Regulatory Concerns for Nanomaterials in Sunscreen Formulations

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Abstract: Background: There has been a phenomenal rise in the nanomaterial-based cosmetic formulations in the market, raising serious concerns over the possible biological impact on humans, animals and the environment as a whole. However, scarce reports can be found on the safety assessment of nanomaterials incorporated in cosmetic formulations including sunscreens. Hence, uncertainties loom for their safe use in cosmetics including those applied dermatologically. Unfortunately, not much research has been devoted to assess the safety profile of nanomaterials in cosmetics and the possible health hazards. As a large number of nanotechnological sunscreen products containing diverse sun filters against UV exposure are penetrating the market, the importance of adequate assessment of nanomaterial exposure, its toxicokinetics including biodistribution, and other health risks is now widely recognized.

Objective: The write up presents an overview of the nanomaterials used in sunscreen products and discusses the various laws and regulations in force in various countries. The review focuses on the current safety and regulation of nanomaterials in sunscreens.

Conclusion: While many countries have their own set of regulatory guidelines, it is high time to have a globally acceptable guideline framework to protect both the consumers and manufacturers for safe use, manufacture and sale of nanotechnology-based cosmetics. Harmonization across the globe is desirable.

Keywords: Sunscreen, nanomaterials, nanoparticles, regulations, SPF, ultraviolet.

1. INTRODUCTION

Cosmetics serve the primary function of maintaining/modulating the physical appearance, correcting body odors and maintaining the skin in ambient condition under various (unfavourable) circumstances. Furthermore, the recognition of the functional aspects of skin care products has led to understand the efficacy and safety of skin care products in promoting good health as well [1]. The nanotechnological science has helped the researchers to find novel and purposeful cosmetics. Highly promising and extraordinary qualities of nano-ingredients have paved the way for the next industrial revolution in cosmetic industry including sunscreen formulations. Superior UV protection, improved dermal penetration, extended effect and superior organoleptic properties rendered by the nano-ingredients have attracted the cosmetic manufacturers [2]. The market, of lately, has witnessed a plethora of nanomaterials based consumer products which may be attributed to the nanotechnological advancements. Owing to the wonderful and unique physical characteristics possessed by the nanomaterials, a noticeable transformation in the performance and applications of these consumer products and other healthcare products has been realized [3]. The consumer acceptance of nanotechnology-based cosmetics is the driving force for tremendous rise in the research inputs for the same. However, the assessment of...
the toxicokinetics and safety aspects of nanomaterials is of paramount importance both to the pharmaceutical industry and regulatory authorities. As more and more nanotechnology-based products are entering in the market, the development of nanotechnology-related policy frameworks, safety guidance and nanomaterial handling has been initiated by various regulatory bodies internationally [4].

2. SUNSCREENS ULTRAVIOLET

(UV) radiation emitted by the sun is composed of three distinct wavelengths: UVA rays, UVB rays and UVC rays [5]. The ozone layer fails to completely absorb the UVA rays in the wavelength range of 320-400 nm and UVB rays ranging between 290 and 320 nm making the skin vulnerable to the detrimental exposure to irradiation, while the UVC rays are blocked by the ozone layer. This irradiation may lead to generation of reactive oxygen species, DNA damage, skin tissue damage challenging skin’s defence format and activation of various signal transduction pathways [6, 7]. Sun protection is essential for prevention of skin cancer as more than 90% of skin cancers (non-melanoma) and about 86% of melanos are directly linked to ultraviolet rays of the sun.

