40, 50
Moderate/Medium	SPF 8 – 14	SPF 15, 20, 25
Low	SPF 4 – 7	SPF 4, 6, 8, 10

The testing of sunscreen products to analyze the broad spectrum performance has been adapted according to the International Standard ISO 24443:2012. The in vitro test procedure is the same as in the old Sunscreen Standard AS/NZS 2604:1998, but there are other criteria for the validity of the testing results. The adjustment of the ISO 24443:2012 also leads to an amendment of the correctness and repeatability of the testing results. The level of UVA protection is rising with the increase of the SPF value. The broad spectrum test procedure is obligatory for all therapeutic sunscreen products with an SPF 15+, whereas sunscreens with a lower SPF do not require a broad spectrum performance. The update of the Sunscreen Standard also has an impact on the labelling of claims for water resistance. The new

Sunscreen Standard allows labelling of "*water resistant up to 2 hours*" for sunscreen products with an SPF 15 and less than 30 and "*water resistant up to 4 hours*" for sunscreen products with an SPF 30 and more. The use of claims on the label, e.g. "*sun block*", "*waterproof*" or "*sweatproof*", are prohibited [23].

Table 3 Labelling of water resistance – Sunscreen Standard 1998 / 2012 [23]

Label of water resistance	Sunscreen Standard 1998	Sunscreen Standard 2012
Up to 2 hours	SPF 15 - 19	SPF 15, 20, 25
Up to 3 hours	SPF 20 - 24	
Up to 4 hours	SPF 25+	SPF 30, 40, 50, 50+

2.2.2 Classification of sunscreens products in Australia

In Australia, sunscreens are classified as therapeutic goods or cosmetic products. Therapeutic goods are equivalent to medicinal products.

"Medicine means: *therapeutic goods (other than biological) that are represented to achieve, or are likely to achieve, their principal intended action by pharmacological, chemical, immunological or metabolic means in or on the body of a human"* [29].

"Cosmetic means: *substance or preparation intended for placement in contact with any external part of the human body, including:*

- *the mucous membranes of the oral cavity; and the teeth; with a view to:*
- *altering the odours of the body*
- *changing its appearance*
- *cleansing*
- *maintaining it in good condition*
- *perfuming*
- *protecting"* [40]

Therapeutic goods were regulated by the Therapeutic Goods Administration (TGA) because the primary purpose of the therapeutic good is to help to prevent a disease. Therapeutic sunscreen products are divided into three categories, namely primary, secondary and exempt sunscreen products.
Primary sunscreens are products that are mainly used for UV protection with an SPF > 4 or contain an insect repellent. Moisturizers that contain sunscreen with an SPF > 15 or sunscreen product that contains ingredients from human or animal origin also belong to the therapeutic sunscreens.
Secondary sunscreens are sunscreen products that contain a sunscreening ingredient, even though the primary purpose is neither therapeutic nor sunscreening. Moisturizers that are combined with sunscreen and have SPF $\leq$ 15, as well as sunbathing products with SPF 4 – 15 or make up products and lip balm products with any SPF, belong to the category of secondary sunscreen products. Most of the secondary sunscreens are regulated as cosmetic products by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS). Cosmetic sunscreen products are also named as "*excluded*" sunscreen products, because they are

excluded from the regulation by the TGA. Only some secondary sunscreens fulfill the requirements of a therapeutic good, which is why they are regulated by TGA.
The "*exempt*" sunscreen products also belong to the therapeutic sunscreens. They are characterised by an SPF > 4, do not contain any ingredients of human or animal origin and do not claim an indication for the therapy of a serious disease, disorders or defect.

Furthermore, most of the therapeutic sunscreen products that are marketed in Australia have to be listed in the Australian Register of Therapeutic Goods (ARTG). All sunscreen products that are not listable have to be registered in the ARTG. A special category is the "*exempt*" therapeutic sunscreen products that are excluded from listening or registering in the ARTG [24], [25],[26].

Table 4 Classification of therapeutic and cosmetic sunscreens [24]

Product class	Sub-group	Authority
Listable Sunscreens	• Primary sunscreens with claims of SPF 4 and not greater than SPF 50+ • Secondary sunscreens that fulfill the criteria for therapeutic sunscreens • Primary and secondary sunscreens with ingredients of human or animal origin without any SPF claims	ARTG (listing)
Registrable sunscreens	Sunscreens with therapeutic claims other than sunscreening and/or reduction of risk for skin cancer, solar keratosis, sunspots or premature ageing	ARTG (registering)
Exempt sunscreens	Primary sunscreens without ingredients of human or animal origin and SPF claims less than 4	Exemption (no listing/registering in ARTG)
Cosmetic sunscreens (excluded sunscreens)	Secondary sunscreens that are not in compliance with the regulation but fulfill the requirements of cosmetics	NICNAS and ACCC

2.2.3 Listing and registering of therapeutic sunscreens

Most of the therapeutic sunscreen products must be listed in the ARTG. These are all therapeutic sunscreens containing an active ingredient that is listed in the guideline and is allowed for use in therapeutic sunscreens. Furthermore, all sunscreens with an SPF 4 or SPF less than 4 with ingredients of human or animal origin must be listed. The testing and labelling of the sunscreens has to comply with the Sunscreen Standard AS/NZS 2604:2012 (Therapeutic Goods Regulation, 1990; Australian Regulatory Guideline for Sunscreens, 2012). For the listing, the following data is necessary: contact details of the applicant, product details, TSE certificate (if applicable) details about manufacturing and other information. The Electronic Listing Facility (ELF) of the TGA has to be used for the listing process [24], [27].

Sunscreen products using therapeutic claims or with an active ingredient that is not listed in the regulatory Guideline for sunscreens have to be registered in the ARTG. They are regulated as OTC or non-prescription drugs, depending on the kind of active substance and the type of claim [24].
Furthermore, all sunscreens that do not belong to the category "listable, exempt or cosmetic (excluded)" have to be registered by the TGA. For the registration, sufficient data has to be submitted to establish the quality, efficacy and safety of the sunscreen product according to the Australian Regulatory Guidelines for OTC Medicines (ARGOM) [24], [28].

The following therapeutic sunscreens have to be registered:

- Sunscreens with active ingredients that are not listed in the Australian regulatory guideline for sunscreens or under the Therapeutic Goods Act
- Sunscreens with therapeutic claims instead of sunscreening claims
- Sunscreens containing ingredients that are listed in the SUSMP (Standard for the Uniform Scheduling of Medicines and Poisons)
- Sunscreens that are not listable, exempt or excluded [24]

2.2.4 Essential requirements for therapeutic sunscreen products

2.2.4.1 Responsible Person

In Australia, the responsible person is the "sponsor", namely a legal person who exports, imports and/or manufactures a good or is responsible for arranging its export, import and/or manufacture, as well as its supply. However, this does not mean that the sponsor works on behalf of another person, who is a resident or carrying out business in Australia during the time of exportation, importation or manufacture [29].

2.2.4.2 Reporting of adverse reactions

Sponsors have the obligation to report any adverse event to the TGA, while customers, pharmacists, medical doctors can also report an adverse event about any medicine to the agency. The TGA is interested in receiving the following details of the adverse event:

- "*Patient identifier (initials, date of birth or age)*"
- "*Contact details of the reporter*"
- "*Description of the adverse event*"
- "*Name of the Medicine (adverse event)*"
- "*Other medicines taken by the patient*"
- "*Date of onset of the adverse event*"
- "*Date of starting and stopping the suspected medicines*"
- "*Date of starting and stopping any other medicines*"
- "*Details of how the adverse event was treated*"
- "*Outcome of the event, date of the outcome*"[30]

The TGA enters all the reports into a database (Australian Adverse Drugs Reactions System) and analyses the data periodically to identify safety concerns. The information is also available for the public. The TGA must take regulatory action to assure that the patients and health professionals are more sensible about safety concerns. Changes to the product information or consumer medicine information are undertaken accordingly to make aware of a secure use of medicine. It is also possible that the agency makes a safety update with some public alerts or articles. Sometimes the agency decides that the sponsor has to conduct further post-marketing studies or the sponsor has to offtake the medicine from the market [30].

2.2.4.3 Labelling and advertising

The sponsor has to ensure that the labelling and advertising of the sunscreen products comply with the legal requirements. The basis of all the requirements for the labelling and advertising of therapeutic sunscreen products are laid down in the Labelling Order [31], Therapeutic Goods Advertising Code [25], Australian/New Zealand Standard AS/NZS 2604:2012 [23] and Required Advisory Statements for Medicine Labels (RASML) [32]. RASML and Therapeutic Goods Advertising Code are not valid for cosmetic sunscreen products [24].