The high prevalence of malignant melanoma in spite of significant awareness and usage of sunscreens is a matter of serious concern. Sunscreens/sunblocks have been in use since 1930s, to prevent or minimize the adverse dermatological effects of the sun rays on skin [8-10]. Sunscreens usually contain UV filters/blocks (Table 1) which either absorb (organic filters) or scatter and reflect (inorganic filters) the UV radiation and hence afford skin protection against the detrimental effects of sun exposure [11]. It is a common practice to use an appropriate blend of the sun filters to optimize the efficiency of the sunscreen/ sunblock product. With the advent of nanotechnology, the sunscreen manufacturers have been liberal to incorporate nano-ingredients in these products to improve product performance and consumer acceptance. However, safety of these ingredients in sunscreens is debatable and environmentalists have raised serious concerns regarding potential toxicities [12]. In a manufacturing unit set up, the workers are at constant risk of exposure to airborne nanoparticles. Inhalation of nanoparticles may pose serious threat to health on account cumulative deposition in lungs and is significantly dangerous occupational hazard. Regulatory bodies across the globe have strongly discouraged the use of fine (nanosized) powder form of any cosmetic materials, including spray sunscreen products that incorporate titanium dioxide or zinc oxide particles in the formulation. Titanium dioxide, which is quite often used in many sunscreen products, has been classified as a possible inhalation carcinogen [13]. As complete elimination of metal nanoparticles from the lungs is practically impossible and the particles may reach the bloodstream from the lungs following inhalation, continual exposure to nanoform is a serious biological threat. Once in the systemic circulation, the insoluble nanoparticles can cause extensive organ/tissue damage. Likewise, oral ingestion of nanomaterials from cosmetics is yet another serious concern. Further, nanoparticles in the lip sunscreen formulations are likely to be ingested orally which may cause damage to the gastrointestinal lining by adhering to it [14]. However, the risks of nanoparticles ingestion may be unpredictable following biotransformation in vivo. Though titanium dioxide has a proven track record of safe usage as a coloring material in food items, a very careful toxicokinetic evaluation is highly sought, especially for the sunscreen products intended for pediatric use. Despite alarming concerns across the globe regarding the biological hazards of using nanomaterials in sunscreen, fewer research activities have been put on record to assess the potential risks. The human race cannot let itself be ignorant about the risk associated facts. Undoubtedly, the huge effective surface area that garners beneficial effects supposedly plays a key role in biological toxicity via increased production of free radicals leading to protein(s) and DNA damage [15]. Keeping in view the enormous damage potential, the practicing skin physicians have recommended for compulsory package labelling guideline on cosmetics containing nano-ingredients. Logically speaking, this is essential to protect the susceptible group of the population [16, 17].

3. NANOMATERIALS

Nanomaterials are defined as materials with either external or internal dimension in the nanoscopic range, with ‘nanoscope’ defined as the particle in size range of 1 - 100 nm [18, 19]. The
European Union definition exclusively includes natural or accidentally produced nanoparticles [20], while the definitions across the globe clearly define nanoparticles as nanomaterials that are manufactured, engineered or produced “intentionally” [4]. The properties of materials significantly change at nanoscale, as the laws of classical physics give way to quantum effects. Therefore, the physicochemical behavior of nanomaterials can be quite different from those of larger particles of the same substance. To name a few, the altered properties can include organoleptic properties like colour and texture; and physicochemical properties like solubility, physical strength, electrical conductivity, surface area and magnetic behaviour. The large surface area-to-mass ratio makes the nanomaterials highly reactive and the increased reactivity, in turn confers explosive and photoactive characteristics to the nanosized particles [17].

4. NANOMATERIALS IN COSMETICS

The appealing properties of nanomaterials have garnered considerable interest amongst cosmetic manufacturers for its increased usage. In cosmetic product development, nano-ingredients find a place in products with anti-aging effects, improved penetration deep into the skin layers, thereby enhancing the therapeutic effects of the drug moiety and for products offering photoprotection [21]. The so-called “nano-cosmetics” are thus the cosmetic formulations that include actives (nanosized) or other nanostructured ingredients with superior performance in comparison to the conventional products [22]. Diverse nanomaterials are already in use in the currently marketed cosmetic products, including nanoemulsions, lipid nanoparticles, nanovesicles and mineral nanoparticles namely silver, calcium fluoride, titanium dioxide, alumina, zinc oxide, silicon dioxide and copper [21]. Nanoparticles in cosmetics are classified as (i) labile nanoparticles (liposomes, microemulsions, nanoemulsions) and (ii) insoluble particles (titanium dioxide, quantum dots, fullerenes). Nanovesicles (liposomes and niosomes) have found applications in beauty products as delivery vehicles for anti-aging actives and the lipid nanoparticles have been identified as better performers. Carbon nanomaterials are also being investigated for cosmetic product development. Apart from nanocarriers, the actives like avobenzone, retinol/isotreti-