The following information must be stated on the label of therapeutic sunscreen products.

- Language: English
- Printed letters: clear, legible and characteristic
- Height of letters
- Printed or safely added on the container
- During use, it should not become detached or unreadable
- Opening of the container: label should not be damaged or removed
- Avoidance of confusion by any other label or object

The labelling does not include claims, statements or pictures that:

- lead to irresponsible and fanciful expectations according to the effects of the product
- are untrue, one-sided or misleading the user
- misuse the faith and inexperience of the user or use language that triggers anxieties
- support or likely to support improper use
- the sunscreen product is failsafe, infallible, magic and is always effective
- the sunscreen product is recommended by any public institution (agency, hospital, healthcare service)

Listed therapeutic sunscreens are allowed to use the following indications if they comply with the requirements of AS/NZS 2604:2012 [24].

2.2.4.3.1 Indications for Broad spectrum sunscreens with an SPF of 30 or higher

”*May assist in preventing some skin cancers”*.
“*May reduce the risk of some skin cancers”*.
“*Can aid in the prevention of solar keratoses*”.

"Can aid in the prevention of sunspots".

2.2.4.3.2 Indications Broad spectrum sunscreen with an SPF of 4 or higher

"Can aid in the prevention of premature skin ageing".

The indications for listed sunscreens are appropriated for the unendangered and effective use without the help of a physician. However, the use of indications that refer to a serious disease, e.g. skin cancer, are only allowed for therapeutic sunscreens that have been approved by the TGA. The sponsor has to provide proof of evidence about the indication and claims of the sunscreen product at the time of listing in the ARTG. The indications and claims of the product have to be "*true, valid and not misleading*." Data about efficacy is not needed at the time point of listening, although the TGA will request sufficient data, for instance "*copies of labelling, results of premarket SPF, broad spectrum performance, water resistance or stability testing*" after the listing process. Therapeutic sunscreen products are allowed to make established non-therapeutic claims on a scientifically founded basis, for instance "*contains Vitamin E, contains aloe vera, moisturising, antioxidant, free radical barrier."* The use of "*company logos, other symbols and consumer information*" on the labelling is permitted as long as it does not lead to confusion for the users and does not contradict the predetermined legal requirements. The sponsor has to ensure that the ingredients or excipients used are stated on the label [24].

2.2.4.3.3 Labelling of container and primary package

The requirements for the container and primary package are manifested in the Labelling Order and the Sunscreen Standard (AS/NZS 2604:2012). The container and the primary package must detail the following information:

- Product name
- Dosage form (cream, lotion)
- Sun Protection Factor (SPF) and Broad Spectrum
- Quantity (mL or g)
- AUST L or AUST R number
- Name of active ingredients (Australian Approved Name, AAN)
- Proportion of ingredients (mg/g or mg/mL)
- Storage conditions
- Batch number of the product
- Expiry date of the product
- Use of the product
- Warning statements (included in the RASML)
- Contact details and phone number of the sponsor/Australian supplier

The level of protection can be described with "*low, medium, moderate, high, very high protection*". The use of the term "*sunblock*" is not allowed, because a sunscreen product cannot provide 100% sun protection. If the sunscreen product is also water resistant

according to AS/NZS 2604:2012, this should also be stated on the container/primary package. The terms "*waterproof or sweat proof*" are not allowed, because sunscreens are not entirely waterproof. It should be clearly stated on the label whether the product is a sunscreen or moisturizer with sunscreen (with SPF), that the sunscreen should be applied on the skin 20 minutes before sunbathing and reapplying is necessary every two hours or after swimming and towelling or sweating. Moreover, it should also be mentioned on the label that a sunscreen should not applied on diseased skin and contact with the eyes should be avoided. On the label of spray sunscreens, it must be mentioned that inhaling has to be avoided. Small containers with a volume of ≤ 20 ml that are enclosed in a carton (primary pack) must include the following information:

- Name of the sunscreen product
- Name of the pharmaceutical form
- Quantity of the container
- Batch number
- List of all active ingredients [24]

2.2.4.3.4 Advertisements for therapeutic sunscreens

The legal basis for the advertisement of therapeutic goods is established in the Therapeutic Goods Advertising Code 2007. Advertisements leading to expectations that the product cannot not fulfill or lead to self-diagnosing or inacceptable treatment by the consumer are prohibited. Claims can contain scientific matters, although the information has to be true, precise, unmistakable and adapted to the target group. For the use of publications, the naming of the originator is essential. Advertisements that imply an agreement with public institutions or sponsorships are only accepted when it does not lead to endorsement.

1. Minimum Requirements

- Name of the therapeutic good
- Information about the indications for use (approved/allowed)
- Listing of all ingredients

2. Direct/Internet Marketing:

- Naming of active ingredients
- Warning and advisory information
- Contraindications and known serious adverse events [25]

2.2.4.4 Nanoparticles

Sunscreen products often contain zinc oxide and titanium dioxide. The size of nanoparticles is variable. Primary particles have a size of 5-20 nm, aggregates 30-150 nm and agglomerates 1-100 microns. Primary particles accumulate together, which leads to the formation of aggregates. Aggregates are the smallest units used in sunscreen products. The TGA monitors the scientific literature to detect any risk for the use of nanoparticles in sunscreen products. A spectrum of in vitro and in vivo studies have manifested that titanium dioxide and zinc oxide

are able to penetrate into the stratum corneum, but they are not able to penetrate into the dermis. This leads to the conclusion that systemic effects are improbable. Based upon the current state of knowledge, the nanoparticles zinc oxide and titanium dioxide, which are used in sunscreens, do not harm human health [24], [33].

2.2.4.5 SPF testing

The SPF of sunscreen products have to be tested in accordance with AS/NZS 2604:2012 and ISO 24444:2010. The test results represent an estimation, although the results are not a precise measure of the SPF when the sunscreen is applied on the human skin. The results show a certain variance, which has to be taken in consideration during the evaluation of the test results. This is also necessary for the labelling and retesting of a product. The minimum number of subjects is 10 and the results have to be significant regarding a statistical perspective [24].

2.2.4.6 Water resistant testing

The water resistant testing was originally laid down in the Sunscreen Standard AS/NZS 2604:1998 and remains the same, although the SPF testing was adopted according to the ISO 2444: 2012. However, the claims allowed about water resistant have changed. All sunscreen products with an SPF of 15 to 30 can use the water resistant claims up to 2 hours and sunscreen products with and SPF 30, 40, 50 or 50+ can use the water resistant claim up to 4 hours [23].

2.2.4.7 Stability testing

The label of therapeutic sunscreen products must contain an expiry date. The sponsor is responsible for the testing of shelf life and storage conditions for the sunscreen product. The testing has to be performed with the container that will be marketed afterwards or with a similar container. Data about the microbiological, chemical and physical stability have to be evaluated by the sponsor to claim the shelf life and storage conditions of a sunscreen product. Before a sunscreen product is listed or placed on the market, the shelf life has to be verified with real time testing for the full required shelf life. Another option is accelerate testing, which involves storage for 6 to 9 months at storage temperatures of 10 °C or 15 °C. At least two pilot-scale batches should be tested in stability studies and should be manufactured similar to the production scale batches, which will be commercialized, in order to ensure coincidental features. Real time studies of shelf life are also required, whereas at least two production-scale are stored at the highest proposed storage temperature. These production-scale batches have to be tested after manufacturing and then once a year until the end of the shelf life of the batches.
Microbiological stability has to be investigated if the sunscreen product contains water. The efficacy of the preservatives has to be tested at the beginning and end of the accelerated stability testing, as well as the end of the shelf life during the real-time stability testing. It is absolutely required that the temperature used for the stability studies is continuously checked, monitored and documented to provide true testing results. The limit for shelf life for therapeutic goods is five years [24], [34].