5. NANOMATERIALS IN SUNSCREENS

Increased awareness of detrimental effect of sun exposure has catapulted the use of sunscreens/sunblocks. Frequently, formulation development of sunscreen products involves using contrasting ingredients for opposite functions in the same formulation leading to various technical and toxicological issues. From consumer’s viewpoint, optimal spreadability is often the primary requirement which is opposite of the water resistance property. Likewise, the optimum concentration of sun filters may hamper the textural attributes and affect the solvents needed for product stability. Sun filters range from particulate sunscreens (organic and inorganic particulate sunscreens) and soluble sunscreens (oil and water soluble). Among the ingredients used, the popular ones are the metal oxides (ZnO and TiO2) because (i) these confer efficient protection against sun radiations with relatively lesser health issues; and (ii) do not degrade in the sun. In comparison to titanium oxide, ZnO provides stronger protection against UVA radiations but TiO2 has superior protection capabilities than most commonly used other ingredients. The limitation on use of these materials is that the conventionally available products of these leave behind a chalk-like residue on the site of ap-
lication, however, upon size reduction to nanoscale, it appears transparent [17]. The nanoparticles based sunscreens commercialized in US market contain either ZnO or TiO2. The ZnO sunscreen lotions that were white and chalky are now produced using ZnO nanoparticles with more elegant look and texture [25]. Furthermore, the attributes like dispersibility, efficacy, photostability and minimal skin contact have been improvised by using nanofilters coated with neutral materials like aluminium oxide, silica, glass, polysiloxane compounds [24]. Titanium dioxide has capability to block both UVA and UVB rays. An ingredient of many sunscreen formulations is considered the most versatile sunscreen [26]. Till date, metal oxide based sunscreen lotions are most popular due to the following reasons: (i) Particle structure: Smaller the particles better the sun protection and lesser the protection against UVA radiation. The manufacturers must keep in mind that greater transparency (cosmetic appeal) is provided by smaller particles but on the other hand, larger particles are needed for better UVA protection. This is why, zinc oxide (larger particles) based sunscreens afford superior UVA protection than titanium dioxide (smaller particles) based sunscreens that often looks clear on the skin. (ii) Poor skin penetration: Research inputs claim that administration of large doses of nanoparticles may prove hazardous to living cells, tissues and organs due to possible internalization. But studies also have reported that topical application of ZnO nanoparticles may result in insignificant skin penetration [27]. A clinical study investigated the skin penetration capability of zinc oxide nanoparticles of two average size fractions, namely 19 and 110 nm. The results revealed less than 0.01% absorption of applied dose [28]. However, the study failed to confirm the form of zinc, ionic or insoluble nanoparticles, in the bloodstream leaving a void for positive regulatory decision [27]. Other FDA and EU- sponsored investigations confirmed the non-penetration of the ZnO nanoparticles into the skin [29, 30]. Both ZnO and TiO2 are photocatalysts and form free radicals following exposure to UV radiation that potentially can damage the living cells in its vicinity. Nanosized particles of these mineral oxides are more sensitive to UV radiations than larger particles [15] hence the related toxicity issues need attention.

6. EMERGING REGULATORY NEEDS FOR SUNSCREEN PRODUCTS

Despite the fact that nanomaterials already being used in a plethora of consumer products, the potential health and environmental risks associated with the commercial use of nanotechnology cannot be ignored [31]. This calls for a systematic assessment of the health and environmental hazard associated with nanoparticles as the usage of these is rapidly growing. The existing inability to comprehensively evaluate the associated risks is primarily due to a limited understanding of the biological behaviour of nanoparticles. Despite advancements, there is insufficient knowledge on nanoparticle evaluation, their isolation and measurement in biosystems, the fate in humans and in the environment, and the toxicological and environmental toxicology related aspects of nanoparticles [32]. This compulsorily necessitates thorough toxicokinetic evaluation including biodistribution of the nanomaterials in animal models and thereafter in humans. According to European Regulation, cosmetic product is defined as “a cosmetic product is any substance or mixture of substances which is intended to be in contact with the external parts of the human body or with teeth and the mucous membrane of the oral cavity with the primary purpose of cleaning, perfuming, changing their appearance, protecting, maintaining them in presentable condition or modulating body odour”. Amongst all these uses, the protection of skin from sunburn is considered as a cosmetic action. In the European countries, the Scientific Committee on Consumer Safety’s (SCCS) provides a constant update on the safe usages of the cosmetic ingredients [27]. The recommendations were given by SCCS regarding both health and safety issues related to non–edible consumer products and services like sun tanning and tattooing. The recommendations are generally an update to the preexisting guidelines; the annexes of which need to be designated as new products are introduced for commercial use including a sunscreen product [33]. Interestingly, few suppliers sell sunscreens as products containing “non-nano” titanium dioxide or and zinc oxide, the claim is debatable. Although the diversity exists in particle size among producers, almost all would fall under the broad definition of nanomaterials coined by the USFDA [34]. In an interesting case, a commercial supplier who initially supplied a “non-nano” form of ZnO to the
sunscreen manufacturers, later on, insistence of “Friends of the Earth Australia”, endorsed that its ZnO be labelled as nanoingredient which necessitates special labelling in Europe [35, 36]. The physicochemical characteristics of nanoparticles often differ significantly posing challenges for manufacturers in obtaining regulatory approvals. Consumers remain unaware about the type and properties of the ingredients used in the products as it is not mandatory to disclose the same in their sunscreen products [15]. It has been found that free radicals are generated upon exposure of nanomaterials (present in cosmetic products) to ultra-violet light [37]. Some nano-ingredients used in sunscreens are aggressive producers of free radicals. A recent study has clearly indicated faster breaking down of pre-painted roofs upon contact with few marketed sunscreens containing nano-ingredients confirming an underlying free radical degradation mechanism initiated by photocatalysis [38]. Though, the study did not verify the effect of nanoparticles based cosmetics on biological skin, it threw light on possible adversities of paramount importance to the scientific fraternity. Subsequently, an investigation by CSIRO confirmed a very narrow size distribution (impracticable) of TiO₂ with acceptable qualities which eventually suggested for stringent control over particle size and size distribution [39].

A survey conducted by “WHICH?” a consumer group in United Kingdom, revealed that merely 5% of the consumers in the survey were aware of nanotechnology being used in cosmetic and skin care products, and only 2/3rd of adults assumed and expected that cosmetics produced by nanotechnology are the ones that have been tested for safety and labelled so. Despite the fact that nanotechnology here to stay, the FDA, till date has not given much attention to regulate the use of nanotechnology in cosmetics. The Nanotechnology Safety Act of 2010, can be considered as the first nanotechnology-related bill, is a positive move towards framing stringent regulations for nanotechnology-based products. While cosmetic companies have used nanotechnology for more than a decade, the risks of litigation are high owing to the fact that consumers across the globe are learning about nanotechnology and are increasingly becoming aware of its potential adverse effects on human health [1, 40].

7. REGULATIONS FOR NANOMATERIALS IN SUNSCREENS

As the risk to the health of humans and the environment takes an upsurge, regulations are being drafted by various countries to cautiously optimize safety concerns to avoid various risks in humans and market growth. The preceding text describes the regulations implicated in select countries.