2.2.4.8 Manufacture and quality control

The requirements for good manufacturing practice (GMP) are determined by TGA. A manufacturer of Australia must have a license issued by the TGA, allowing the manufacturer to manufacture sunscreen products. A manufacturer outside of Australia needs a GMP clearance issued by the TGA, allowing the foreign manufacturer to import sunscreen products [24].
The manufacturer is responsible for the quality of the finished therapeutic good, as well as the quality of the active ingredients and excipients used for the sunscreen product. The manufacturer has also to comply with the Therapeutic Goods Order No. 69 for labelling, as well as the Therapeutic Goods Order No. 77 for microbiological quality and has to guarantee that the product complies with any product standard. Predetermined standards used for listed or registered therapeutic goods are the "*British Pharmacopoeia (BP), European Pharmacopoeia (Ph Eur) and United States Pharmacopeia-National Formulary (USP-NF)"* [29], [31] [35].
Furthermore, the manufacturer must guarantee a qualified control of testing procedures and validation to assure that the quality specifications of all essential chemical, physical and microbiological features are fulfilled. If an ingredient is part of a monograph in one or more Pharmacopoeias, the ingredient has to comply with at least one of the monographs affected, unless the responsible authority has issued another legal binding requirement instead of the monograph. Furthermore, many excipients (solvents) that are part of sunscreen products are a matter of one or more monographs. Unless the ingredient is not part of a monograph, the control of the product quality specifications has to be conducted "in-house", whereby the purity, identity and all required chemical and physical characteristics have to be carefully investigated. The methods for testing have to be validated adequately. The manufacturer has the responsibility that batches of the sunscreen product meet the required specifications before the product is placed on the market [24].

2.2.4.9 Permitted active ingredients and excipients

All active ingredients and their permitted maximum concentration (weight/weight) that are allowed for use in therapeutic sunscreens are listed in the Australian Regulatory Guidelines for Sunscreens. The list contains the following information about the active ingredients: "*synonyms, abbreviations, trade names, International Non-proprietary Names (INN), International Nomenclature Cosmetic Ingredient (INCI) names and Chemical Abstract Services (CAS) numbers*". The sponsor has to provide essential data about the safety and efficacy for active ingredients that are not listed in the Australian Regulatory Guideline for Sunscreens.
Furthermore, the TGA has also compiled a list of approved excipients that are allowed for use in therapeutic sunscreens or for other ointments. For some excipients, the TGA set some limits concerning the quantity as well as some restrictions for use of the excipients [24].

2.2.4.10 New active ingredients

Some conditions must be fulfilled to use new active ingredients. The sponsor has to submit an application with a proposed name for the new active ingredient. The TGA reviews the proposal and will come to a decision about the identity and the AAN for the active ingredient. In addition, the sponsor has to submit appropriate data that verifies the safety and efficacy of the new active ingredients, which is not included in the TGA list. Appropriate studies have to be conducted to obtain scientific data, e.g. about photostability, allergenicity, local tolerance, carcinogenicity or interactions potential. The sponsor also has to provide data about the UVA/UVB absorption profile of a new substance.

If the sponsor cannot provide all the required studies, he has to submit an appropriate scientific justification instead of the relevant study. Another option includes searching for alternative methods to find supporting scientific data that could be used for significant argumentation [24].

2.2.4.11 New excipients

If a therapeutic sunscreen contains an excipient that has not been used before, additional data is required for the TGA to evaluate the new excipient. There are minimum requirements for the scientific data.

- Name and identification of an ingredient name as an AAN
- Identifying of the excipients as a substance and inclusion in the "*Personal Care Products Council International Cosmetic Ingredient Handbook (Dictionary)"*
- Confirmation that the substance is not mentioned in the EEC Directive 76/768
- Objective evidence that the excipients have been placed on the market for a minimum of two years or that they have been approved by a regulatory agency of Sweden, Canada, USA, UK or Netherlands
- Study data about acute oral toxicity
- Study data about skin irritation (animal or alternative method)
- Study data about skin sensitisation (skin, animal or alternative method)

As soon as the substance is approved and AAN is specified, it is allowed to use this substance in any other therapeutic sunscreen or medicine for topical use, up to the predetermined limit. Further data is required if the substance will be used outside the predetermined limits or conditions, as well as if the formulation or the pattern of use has changed. It is acceptable to use alternative data sources, e.g. NICNAS or US Cosmetic Ingredient Review (CIR) group.
The identity of the substance investigated in all studies has to be ensured by using laboratory codes, trade names and synonyms, while it also has to be linked with the substance verified in the application form of the new substance for the AAN. In the documentation, not only should the final concentration of the new substance in the therapeutic good be clearly specified, but also the concentration used in the studies, thus rendering a comparison is feasible.

Scientific data is required for the substance that is classified as an excipient, in order to verify its purpose and function. A justification is needed if the excipient is used as an active ingredient. If the concentration of the substance in higher than in listed products, it is obligatory to register the product. Some excipients also have active functions, but whether they are classified as excipients or active ingredients depends on the concentration. If the excipients are available in a concentration above the minimum limiting value, they have to be classified as an active substance due to their active function. If this the case, the therapeutic sunscreen has to be listed or registered with the ARTG [24].

2.2.5 Cosmetic sunscreen products in Australia

All products that contain an ingredient with sunscreening characteristics belong to the category of "cosmetic sunscreens". These products are regulated as cosmetic by NICNAS and not by TGA. Cosmetic sunscreens must be in line with the definition of a cosmetic, as well as all the requirements of the Cosmetics Standard and the Cosmetic Guidelines of NICNAS. It is a general guidance for new legal requirements in a simplified manner, but it is not legally binding [36]. The labelling criteria of all cosmetic products are obligatory and are stated in the Cosmetic & toiletries ingredient labelling, which is published by the Australian Competition & Consumer Commission (ACCC) [24].

2.2.5.1 Types of cosmetic sunscreen products

a. Make-up products for the face and nails:

- *"tinted bases or foundation (liquids, pastes or powders) with sunscreen"*
- *"products (tinted or untinted) intended for application to the lips with sunscreen"*

b. Skin care products:

- *"some moisturising products with sunscreen for dermal application, including anti-wrinkle, anti-ageing and skin whitening products"*

- *"some sunbathing products (for example, oils, creams or gels, including products for tanning without sun and after sun care products) (Australian Regulatory Guideline for Sunscreens, 2012)".*

2.2.5.2 Revised Sunscreen Standard for Cosmetic Sunscreen products

The update of the Sunscreen Standard AS/NZS 2604:2012 also influences the Cosmetic Standard 2007, which refers to the old Sunscreen Standard AS/NZS 2604:1998. Consequently, the Cosmetic Standard 2007 was also amended in 2013 to comply with the Sunscreen Standard AS/NZS 2604:2012. The Cosmetic Amendment (Sunscreen) Standard 2013 is published under the Industrial Chemicals (Notification and Assessment) Act 1989, section 81. Within a period of five years, all the cosmetic sunscreen products have to be adjusted to the new Sunscreen Standard AS/NZS 2604:2012 [37].

2.2.5.3 Important changes of the Cosmetic Amendment (Sunscreen) Standard 2013:

- The maximum SPF for face and nail products is SPF 50+, SPF 15 for skin care products
- Allowed SPF claims: 4, 6, 8, 10, 15, 20, 25, 30, 40, 50 and 50+
- No water-resistant claims or therapeutic claims
- Change of the level of protection criteria: low, medium/moderate, high, very high
- Minimum SPF is 4, SPF 2 is no longer allowed
- Broad spectrum performance is obligatory for all skin care cosmetic sunscreens
- Broad spectrum performance is obligatory for face and nail sunscreen products with SPF 30 or more
- Update of the broad spectrum performance according to International Standard ISO 24443:2012
- Increasing of SPF is related with an increase of UVA protection [38]

2.2.5.4 Essential requirements for cosmetic sunscreen products

2.2.5.4.1 Registration by NICNAS

NICNAS is the National Industrial Chemicals Notification and Assessment Scheme, which was founded in 1990 under the Industrial Chemicals Act 1989. The aim of NICNAS is to protect people from the noxious effects of industrial chemicals. All cosmetic ingredients belong to the category of industrial chemicals. One of the main tasks of NICNAS is to evaluate new industrial chemicals, as well as chemicals that are already in use, in order to see the effects on public health or the environment. In the first place, NICNAS wants to assure that the chemicals are safe for use by performing a risk assessment.
It is obligatory that importers and/or manufacturers of industrial chemicals register with NICNAS (The Industrial Chemical (Notification and Assessment) Act 1989), before they are allowed to import and/or manufacturer industrial chemicals. A yearly fee and a tax for registration have to be paid and the registration has to be renewed every year. After the registration, the importer and/or manufacturer receive a registration number and a registration certificate. The name of the importer/manufacturer will be listed on the "Register of Industrial Chemicals Introducers" [39].

2.2.5.4.2 Labelling requirements

A cosmetic product has to fulfill all the labelling requirements stated in the "Trade Practices (Consumer Product Information Standards) (Cosmetics) Regulations 1991". The Australian Competition and Consumer Commission (ACCC) manages these requirements.

The following requirements are necessary for the labelling.