7.1. European Union (EU) and New Zealand (NZ)

With an increasing emphasis for nano-specific regulation in EU and NZ, these countries are heading to regulate nano-materials in sunscreen. A report from UK clearly emphasized that the nanomaterial toxicity cannot be forecasted from the recognized properties of larger particles having same chemical composition. This means that the nanomaterials should be treated as a new chemical entity and preformulation studies should be carried out to characterize novel solubility, reactivity, bioavailability and toxicity of the said nanomaterial. The fact that nanomaterials behave as a novel material, the UK Royal Society recommended that: 1. For regulatory purpose, nanomaterials should be considered as new chemical entity [41]. 2. Nanomaterials should be subjected to new safety evaluation before being permitted for incorporation in cosmetic products [42]. 3. Labelling of nano-ingredients in consumer products should be mandatory [43]. After a series of comprehensive investigation, an empowered committee of EU recommended a strong need to review acceptability of the metal nanoparticles currently in use as sun filters. The committee strongly recommended that all nano-ingredients used in sunscreens and cosmetics should be subjected to a case-by-case risk evaluation [44]. These recommendations resulted in an updating of regulations, which are now significantly important considerations for formulation development of a sunscreen product. These include: (i) Acceptability profile of cosmetic ingredients; (ii) Materials not approved for use in cosmetics; (iii) Restricted/Banned materials in cosmetics; (iv) Colouring materials for use in cosmetics; (v) Preservatives approved for use in cosmetics; and (vi) Ultra-violet filters approved for use in cosmetics. The existing list of UV filters details 28 filters including specifications of approved range of concentration and strict warnings for the label instructions on the package. The other
recommendations describe specification pertaining to the ratio UVA/B and labelling requirements for values of sun protection factor. The recommendations include (i) minimum efficacy (minimum allowed: SPF 6); (ii) UVA/UVB ratio (UVA must be at least 1/3 of UVB protection); (iii) Testing wavelength at least 370 nm ; (iv) Protection category; (v) precautions and instructions for use [45]; and (vi) testing done according for SPF [33]. Later on, the European Parliament also passed laws according to which nano-ingredients in cosmetic products have to undergo toxicity evaluation prior to marketing [46]. These laws were implemented from July 2013 in European countries. Compulsory label instructions regarding nano-ingredients in cosmetic products have came into practice in New Zealand since 2015 onwards [18].

7.2. USA

The sunscreens in USA are classified as OTC (Over the counter) products. The Final Rule (5), 2011 and the Sunscreens Innovation Act (SIA), 2014, are used as the main reference documents. Stringent approval and label instructions are in force for this group of sunscreens classified under OTC products. The SIA, 2014 was passed with an intention to make few novel sun-filters available to the US market. The SIA was prepared as per the “material time” and “material extent concept”, indicating that the sunscreen nano-ingredients that were marketed “to a material extent” and “for a material time” in another country with required safety profile to be included as “over the counter” drug monograph and hence for sunscreen products. The FDA in 1970 made the decision to designate sunscreens under the OTC class eventually prevented entry of some newer sunscreen products to enter US market. The SIA also did not improve the condition much and the possibility of bemotrizinol, drometrizole trisiloxane, miloxate, bisoctrizole, octyl triazone, enzacamene, ecamsule, and iscotrizinol getting their entry into a distant dream. Furthermore, owing to the insufficient safety information and funds, no newer sunscreens were able to get the positive nod from the regulatory body for quite some time. One of the aspects of the Final Rule (5) is co-relatable to labelling of sunscreen products. The word “Label” is strictly regulated, and guidelines are very clear. For example, (i) how and where to write the necessary information namely water resistance, or (ii) for sunscreens with SPF >15, which formulations can have the claim: “if used as directed with other sun protection measures, (the product) decreases the risk of skin cancer and early skin ageing caused by the sun”.

Monographs can also act as a regulatory format for sunscreens as they provide specific standards for active ingredients. If a monograph for an active ingredient is available, then the manufacturer needs to validate the standards of the monograph to be able to launch its product in the market. This can be a convenient method to introduce new formulas commercially and is quite different from the regulations mentioned for novel active ingredients.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Maximum Concentration (% by Weight)</th>
</tr>
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<tbody>
<tr>
<td>Titanium dioxide, Zinc oxide</td>
<td>25</td>
</tr>
<tr>
<td>Para-aminobenzoic acid, Homosalate</td>
<td>15</td>
</tr>
<tr>
<td>Trolamine salicylate</td>
<td>12</td>
</tr>
<tr>
<td>Octinoxate, Octyl methoxycinnamate</td>
<td>7.5</td>
</tr>
<tr>
<td>Sulisobenzone, Octocrylene</td>
<td>10</td>
</tr>
<tr>
<td>Padimate O</td>
<td>8</td>
</tr>
<tr>
<td>Oxybenzone</td>
<td>6</td>
</tr>
<tr>
<td>Meradimate, Menthyl anthranilate, Octisalate, Octyl salicylate,</td>
<td>5</td>
</tr>
<tr>
<td>Ensulizole, Phenyl benzimidazole sulfonic acid</td>
<td>4</td>
</tr>
<tr>
<td>Cinoxate, Avobenzone, Dioxybenzone</td>
<td>3</td>
</tr>
</tbody>
</table>
Currently, FDA is regulating following ingredients through its monographs. The sunscreen ingredients are regulated via OTC monograph (21 CFR 352.10) [33, 47] are given in Table 1.