- Listing of all ingredients (container or product by descending order by volume/mass, depending on concentration, colour additives last of all)
- Securing that consumers have access to information about the ingredients, if the size, shape or nature of the container is not acceptable

- Supplier: number of products with similar composition or same use
- Colour additives: name of the additives plus symbol +/-
- Flavours: listing of flavour(s), aroma(s)
- Fragrance: listing of fragrance(s), parfum(s)
- Listing of ingredients must be easy readable and salient for the consumer
- Names of the ingredients: use of English names or use of International Nomenclature Cosmetic Ingredient names; list of names in different language is allowed [40]

2.3 Sunscreen products in the United States

2.3.1 History of the sunscreen rulemaking

In 1978, the Advance Notice of Proposed Rulemaking (ANPR) was published, which contained recommendations about the secure and effective use of Over-The-Counter (OTC) sunscreen products. At the time, 21 active ingredients were recommended as generally being recognized as safe and effective (GRASE) for sunscreens. The SPF level was proposed from SPF 2 to 15. There was also a discussion about dosage forms (oil, lotion, cream, gel, butter, paste, stick, ointment, spray), without a final recommendation.

In 1993, a proposed rule came into force that included the proposed GRASE conditions. Therefore, 20 ingredients of the ANPR were accepted for use in sunscreen products, while the maximum SPF level was proposed at SPF 30.

In 1996, the active ingredient “Avobenzone” and in 1998 “Zinc oxide” were integrated in the proposed rule.

In 1999, a final rule came into force that established the final sunscreen monograph (21 CFR part 352), which became effective in 2001. Some new active ingredients were included. A combination of ingredients in a sunscreen product was accepted, whereas the minimum SPF value of each ingredient in the finished product was fixed. The maximum SPF 30 was determined.

Since 2000, the effective date of the final rule has been postponed twice, although no new effective date has been mentioned. The reason for this procedure was that the labelling requirements and the UVA/broad spectrum testing had not yet been established. Consequently, the OTC monograph for sunscreens has never come into force.

In 2007, an ANPR was published to request more information and remarks on safety and efficacy aspects of sunscreen products, when they are in combined with an insect repellant ingredient registered by the Environmental Protection Agency (EPA).

In 2011, a final rule came into force that laid down the labelling and testing criteria for OTC sunscreen products that are marketed without an approved application. The following topics were included: labelling of SPF and broad spectrum protection and its testing methods, water resistant labelling and testing, special labelling topics as warnings and direction for use. Special claims that would not be permitted for the use for OTC sunscreen product without

approved application were also described in the final rule. Labelling and testing criteria of the ANPR of 2007 were included, but not the topic of active ingredients or combinations of ingredients. At the same time, a proposed rule was also published to determine a maximum SPF level of 50+ for sunscreen products.

Furthermore, an ANPR was also published in 2011 to obtain more information about OTC sunscreen products in various dosage forms (oil, lotion, cream, gel, butter, paste, stick, ointment, spray). The data about the different dosage forms should be included in the OTC sunscreen monograph. More data about safety, efficacy as well as labelling and testing for sprays is necessary. Other dosage forms (body wash, shampoo, powders etc.) were also discussed, but they will not be included in the OTC sunscreen monograph. Sunscreen products with ingredients that are not listed or with insect repellents that are not registered by EPA are not covered by this enforcement discretion [41].

2.3.1.1 OTC monograph system

Only substances that are recognized as safe and effective by FDA are included within a monograph. All drugs marketed that comply with a final monograph can be directly put on the market without FDA approval of a marketing application [42].

The Division of Nonprescription Regulation Development is responsible for the evaluation of safety and efficacy data of substances. If a drug does not comply with the monograph, an Investigational New Drug (IND) has to be submitted and approved before the product can be marketed [43].

2.3.2 Final Monograph and current Enforcement Policy

The final monograph contains the following details. OTC sunscreen products are intended for topical application . They have to be safe and effective and have to fulfill all the conditions that are stated in the final monograph. These are e.g. definitions about the SPF value and the minimal erythema dose. All active ingredients and its concentrations but also all allowed combinations are listed in the monograph. General directions for the labelling but also for the testing procedures e.g. SPF testing, water resistant testing are determined in the final monograph [64].

The final monograph for OTC sunscreen products is not yet completed. Therefore, the current enforcement policy will continued as long as the OTC sunscreen monograph comes into force. There is no reason to object OTC sunscreen products that are marketed without an approved application, as long as no potential risk to human health occurs and the following criteria are fulfilled:

- Active ingredients or combinations are in accordance with the Guidance
- Compliance with OTC drug requirements and adverse events reporting
- Compliance with labelling and testing requirements

The sunscreen ingredients used in OTC sunscreen drug products help to prevent a sunburn, skin aging and skin cancer [44]. In general, the intended use of a drug is to *"diagnose, cure, mitigation, treatment or prevention of disease"*. Cosmetics are also defined by their intended use as *"articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance"*. Cosmetic products that are labeled with sunscreen claims have to be regulated as drugs, because their primary purpose is to absorb, reflect or scatter harmful sun rays and is responsible for the prevention of a disease or has an effect regarding structures or functions of the human body. [41], [45], [65].

2.3.3 Legal requirements of OTC sunscreen products

2.3.3.1 Responsible Person

In the United States, the person mentioned on the label is the so-called responsible person, which can be the manufacturer, distributor or packer [46].

2.3.3.2 Registration or listing of drugs

The owner or operator of an establishment has the task of registering the establishment with FDA within 5 days after the start of the operation or within 5 days after the submission of a drug application. The registration information must be renewed every year. In case the company is outside of the United States and the product will be imported to the USA, the registration or annual registration has to be completed at once. The registration process can be conducted electronically. If the owner does not register the drug, then it is misbranded. For the registration, the following information is required:

- Name and address of establishment(s)
- trade name(s)
- name and type of ownership (corporation, partnership)

If the registrant is from a foreign country, the following additional information has to be submitted:

- Name and contact details of agent of the USA on behalf of the owner (phone, email)
- Name of all importers (phone, email)

For the correspondence between registrant and FDA, the foreign registrant has to submit all phone numbers and email addresses of the agent or the importers. Additionally, the form FDA 2656 has to be completed, which requires name, address, phone number, email address and the operation type. For the electronic submission, a Data Universal Numbering System (D-U-N-S®) is necessary. This number will be assigned from FDA.

The initial listing information has to be submitted by the registrant for all drugs in commercial distribution at the time point of the first registration. The establishment registration information from private label distributors (PLDs) will be not accepted by FDA.

The PLD has to apply for a NDC Labeler Code so that he is able to submit drug listing information to FDA. The PLD is responsible for complying with all the listing requirements and has to inform the registered establishment that the drug listing submission has been completed. If the drug is listed by the PLD, no listing of the owner of the establishment is allowed. Updates of listed drugs and their labelling can be completed twice a year, but it is also possible to submit more often if some changes arise by the registrant. For the listing, the following additional information is required:

- Name of establishment (manufacture)
- Drug Enforcement Administration (DEA) schedule
- Ingredients (inactive)
- Route of administration
- Information about application and marketing
- Package type/size
- NDC product code for source drug repacked/relabeled
- Unique Ingredient Identifiers (UNII), other codes
- Confidentiality Flag
- Flavour, colour
- Image: actual image for solid dosage forms required [47]

2.3.3.3 Final Rule 2011

The final rule was published in June 2011 and came into effect in June 2012. All OTC sunscreen drug products that are marketed without an approved application come under the scope of the final rule. The information in the final rule will be beneficial in terms of marketed sunscreen products being labeled and tested for UVA and UVB protection. The final rule will support the consumer to gain better information about the sunscreen use, as well as its protection from harmful UV radiation. Furthermore, the final rule clarifies which claims are allowed and needed or which are not allowed for OTC sunscreen products. The previously accepted ingredients for sunscreen products are permitted to use.

The most important revision of the final rule is the use of the "*Broad Spectrum SPF*" statement on the PDP. If a sunscreen product does not pass the broad spectrum test, then the information on the label has to inform the consumer that the product helps to prevent sunburn but not skin cancer or skin ageing. For the SPF testing only ten subjects are required anymore. Only one in-vitro test is necessary, in order to verify the broad spectrum protection. The "Sun Alert" warning is not required anymore. The use of other sun protection measures should be stated on the label, so that the consumer is informed that the risk for skin cancer and skin ageing can be reduced.

There are some issues that are still open and they do not fall under the scope of the final rule. One issue is the determination of GRACE (safe and effective) sunscreen products and ingredients that are not included as active ingredients of the proposed rule. Sunscreen active ingredients and its safety aspects need further evaluation and will be part of the future rule making. Another issue concerns the information about an expiration date on the label. Within

the current regulation an expiration date was not necessary, if an OTC drug product stays stabile for a minimum of three years. Furthermore the declaration of the country of origin for all active and inactive ingredients that are used for the sunscreen product is also an issue that will not be discussed in the final rule [48].