An up to date monograph has been undertaken, that would be ready for use by 2019-2020 and is expected to solve various questions related to higher SPF values, newer product forms (powders, wipes, sprays), ingredients, etc. In US, there are certain cases where single states like California, have made their own specific rules for their state that has resulted in more complexity, e.g. PROPOSITION 65 of the State of California passed in 1st January 2015. As per the proposition, it is mandatory that the products containing benzophenone must display the following instructions on their labels: “WARNING: This product contains benzophenone, a chemical known to the State of California to cause cancer” [33].

7.3. Australia

The “Monash Review” i.e. Australia’s regulation of nanotechnology was reviewed in 2007 commissioned by their Government, which identified a major regulatory gap that nano-forms of existing substances cannot be treated as new chemicals [48]. Later, in 2008 the Parliamentary Inquiry by NSW (New South Wales) regarding Nanotechnology affirmed that nano-forms of existing substances should be evaluated as new chemicals [49]. Further, it also proposed compulsory labelling of nano-ingredients present in cosmetic and sunscreen products [18]. In Australia, the sunscreen regulations consist of essential specifications that show country’s awareness regarding sun protection. This specific requirement is because of its geographical and meteorological location [33]. Technically, sunscreens may be classified into therapeutic or cosmetic categories [50]. Therapeutic sunscreens are: (i) Primary sunscreens with SPF ≥4; (ii) Secondary sunscreens include all except those designated as cosmetic sunscreens; (iii) Primary/secondary sunscreens with SPF ≥ 4 containing an insect repellent; and (iv) Products containing sunscreens with SPF < 4 that are currently designated as listable sunscreens. Cosmetic sunscreens can be defined as formulations containing an excipient with sunscreen characteristics but the formulation is neither used primarily as a sunscreen nor as a therapeutic substance.

In accordance with The National Industrial Chemicals Notification & Assessment Scheme (NICNAS), these products are regulated as cosmetics instead of therapeutic products and are classified by the TGA (Therapeutic Goods Administration) [33]. In January 2011, new regulatory measures regarding nano-forms of new substances were introduced by the Australian NICNAS – which regulates the cosmetics, secondary sunscreens and industrial chemicals. Within a year, NICNAS started consulting to establish improvement of regulations related to nano-forms of existing substances. It implied nano-specific regulations by NICNAS. On the other hand, the TGA (regulator of primary sunscreens), rejected calls regarding nano-specific regulation and labelling of the formulations. This approach of TGA was questioned by various medical and legal academicians according to whom the possibility of health hazard strictly requires a preventive approach for regulating nano-ingredients in sunscreen products [18, 51] Among the various specific regulatory rules for this country, the permissible sun filters, as well as their concentration, are regulated by norms and there are also specified rules for the claims. These differ according to the category of the product.

The label for therapeutic sunscreens (SPF ≥ 30) should provide the following indications:

(i) May help in reducing the risk of certain skin cancers; (b) May assist in preventing certain types skin cancers; (iii) May help in preventing solar keratoses; and (iv) May assist in preventing sunspots. In Australia, since both TiO2 and ZnO are generally used as nano-forms in sunscreen products there is no need to mention the particle size of these actives in the label of therapeutic sunscreens. For the products containing secondary sunscreens (SPF < 15) and for make-up = 50+ (broad-spectrum activity is mandatory), the label should specify the levels as Low, Medium, High, Very High (Table 2) [33, 45, 50].

### Table 2. SPF Classification of secondary sunscreens.

<table>
<thead>
<tr>
<th>SPF Range</th>
<th>Class</th>
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<tbody>
<tr>
<td>6-10</td>
<td>Low</td>
</tr>
<tr>
<td>15-25</td>
<td>Medium</td>
</tr>
<tr>
<td>30-50</td>
<td>High</td>
</tr>
<tr>
<td>50+</td>
<td>Very High</td>
</tr>
</tbody>
</table>
7.4. India