2.3.3.3.1 Labelling of the Principal Display Panel (PDP)

The statement about the type of UV protection is no longer required on the principal display panel. All sunscreen products that pass the broad spectrum test are permitted to label “Broad Spectrum SPF”. It is also recommended that the broad spectrum SPF statement is not mixed with another text or picture and the entire text should have the same font style, size and color on the same background color. The final rule changes the statement about the item “water resistant”, whereby the old description “water resistant” and “very water resistant” is exchanged with the statement “water resistant” (40 minutes) or “water resistant” (80 minutes), when the product offers better water resistance properties. The educational statement about UVA and UVB (proposed rule 2007) is cancelled [48].

Table 5 Label of PDP in accordance with the final rule [48]

Information on the label	**76 FR 35620 - Final Rule**	
SPF value	**SPF < 15**	**SPF > 15**
Rating of effectiveness	SPF 2 -14	Broad Spectrum SPF 15 or higher
Water Resistance	No statement	Water Resistant (40 minutes or 80 minutes)

Sunscreen products with SPF level between 2 and 15 are only allowed to label “Helps to prevent sunburn”, because these products do not have broad spectrum protection. Sunscreen products with SPF level 15 and higher can make a claim that sunscreen use together with other protective actions may reduce the risk of skin cancer and skin ageing. There are some additional warning statements in the final rule. Sunscreen products with and SPF < 15 or without broad spectrum protection have an additional warning regarding skin cancer and skin ageing. Sunscreen use is not recommended on damaged skin. The applying of the sunscreen should take place 15 minutes before going in the sun and should be reapplied at least every two hours. The use of a water resistant sunscreen is recommended if the consumer likes to swim or is sweating. However, swimming or sweating reduces the protection of the sunscreen, and thus it should be reapplied after 40 or 80 minutes or after towel drying. An additional statement available regarding sun protective measures is that it is not only recommended to use a sunscreen with broad spectrum protection, but also to wear clothes and sunglasses and avoid the sun over midday, as well as limiting sunbathing in general to reduce the risk of skin cancer. Moreover, there is also a note that a sunscreen product should be protected against heat and direct sun [48].

Table 6 Drug Facts labelling [48]

Information	Final rule
Active ingredients/Purpose	Name of ingredients + amount, purpose: "*sunscreen"*
Uses	"*Helps to prevent sunburn.*" "optional: "*if used as directed with other sun protection measures (see Directions), decreases the risk of skin cancer and early skin ageing caused by the sun.''*
Warnings	*"For sunscreen products that are not broad spectrum or for products that are broad spectrum with an SPF value less than 15, Skin Cancer/Skin Aging Alert [in bold font]: Spending time in the sun increases your risk of skin cancer and early skin ageing. This product has been shown only to help prevent sunburn, not [in bold font] skin cancer or early skin aging."* *"For external use only."* *"Do not use on damaged or broken skin."* *"Stop use and ask a doctor if skin rash occurs."* *"When using this product keep out of eyes. Rinse with water to remove."* *"Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away."*
Directions	*"<u>Non-Water Resistant Product</u>"* • *"apply liberally 15 minutes before sun exposure"* • *"use a water resistant sunscreen if swimming or sweating"* • *"reapply at least every 2 hours"* • *"children under 6 months: Ask a doctor"* *"<u>Water Resistant Product"</u>* • *"apply liberally 15 minutes before sun exposure"* *"<u>reapply":</u>* • *"after 40 [or 80] minutes of swimming or sweating"* • *"immediately after towel drying"* • *"at least every 2 hours"* • *"children under 6 months: Ask a doctor"* *"<u>Water Resistant and Non-Water Resistant Products</u>"* *"For sunscreens with Broad Spectrum SPF values of 15 or higher":* • *"Sun Protection Measures [in bold font]. Spending time in the sun increases your risk of skin cancer and early skin ageing. To decrease this risk, regularly use a sunscreen with a Broad Spectrum SPF value of 15 or higher and other sun protection measures including":* • *"limit time in the sun, especially from 10 a.m.–2 p.m."* • *"wear long-sleeved shirts, pants, hats, and sunglasses".*
Inactive ingredients	List of all inactive ingredients in alphabetical order
Other information	"*protect this product from excessive heat and direct sun*".
Questions	No statement required

For the labelling of sunscreen products, it is prohibited to use claims such as. "*Sunblock*", "*Waterproof" or "Sweatproof*". The claims are misleading for the consumer, because the sunscreen products do not fulfill these properties [48].

2.3.3.4 SPF Testing

The recommended SPF test is similar to the COLIPA SPF test, albeit with a few various test parameters. The number of test subjects, to analyze the SPF of a sunscreen product, has been reduced to 10 - 13 subjects. A minimum requirement of the SPF testing is to receive 10 valid tests. Furthermore, the test site/subsite specifications (test site: 30 cm^2, subsite: 1 cm^2, subsite separation" 0,8 cm) have been adopted to equalize the specifications of the SPF testing methods with global tests. The solar stimulator specifications used in the COLIPA SPF test have been adopted, whereby it is permitted to use a smaller beam multiport simulator. The UVA irradiance (UVA I: 340 - 400 nm; UVA II: 320 - 340 nm) should be 20% and 60% of the overall UV irradiance. The sunscreen standard should show consistency in the test performance. The "padimate o/oxybenzone standard" is the most suitable sunscreen standard used for SPF 15 and more. The sample application is conducted with fingercot, although pre-saturation is no longer required [48].

2.3.3.5 Broad Spectrum testing

In vitro broad spectrum testing has to be performed to evaluate the UVA and UVB protection properties in accordance with the 21 CFR 201.327. Not all active ingredients are able to pass the broad spectrum test, which means they are allowed to claim SPF values but are not allowed to claim broad spectrum protection [49].
FDA recommends using a modified "critical wavelength test" instead of the current "critical wavelength test". The modified test has changed a few characteristics and differs from the ISO in vitro UVA test method. For this "critical wavelength test method", PMMA (polymethylmethacrylate) plates are required that have to be rough (2 - 7 microns) and the density of the sunscreen application has to be 0.75 mg/cm^2. The sunscreen product should be applied on the plate. The dose of irradiation should be 4 MED (minimal erythema dose), which is equivalent to an erythemal effective dose of 800 J/m^2. The critical wavelength is defined as the wavelength at which 90% of the UV absorbance area is available under the curve (UV spectrum 290 - 400 nm). The critical wavelength provides information about the extent of protection. Broad spectrum protection means protection against wavelengths of 370 nm [50], [51].
with CFR

2.3.3.6 Water resistant testing

A sunscreen product with an SPF protection label indicates to the consumer that the protection retains for some time after immersion in water. Water resistant tests are an alternating to the water-immersion and drying phase. After the application of the sunscreen, the subjects are immersed in the water for 20 minutes for two times with a 15-minute drying period in between. Subsequently, subjects are be tested in accordance with the SPF test

method. The water resistant claim that can be used is “40 minutes”, although claims of 80 minutes can be used if the immersion-drying period can be repeated four times [49], [50].

2.3.3.7 Stability testing

First of all, a testing program has to be compiled so that the stability parameters of a drug product can be investigated. The testing results are needed to determine suitable storage conditions and expiration dates. In the testing program, the sample size and the time intervals of testing should be included, based on statistical criteria so that the results are valid. The storage conditions for the testing samples and the testing methods have to be assigned. It is also very important that the testing samples have the same container-closure system as the marketed product. The number of batches for testing should be sufficient to obtain data about the expiration date. A tentative expiration date can be determined by conducting accelerated studies. It is also recommended to investigate full shelf life studies to verify the expiration date [52].

2.3.3.8 Proposed Rule 2011

The main object of the proposed rule is to limit the highest SPF value to 50+ for OTC sunscreen products. The SPF limit of 50+ is harmonized with other countries, e.g. European Union, Australia and Japan. Consequently, sunscreen products are only allowed to use the maximum SPF label of 50+. The use of SPF values of 60 or 80 is prohibited, because FDA has not received sufficient data about an extra clinical benefit for SPF value above 50. Furthermore, the validation of the SPF test is conducted for sunscreen products with an SPF value of 50 and not with SPF above 50. This is important for the preciseness and reproducibility of the SPF test. Finally, the SPF value on the label is very important for consumers’ safety and the label should not mislead the consumer [53].

2.3.3.9 Advanced notice of proposed rulemaking (ANPR)

FDA requested additional information for OTC sunscreen products to receive more data about different dosage forms (oils, lotions, creams, gels, butters, pastes, ointments, sticks, sprays). This information should be incorporated in the prospective OTC monograph. In particular, FDA requested data about sprays, or safety and efficacy reasons. Furthermore, FDA also needs additional data on the labelling and testing of spray dosage forms. FDA identified some dosage forms (e.g. wipes, towelettes, powders, body washes, shampoo) that were not considered suitable for the inclusion in the future OTC monograph [54].

2.3.3.10 Advertisement

The Federal Trade Commission is responsible for the advertisement and promotion of OTC drug products in the United States. FDA is only responsible for the advertisement and promotion of all drug products with a prescription. Both agencies are interested in protecting the consumers and ensuring public health. Advertisements and promotion have to fulfill some standards to be accepted by the Federal Trade Commission, as follows:

- Advertisements have to be true and not mislead the consumer

- Only evidence-based claims are accepted
- No unfair advertisements

The Federal Trade Commission is conducting a special assessment to evaluate advertisements from the consumer perspective. The evaluation is characterized by checking words, phrases and pictures and their expression, as well as whether they are misleading. Claims that are related to health must have scientific evidence [42].

2.3.3.11 Nanoparticles in sunscreen products

In 2008, a citizen petition was filed to point out that a lack of safety testing regarding the use of titanium dioxide and zinc oxide in sunscreen products. The users were worried that nanoparticles could penetrate the skin and could cause inflammation and a reaction of the immune system. The Center for Drug Evaluation and Research (CDER) made a statement concerning this issue, namely that the FDA has recently conducted animal testing and concluded that the nanoparticles are unable to penetrate the human skin. The review of published studies demonstrates no safety issue regarding sunscreen products in liquid dosage forms. Nanoparticles in sunscreen products that are applied on undamaged skin are unable to penetrate through the epidermis and cannot reach the bloodstream. Spray sunscreen products show a lack of safety data, prompting the necessity of further investigation [55].

2.3.3.12 Good manufacturing Practice

In the Federal Register 21 CFR part 211, the GMP requirements for finished pharmaceuticals are determined. It is a detailed description of different requirements, e.g. qualification of the staff and its responsibilities, rooms and facility, equipment, all required testing methods, as well as checking labelling and packaging, etc. The manufacturer has to take into consideration all requirements to assure a good quality of the drug product [56].

2.3.3.13 Reporting of Adverse Events

The responsible person (manufacturer, packer, distributor) is accountable for the submission of any report of a serious adverse event connected with a drug. Together with the report, the label and the retails package also have to be submitted. Additionally, the responsible person is also responsible for the submission of follow-up reports of new medical information related to the serious adverse event. All reports received within one year of the first report also have to be submitted to the agency. All serious adverse event reports submitted via mail or telephone or follow-ups of new medical information have to be submitted to FDA within 15 business days of receipt. The following information has to be provided:

- Data of the patient/consumer (initials, gender, age, date of birth, patient identification number)
- Data of the reporter (patient/consumer, doctor, pharmacist)
- Information about the drug (active ingredient, brand name of the drug)
- Serious adverse event (death, life-threatening event, inpatient hospitalization, disability or incapacity, birth defect) [57]

3 COMPARATIVE DISCUSSION

3.1 Classification of sunscreen products

Sunscreen products are regulated differently in all three regions. The purpose of a cosmetic and drug is variable; for instance, a cosmetic sunscreen product has a different primary purpose than a therapeutic sunscreen product or OTC sunscreen product.

In Europe, sunscreen products are regulated as cosmetic products within the scope of the Directive 76/768/EEC and the Regulation 1223/2009/EC. The Regulation provides a clear legal framework for all demanded requirements of cosmetic products (see section 2.1).

In Australia, sunscreen products are regulated as therapeutic goods and cosmetic products. The TGA is responsible for the therapeutic sunscreens and NICNAS, while ACCC are responsible for the cosmetic sunscreen products (see section 2.2.2).

Therapeutic sunscreen products are regulated within the scope of the Australian Regulatory Guideline for Sunscreens, whereby the guideline refers to the Therapeutic Goods Act, Therapeutic Goods Regulation, Labelling Order and Therapeutic Goods Advertising Code, as well as the revised Sunscreen Standard (see section 2.2.2). Therapeutic sunscreen products are divided into “listable” (primary and secondary sunscreens) and “registrable” (sunscreens with other therapeutic claims) and “exempt sunscreen products” (primary sunscreens with ingredients of human/animal origin, SPF < 4). Sunscreen products that are not listable, registrable, exempt or cosmetics must be assessed by the TGA (see section 2.2.1).

The cosmetic sunscreens (excluded sunscreens) are regulated by the Industrial Chemicals (Notification and Assessment) Act, Cosmetic Standard and Cosmetic Guidelines. Cosmetic sunscreen products are divided into “make up products for the face and nails” and “skin care products” (section 2.2.3).

In the United States, sunscreen products are regulated as OTC drugs without an approved application by the FDA. Cosmetic products with sunscreen claims are regulated as drugs, because the prevention of a disease or other effects on the human body are essential. For products marketed without an approved application, a final monograph is the legal base. The monograph for sunscreen products was planned to become effective in 2001, although it has been postponed without a new effective date. Accordingly, this means that no effective monograph is available for sunscreen products. However, there exists an enforcement policy as long as the monograph does not come into force. This enforcement policy is based on the final and proposed rule, as well as the advanced notice of proposed rulemaking (see section 2.4.1).

3.2 Responsible Person

In all three regions, a responsible person or sponsor has the responsibility of ensuring that the sunscreen products comply with the legal requirements. The product has to be tested to be safe and effective in use. Moreover, the labelling of the product has to be checked.

In Europe, a responsible person is a legal or natural person assigned within the European Union, who has to ensure that a sunscreen product complies with the legal requirements. This person can be the manufacturer, importer or distributor. The manufacturer is responsible for the manufacturing according GMP and the distributor has to monitor the correct labelling and shelf life of the product. The responsible person has to undertake corrective measures to ensure that an incompliant product is recalled or withdrawn from the market. By incurring a risk to human health, the responsible person must inform all the authorities where the product is marketed. The authority can request specific data about the sunscreen product (see section 2.1.4.1).

In Australia, the responsible person for a therapeutic good is named the “sponsor”. This is a legal person who is responsible for the import, export and/or manufacture of a product or its arrangement. The sponsor does not work on the behalf of another person. The sponsor has to ensure that the sunscreen product complies with the legal requirements, e.g. testing of the product. The sponsor has to report all adverse events to the authority (see section 2.2.4.1).

The name of the responsible person has to be on the label of the sunscreen product in the US. This can be the manufacturer, packer or distributor (see section 2.4.3.1).

3.3 Submission Type

In Europe, sunscreen products have to be notified via the Cosmetic Products Notification Portal. The responsible person has to provide data about the sunscreen product and its ingredients, name of the countries where the product will be marketed, contact details, labelling of the product, etc. This information is also accessible for all national authorities. The authorities are responsible for the monitoring of cosmetic products. Poison centers also have access to this information to help people in the case of an emergency (see section 2.1.4.2).

In Australia, most therapeutic sunscreen products have to be listed in the Australian Register of Therapeutic Goods. These are primary and secondary sunscreens with established claims and SPF > 4 or those that contain ingredients of human/animal origin. The required information has to be completed in the Electronic Listing Facility. Information that has to be provided includes SPF testing results, data that the sunscreen does not cause skin irritations or a TSE certificate providing information about the risk transmitting TSE (see section 2.2.3).

Sunscreen products that are not listed, exempt or cosmetics must be registered. Sunscreen products with active ingredients that are not listed in the Australian Regulatory Guideline or sunscreens with ingredients listed in the SUSMP, as well as those with therapeutic rather than sunscreening claims, have to be registered. For the registration process, data about quality, safety and efficacy has to be submitted to the TGA for the assessment procedure (see section 2.2.3).

In Australia, cosmetic sunscreen products have to be registered by NICNAS before they are placed on the market. For importers and manufacturers of industrial chemicals, it is mandatory to register with NICNAS. An application form and the proof of payment has to be

sent to NICNAS, before a registration certificate is issued. The registration must be renewed every year (see section 2.3.4.1).

In the United States, OTC sunscreen products have to be registered and listed by FDA. Therefore, the owner or operator of an establishment is responsible for the submission of a drug application, which has to be renewed every year. Special information is required for the submission and a D-U-N-S® is also needed. At the time point of the first registration, listing information also has to be submitted. The private label distributor (PLD) first has to apply for a NDC Labeler Code and subsequently can perform the submission with the required information. The PLD is responsible for the fulfillment of all requirements for the listing and he has to inform the owner of the establishment that the listing by FDA has been completed. If an update of the listed drug or labelling occurs, the change has to be reported to FDA (see section 2.4.3.2).