In India, cosmetics must be registered and the claims permitted should make reference to “sunblocker”, broad-spectrum along with SPF value, the UVA protection expressed as PA++ and water resistance [33]. Till date, the maximum value of SPF has not been fixed. The products of ayurvedic and herbal origin with high SPFs can be found commercially. As per the existing regulation of cosmetic products, the revelation of composition of the excipients is not mandatory and the guidelines for claims are yet to be framed. Claims like “broad spectrum” or “water resistant” should be suitably evaluated. Due to these loopholes, the cosmetic manufacturers launch sunscreen products with any SPF rating and exaggerated claims. Sunscreen products claiming SPF value as high as 40 are marketed as a cosmetic product in India and at the same time similar sunscreen products are manufactured and sold as a cosmetic or drug in India. Approval has also been accorded for a sunscreen lotion containing octinoxate, oxybenzone, avobenzone and titanium dioxide as a new drug in the country [52].

7.5. Brazil

As specified by the country regulations, a sunscreen formulation is required to be in contact with the skin and lips with the aim of imparting protection against harmful effects of UVA/UVB radiations by reflecting or dispersing the radiations. Sunscreens claiming safety against ultraviolet radiation as an extra benefit instead of as their primary objective comes under the extent of their regulations. The requirements as per the technical framework derived from EU recommendations of 2006 are the SPF, the water resistance feature and the UVA/UVB ratio should be at least 1:3. Sunscreen formulations must be registered; at the same time labelling has a different set of rules. The SPF is displayed as “FPS” or the words “Factor de Protección Solar” plus the logo of UVA. For the products claiming sun protection as an added advantage, the minimum sun protection factor and FPUVA (Fator de protecao UVA) must be 2, also mentioning a definite warning: “this product is not a sunscreen”. Rules according to the claims also require that the label should not have language indicating total protection from UV radiation nor can they contain statements claiming to provide 100% protection against UV radiation, or stating that the formulation does not require to be reapplied under any conditions [33].

7.6. Regulations Followed in Various Other Countries

The regulations followed in various other countries across the globe are summarized in Table 3.

8. SAFETY CONCERNS AND THEIR REGULATORY GUIDELINES

The Therapeutic Goods Administration of Australia, Department of Health and Aging undertook an exhaustive literature survey on the use of micronized ZnO and TiO2 in the sunscreens and submitted a report in January 2006. The findings reported that 30% of sunscreens containing ZnO and 70% of sunscreens containing TiO2 contain these ingredients as nano-form. Additionally, TiO2 is being used in this form since 1990 and ZnO from 1999. According to the report, no evidence for risk for the users could be found for the sunscreens consisting of these ingredients. Further, a scientific review was conducted by TGA on the literature related to the use of nanoparticulate TiO2 and ZnO in sunscreens to find out the evidence for theoretical concern that these ingredients in nanoparticulate form could be absorbed and penetrate into skin cells and may cause cellular damage due to interaction with sunlight. Evidence were found from isolated cell experiments that titanium dioxide and zinc oxide have the potential to induce free radical formation in the presence of light and this may result in damaging of these cells (zinc oxide may cause photo-mutagenicity). Although, this can be a matter of concern for those using sunscreens if these nano-ingredients penetrated into viable skin cells. The saving highlight is that these nano-ingredients remain on the skin surface and especially in the stratum corneum [53].

8.1. Regulatory Guidelines for Safety under the FD&C Act

Sunscreen drug products are regulated as drugs. According to the regulation, safety can be defined as “low incidence of significant side effects or adverse effects when (product) used under adequate directions and warnings against unsafe use as well as the poor potential for harm that may result from
misuse when available freely”. The regulation also broadly classifies the data that FDA may request and consider as evidence that the actives of an OTC formulation are generally recognized as safe and effective (GRAS/E). These include studies on animals and humans, relevant marketing experience, documentation of adverse effects, and relevant scientific and scientific literature. The FDA reserves right to exercise scientific judgment to determine whether the tests conducted and the data generated thereof are adequate to determine that the GRAS/E standard has been verified for the action under the relevant conditions of use [54].