3.4 Testing of SPF and Labelling claims

In Europe, it is important to verify the minimum efficacy to receive adequate protection against both types of UV rays. The SPF testing follows the international SPF testing method, measuring the minimum erythemal dose on protected and unprotected. Valid testing results are needed from about 10 to 20 test persons, while in-vitro testing methods and photo-degradation should also be used. The claims allowed for labelling indicate the level of protection, which are “low” (SPF 6, 10), “medium” (SPF 15, 20, 25), “high” (SPF 30, 50) and “very high” (SPF 50+). The UVA protection factor is 1/3 of the labeled SPF value (see section 2.1.4.4).

For the SPF testing, Australia uses the revised sunscreen standard, based upon a minimum 10 valid testing results. For the analysis of the broad spectrum performance, the International Standard ISO 24444:2012 is used. The labeled claims are similar to Europe, with the protection level ranging from low to medium, high and very high. However, some SPF levels are only available in Australia and these are SPF 4, 8 and 40. All primary and secondary sunscreens with an SPF 15+ have to pass a broad spectrum testing. These sunscreen products are allowed to use the claim broad spectrum, which is uncommon in Europe (see section 2.2.4.5).

Subsequent to the revision of the Australian Sunscreen Standard for therapeutic sunscreens products, the revision of the Cosmetic Amendment (Sunscreen) Standard followed shortly thereafter. The level of protection has the same categories of low, medium/moderate, high and very high. The SPF values that can be labeled are between 4 and 50+, whereas only the face and nail products are allowed to use the SPF between 20 and 50+. The highest SPF value for skin care products is SPF 15. Broad spectrum performance is mandatory for all skin care products and all face and nail product with an SPF value of 30 or higher (see section 2.3.2).

The SPF test used in the United States is similar to the COLIPA SPF test, although it differs in the test parameters. The number of test persons is reduced to 10 - 13, whereas 10 positive testing results are sufficient. FDA stated that the padimate O/oxybenzone standard is the most suitable for the testing of SPF 15 or higher. Sunscreen products with an SPF < 15 are not

allowed to claim “broad spectrum”. Only sunscreen products with SPF > 15 can label the claim “broad spectrum”, if the testing was valid (see section 6.3.1 – 6.3.3). In the proposed rule, the maximum SPF value is limited to SPF 50+. There is no sufficient data for allowing higher SPF values. This SPF limit is the same as in Europe, Australia and Japan (see section 2.4.3.3).

3.5 Water Resistant testing and labelling claims

The water resistant testing is principally the same in all three regions. It is a measurement of the SPF after water immersion, which takes place for two times 20 minutes or four times 20 minutes. The difference lies in the labelling of the water resistant claims.

In Europe, the claims that can be used are “water resistant” and “very water resistant”. Claims such as “Sun blocker” or that a reapplication is not necessary are not allowed (see section 2.1.4.5).

In Australia, sunscreen products with an SPF of 15 to 30 can use the water resistant claims up to 2 hours, while sunscreen products with and SPF 30, 40, 50 or 50+ can use the water resistant claim up to 4 hours. The use of claims that a sunscreen product is “waterproof” or “sweatproof” or it is a “Sunblock” are misleading and therefore such claims are not allowed (see section 2.2.4.6). For cosmetic sunscreen products, water resistant claims are not allowed (see section 2.3.3).

In the United States, the claims used for water resistant are different from Europe and Australia. According to the test procedure, the claims used relate to the period of time. This is “40 minutes” or “80 minutes”, informing the customer after which time reapplying of the sunscreen product is necessary (see section 2.4.3.2.1).

3.6 Stability Testing of Sunscreen Products

While sunscreen products have to fulfill physical, chemical and microbiological quality standards, it is also very important to know whether the product is compatible with the container. The condition of storage and use, as well as the transport, will influence the shelf life of a product. The stability is investigated with real time testing or accelerate testing. This process is very similar in all three regions.

In Europe, the stability testing starts during the development of a sunscreen product, whereby samples from laboratory batches are stored under special conditions. The next step is to investigate testing with samples of the batch of the marketed product. Testing with the marketed container is important, especially if different sizes are available. In this case, the smallest size should be used for the stability testing. Accelerate testing is very common by storing testing samples under temperatures between 30 °C to 45 °C for 1 - 3 months, in order to obtain tentative data about the shelf life. Real time testing is essential and has to be monitored to ascertain the precise shelf life. A given statement or symbol have to be put on the label, in order to determine the minimum durability (stable for ≤ 30 months) or period of time after opening (stable for > 30 months) (see section 2.1.4.6).

In Australia, it is also necessary that the expire date is claimed on the label. TGA can request for data about the shelf life at any time, although it is not required for the listing process. Real time studies are performed with production scale batches. The testing takes place directly after production and then once a year until end of shelf life of the batches. Accelerated testing is conducted at lower temperatures between 10 °C to 15 °C for a period of 6 - 9 months. If a sunscreen product contains water, microbiological stability has to be analyzed, while if preservatives are used, then the efficacy also has to be checked. Monitoring during the testing is essential. The shelf life for therapeutic goods is limited to five years (see section 2.2.4.7).

The design of a testing program is very important in the USA. In order to investigate the proper storage conditions and expiration date, a testing program with testing methods, storage conditions, sample size and testing intervals and statistical methods have to be determined at the beginning. Accelerate studies are recommended to identify the tentative shelf life and full shelf life studies are necessary to obtain sufficient information about the real expiration date (see section 2.4.3.5).

3.7 Consumer Information and advertising claims

Apart from the SPF and water resistant claims, further information is required on the packaging and container. In Europe, the contact details of the responsible person, country of origin, content, minimum durability/period after opening, function, list of all substances and protective measures for use are stated on the label. The use of symbols for the minimum durability and time period after opening are also very common.
Advertising claims have to comply with the following principals: truthfulness, evidential support, honesty, fairness and informed decision making. If claims do not apply then they are forbidden. It is worth mentioning that claims about “no animal testing” are explicitly allowed (see section 2.1.4.3).

In Australia, the information on the label of therapeutic sunscreen products must have a special format, namely in English language, in clear and legible letters with fixed height (except AUSTL/AUSTR number), safely printed or added, while using the product should not lead to damaging the label or it becoming unreadable. The label should not lead to confusion with any other product. The information on the label has to be true and not misleading and should not lead to unrealizable expectations.
Listed therapeutic sunscreens with broad spectrum and SPF 30 or more are allowed to label special claims, e.g. “*May reduce the risk of some skin cancers*”. Therapeutic sunscreens with an SPF of 4 or higher are allowed to claim “*Can aid in the prevention of premature skin ageing”*. The use of non-therapeutic claims is also acceptable e.g. “*contains Vitamin E”, etc.* The indications and the claims have to be true and not misleading and the evidence of these claims have to be verified first. Company logos, symbols or consumer information on the label will be accepted as long as they do not lead to confusion and comply with the legal requirements.
The container and the primary package must provide the product name, dosage form, AUSTL or AUSTR number, SPF value together with a description of the protection, broad spectrum and the “water resistant” statement and volume (ml or gram), while the name of the ingredients, storage conditions and expire date and the batch number must also feature on the

container. It has to be highlighted whether the product is a sunscreen or a moisturizer with sunscreen (SPF), while additional information about wearing of cloth and avoiding of extended sun exposure should also be added to the label. The correct use of the sunscreen product should be highlighted, as well as warning statements, e.g. no applying on diseased skin, avoid contact with the eyes and spray sunscreen should not be inhaled. The name and contact details of the sponsor has to be mentioned. Moreover, there are also special requirements for small containers. An immediate container (volume ≤ 20 ml) is enclosed in a carton, upon which the name of the product, pharmaceutical form, list of all active ingredients, volume and the batch number have to be added (see section 2.2.4.3).
The advertisement is essentially the same as in Europe, although certain information has to be provided, e.g. information about the indication, directions for use and warning statements (see section 2.2.4.4).
Cosmetic sunscreen products also have special labelling requirements. The maximum SPF for face and nail products is SPF 50 + and for skin care products the SPF is 15. Water resistant claims and therapeutic claims are forbidden. All skin care products and face and nail products with an SPF 30 must claim "*broad spectrum*". The list of ingredients should include colour additives, flavours and fragrance (if available) and the English name the International Nomenclature Cosmetic Ingredient name have to be used. If the size of the container is too small to list all the ingredients, it should be clearly stated where the consumer can find the essential information (see section 2.2.3).

In the United States, OTC sunscreen products can use broad spectrum claims ("*decreases the risk of skin cancer and early skin ageing caused by the sun*") and water resistant claims (40 minutes/80 minutes) on the PDP, when the SPF value is 15 or higher. These are OTC sunscreen products with an SPF 2 – 14. Claims that are allowed include: "*Helps to prevent sunburn*". A statement about UV protection (UVA/UVB) is not required. The order of the information is exactly predetermined on the label. In particular, the direction for use and the warning statements are consistently specified in order that misunderstandings should be avoided. Advice about storing the sunscreen while sun bathing is also mentioned (see Table 6).

3.8 Safety of the ingredients for use in sunscreen products

All substances that are strictly forbidden, restricted or UV filters that are allowed for the use in cosmetic products are mentioned in the Regulation 1223/2009. Before a sunscreen product is put on the market, a safety assessment is needed in Europe, whereby a product safety report and product information file is required. The safety report contains information about the composition, physical, chemical and microbiological properties, conditions for use, as well as data about any risk potential, together with a toxicological analysis. During the safety assessment, all the information will be evaluated and the results of the safety statement will influence the labelling of the product. In Europe, it is also necessary to create a product information file summarizing information of the safety statement, GMP requirements, animal testing information and all effects of the product (see section 21.4.7-2.1.4.8).
For therapeutic sunscreen products, only the use of approved ingredients and excipients by the TGA is allowed. However, if a new ingredient or excipient is used for a therapeutic

sunscreen product, then scientific data about its safety and efficacy is required (see section 2.2.4.10 – 2.2.4.12).
In Australia, the ingredient of cosmetics are industrial chemicals. New and well-known chemicals will be evaluated during the risk assessment by NICNAS to ensure that no risk for human or environment occurs (see section 2.2.5.4.1).
Substances within an OTC monograph are recognized as safe and effective. Before the substance is included in the monograph, an evaluation of safety and efficacy is required (see section 2.3.1.1).

3.9 Animal testing

Europe is very interested in the prevention of animal testing used by cosmetic products, although there is still a lack of alternative testing methods. The development of new testing methods is still ongoing. The International Cooperation on Alternative Test Methods (ICATM) is a voluntary initiative in Europe, Canada, USA, Japan and South Korea that supports coordinating the scientific evaluation and validation of alternative testing methods. ICATM is also interested in entering into a dialog with the cosmetic industry of Australia, Brazil, China and Saudi Arabia to discuss alternatives to animal testing, nanomaterials, allergens, etc..
In Germany a National Centre for Documentation and Evaluation of Alternatives to Animal Experiments (ZEBET) exists. It was founded 20 years ago and it is engaged in the developing and validation of alternative testing methods for cosmetic products. ZEBET works in line with European and German law. Moreover ZEBET has also established a AnimalALT-ZEBET database that offers plenty of information about alternative testing methods.
In 2007 the REACH Regulation 1907/2006/EC came into force, in order to improve the safety of human health and the environment. The use of alternative methods in order to assess hazards of substances are also included in this regulation. All chemical substances that are used in a cosmetic product for instance a sunscreen product have to be registered. For this step all required data about physical, chemical, toxicological and eco-toxicological properties have to be provided. This means that a lot of substances need to be re-assessed. In this context a new procedure for the acceptance of new alternative testing methods was introduced by all EU member states and the OECD that should ensure a approval process within 5 months (see section 2.1.4.10).

3.10 Reporting of Adverse Events

The serious adverse event reporting for cosmetic products was implemented in the European law by means of the Regulation 1223/2009. This was an important step for cosmetic products regarding public safety. The responsible person, the distributor as well as consumers and health professionals are requested to report every serious adverse event to the competent authorities. In case of need, the responsible person has to recall or withdrawn the cosmetic product or undertake corrective measures (see section 2.2.4.10)

In Australia, it is also mandatory for the sponsor to report any adverse event of a medicine to the TGA, although customers and health professionals can also report (see section 2.2.4.4).

This is similar in the United States, because the responsible person has to report all adverse and serious adverse events, whereby serious adverse events have to be reported within a timeframe of 15 days. Moreover, follow-up reports also have to be submitted (see section 2.4.3.11).

3.11 Good manufacturing practice

If a cosmetic product is manufactured in Europe or Australia, it has to comply with the harmonised standard (ISO 22716), because this is mandatory for all cosmetic companies all over the world (see section 2.2.4.10).
Therapeutic sunscreens are also manufactured according to GMP, whereas the TGA determines the GMP requirements for drugs. A manufacturer needs a license for manufacturing issued by the TGA. If it is a foreign manufacturer, then a GMP clearance is required. If a product standard (monograph) is available for listed or registered therapeutic goods, the manufacturer also has to consider this (see section 2.2.5.5).
In the United States, the manufacturer is also responsible for the assurance of the product's quality. All the requirements determined in the Federal Register have to be fulfilled (see section 2.2.4.11).

3.12 Nanoparticles

Nanoparticles are used in sunscreen products in all three regions. They are recognized as safe if they are available in a liquid dosage form. Nanoparticles in spray dosage forms are not considered as safe, thus prompting the need for further investigation (see section 2.1.4.9; 2.2.5.5).

In Europe, nanoparticles have to be notified, because all the nanoparticles will be evaluated by the Scientific Committee on Consumer Safety and the Commission is responsible for preparing of a list with all known nanoparticles used in cosmetic products (see section 2.1.4.9).

4 SUMMARY

Sunscreen products have a long history, dating back to era of the Egypt's. Sun protection was already important at that time. Since then, sunscreen products have been further developed, while the scientific knowledge about the different UV rays and its effects on the skin has also been investigated. Sun exposure can lead to sunburn, skin ageing and skin cancer. Sunscreen products and other factors play an important role in the prevention of skin cancer. How are sunscreen products regulated in Europe, Australia and Unites States? Is it a cosmetic or a drug?

In Europe, sunscreen products are regulated as cosmetic products. Therefore, a notification is required before a cosmetic product can be put on the market. In Australia, sunscreen products are regulated as therapeutic sunscreen products and cosmetic sunscreen products, the former of which are divided into primary, secondary and exempt sunscreen products and must be

listed or registered by the TGA. The Therapeutic Goods Administration (TGA) is responsible for therapeutic sunscreen products and the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) is responsible for the cosmetic products. All the chemical ingredients of the cosmetic sunscreen product have to be registered by NICNAS. The Australian Competition & Consumer Commission (ACCC) is responsible for the labelling of all cosmetic products. The cosmetic sunscreen products are divided into make-up and skin care products and are also called “excluded sunscreen products”. In the United States, sunscreen products are regulated as Over-The-Counter (OTC) sunscreen products without an approved application and the FDA is the responsible authority. Before an OTC sunscreen product can be put on the market, a registration or listing is required. At present, an OTC monograph for sunscreen products is available, although it has not come into force since it was first published. The reason for this is that FDA is collecting further information, which should be included into the OTC monograph in the future. In the meantime, the current enforcement policy will be continued until the OTC monograph becomes effective.

The three different frameworks of Europe, Australia and the United States show a conformity within the principal requirements. The testing procedures of SPF, water resistant, broad spectrum, stability are similar or identical, based upon the international harmonisation of the testing procedures. Australia is the only country with a Sunscreen Standard, citing all testing procedures and labelling claims.

The use of nanoparticles is also very common in sunscreen products. Not only is the safety of therapeutic sunscreen products or OTC sunscreen products evaluated accurately, but also the safety of cosmetic sunscreen products. The reporting of adverse events or serious adverse events is mandatory for both cosmetic sunscreen products and therapeutic or OTC sunscreen products. The quality of sunscreen products also has to be assured, which guaranteed by the GMP requirements for cosmetic sunscreen products, therapeutic sunscreen products and OTC sunscreen products. The requirements for cosmetics are quite high and thus there is not a significant difference with the GMP requirements for therapeutic sunscreen products and OTC sunscreen products.

The most differences can be found in the labelling of the sunscreen products. The protection level of the SPF is the same for all three regions: low, medium, high, very high. In all three regions, the highest value for SPF claims is SPF 50+. In Europe, the labelling of UVA/UVB is common, whereas in Australia and the United States the term broad spectrum is used. In Europe, the claims water resistant and very water resistant are used, whereas the claims in Australia are water resistant up to two hours and water resistant up to four hours. In the United States, the term water resistant (40 minutes) or water resistant (80 minutes) are common.

Finally, sunscreen products are regulated differently in Europe, Australia and United States, although the commonalties outweigh the differences. Cosmetic sunscreen products are comparable with therapeutic sunscreen products or OTC sunscreen products.

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