9. TOXICOKINETIC EVALUATION/MEC- HANISM AND ENVIRONMENTAL CONCERNS

FDA recommends that animal toxicokinetic data for active ingredients of sunscreen should be collected as these data could present a significant relation between toxic data found in studies conducted on animals any potential human adverse effects associated with systemic exposure to the active(s) of the sunscreen formulation. Toxicokinetic measurement is usually obtained during the course of ongoing toxicity studies, for example in carcinogenicity or development and reproductive
toxicity (DART) studies [55]. Sunscreen active ingredients may reach humans by environmental exposure. Drinking or swimming in contaminated water might increase the contact, and results in absorption (through oral and dermal route) of these compounds. The recent literature review showed that the highest concentrations of UV filters were found in rivers, around 0.3 mg/l for the benzophenone derivatives, whereas lakes and seas contain low concentrations \( i.e. \) ng to \( \mu g/l \) range. Furthermore, ground and tap water also contain low levels \( i.e. \) few \( ng/l \) of organic Ultraviolet filters [56-59]. Organic UV filters may also accumulate in concentrations of mg/l in wastewater treatment plants (WWTPs) and as these plants cannot remove them; these filters are therefore dumped into the lakes, rivers, and finally reach into oceans [57]. Swimming pools also act as reservoirs for Ultraviolet filters and its chlorine byproducts in the concentration of \( \mu g/l \) range, or even higher. The further Scientific analysis also reported that swimming pools in urban areas may have significantly higher concentrations of UV filters in comparison to natural sources of waters, which marks a question whether they are safe for users, especially children [60, 12].

10. RECOMMENDATIONS TO IMPROVE THE EFFICIENCY OF SUNSCREENS

Nowadays, consumers are free to choose from the abundance of sunscreen products, each having different performance claims. The aim of EWG (Environmental working group) is to navigate the FDA and the cosmetic industry to improvise the performance of sunscreen products, to guide the consumers regarding the limitations/disadvantages of sunscreen, and thus assessing a selection of the best available options. The EWG recommends that the FDA must.

1. Improve labelling requirements of sunscreens for SPF values. Due to significant differences between labelled, laboratory and actual performance, the EWG suggests that the FDA must consider for introduction of the SPF system and choose a methodology similar to the European Commission strategy, that suggests four categories of SPF: (1) low sunburn protection, (2) medium sunburn protection, (3) high sunburn protection, and (4) very high sunburn protection [45].

2. Capping SPF values up to 50+.

3. With increasing value of SPF, a higher level of UVA protection be conferred.

4. Assure that active ingredients currently in use meet the high standard for safety and efficacy.

5. Recommend novel UV filters with enough safety profile.

6. Investigate SPF boosters (do not filter UV rays) and ensure that these afford protection from UV-related skin damages.

7. Assure that labelling on the sunscreen products does not overestimate sun protection by forcing companies to withdraw fictitious claims like “cancer prevention” from poor quality products.

8. Alerting consumers that sunscreens sprays and sticks may be more prone to under application of the product.

10.1. In a Situation Where Strict Regulations are Absent, Sunscreen Manufacturers Must

1. Avoid use of sun filters that merely prevent skin reddening and are devoid of offering other meaningful skin protection.

2. Assure that the sunscreen products form a uniform film and ensure homogeneous distribution of sunscreen ingredient(s) to minimize aggregation and poor coverage.

3. The excipients should be incorporated judiciously in the formulation so as to increase the skin adherence of the product and meet the criteria of water/sweat resistance, and “wet skin” efficacy.

4. Assure that the organic sunblocs are photo-stable and provide long-lasting protection.

5. Perform stability testing and mention expiry date on the labels if there are chances that product may break down or lose its effectiveness on long-term storage; and.

6. Report serious side effects (sunburns) and other related complaints to FDA [15].

CONCLUSION

While sunscreens containing nanoparticles can be seen as efficacious products, the safety of these products is a matter of debate and often questionable. Hence, it is high time to propose modalities
to evaluate safe usage of nanomaterial-containing cosmetic products and its regulation. Interestingly, for each country and its regulatory body, there exist varied definitions and regulations for nanomaterials in sunscreens. Lack of a harmonized definition may potentially harm consumers and the manufacturers who feel lost in the absence of harmonized legal guidance related to the use, manufacturing and sale nanotechnology and its products. Harmonization among the regulatory agencies and research centres can create a significant database with a wide array of information resulting if efficacious and safe products.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES


[34] FDA Draft, Not for Implementation: Guidance for Industry. Enforcement Policy - OTC Sunscreen Drug Products Marketed Without an Approved Applica-


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