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Editorial

The Safety of CNS and Non-CNS Products for Skin Health: Current Status and Emerging Plans for the Future

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Abstract

For safety reasons, the development of drugs, biologics and small-molecule therapeutics for central nervous system (CNS) and non-CNS diseases is regulated by the Food and Drug Administration (FDA) and by comparable regulatory agencies in Europe – e.g., European Medicines Agency (EMA). In clear contrast, over-the-counter products such as many dermatological, skin care and anti-aging topical creams and gels are not, as of today, significantly regulated by authorities prior to their release on the market. This said, increasing evidence suggests that significant safety and life-threatening concerns are associated with industrially manufactured skin care products. Indeed, commonly used ingredients (i.e., mainly additives and preservatives) in cosmetics such as aluminum, parabens, butylatedhydroxyanisole (BHA), coal tar dyes, polyethylene glycols compounds (PEGs), fragrance and other chemicals have been shown to dose-dependently promote, both in vitro and in vivo models, cell death, toxicity and carcinogenic activity. As any other organ of the body, the skin is controlled directly and indirectly by a variety of neural systems – for sensory transmission of touch, temperature, pressure or pain signals as well as for the body temperature control, protection against infections, diseases and other external factors. Next-generation skin care products are thus bound to increasingly be tapping into these newly unraveled cellular targets for further efficacy and specificity. As such, it should be considered a priority for authorities and industrial sponsors to urgently develop specific regulations adapted to cosmetics and cosmeceuticals for both safety and efficacy reasons. This editorial aims at summarizing the current status in term of safety regulations and some of the objectives that shall be pursued for safer and more effective products.

Editorial

Mainly for safety reasons, drugs, biologics and small-molecule therapeutics developed as prescription pharmaceutical products against CNS and non-CNS diseases are normally regulated by regulatory agencies in U.S., Canada and Europe – FDA, Health Canada, EMA (e.g., http://www.fda.gov/forpatients/approvals/drugs/ default.htm)[1,2]. During normal drug development processes, most safety and toxicology data are obtained during preclinical experiments using animal models. Hence, if IND approved for subsequent studies in humans, additional key safety data may be obtained with phase I trials (> 50 volunteers) using adapted designs such as dose escalation, randomization, placebo-controlled and blind testing as well as maximum tolerated dose (MTD) identification (www.fda.gov)[3,4]. Dosage is undoubtedly a significant element in safety pharmacology – acquisition of data about the therapeutic window and, if possible, about the MTD is of great value. For efficacy, the pharmaceutical industry (sponsor companies) is required to provide evidence through subsequent trials – phase II (approx. 150 volunteers) and III studies (> 500 volunteers) – demonstrating the extent to which a drug candidate fulfills the targeted unmet medical need in patients. Those tests are by far the most expensive (up to 2.5 billion dollars) - making it unlikely for them to be adapted for the cosmetic industry given obvious financial reasons [5] – i.e., paying $1,000-10,000 dollars for a new potent therapy may be acceptable for patients (and for insurance companies or governments) fighting cancer but probably not for those experiencing chronic dry skin, pruritus or wrinkles [6].

The epidermis, basement membrane, dermis and subcutane-

ous (hypodermis) constitute layers composing the main structures of the skin and serving as the first line of defense against bacteria, viruses, toxins, parasites and fungi [7]. However, those layers are not impermeable to chemicals. As such, the skin is now considered a clinically-relevant route of administration through penetration and absorption that depends on various factors such as dosage (concentration), duration of contact, solubility of medication, and skin integrity and health [8,9]. A good example is transdermal administration of testosterone – often prescribed as a patch against andropause, hypogonadism and menopause – this average size molecule (288 g/mol) penetrates the skin, is released into the blood stream, and achieves significant systemic effects [10]. However, less desirable chemicals such as aluminum against perspiration or preservatives and additives for color, odor or over-the-counter chemical stability (shelf-life) and antimicrobial activity (e.g., BHA, BHT, coal tar dyes, DEA-related ingredients, dibutyl phthalate, formaldehyde-releasing preservatives, parabens, fragrance, PEG compounds, petrolatum, siloxanes, sodium laurethsulfate, triclosan) are also extensively used in industrially manufactured cosmetics and cosmeceuticals (see http://www.davidsuzuki.org for a rather exhaustive list of references) [11-16].

In North America and Europe most of the skin care products are approved and marketed without significant regulatory hurdles (albeit the existence in some countries of a short-list of controlled or banned ingredients – e.g., (http://www.hc-sc.gc.ca/cps-spc/cosmet-person/hot-list-critique/hotlist-liste-eng.php). This is particularly troubling since next-generation skin care products are bound, for increased efficacy and specificity, to act upon central and peripheral mechanisms for significant effects against the many existing skin problems (e.g., xerosis, pruritus, eckema, psoriasis, rosacea, etc). The CNS is indeed directly (via efferent nerves or CNS-derived mediators) or indirectly (via the adrenal glands or immune cells) controlling skin functions. Sensory as well as autonomic (sympathetic) nerves influence a variety of physiological functions (embryogenesis, vasocontraction, vasodilatation, body temperature, barrier function, secretion, growth, differentiation, cell nutrition, nerve growth) and pathophysiological problems (inflammation, immune defense, apoptosis, proliferation, wound healing) that involve different underlying mechanisms cellularly - e.g., α-adrenergic GABAergic, 5-HT1A, histaminergic, interleukin, μ-opioid, κ-opioid or proteinase-activated receptors (e.g., PAR 2, PAR 4) and areas such as the hypothalamus, ventral tegmental area, periaqueductal gray matter, medulla oblongata or preoptic area [17-24].

Thus, stricter regulations inviting sponsors to conduct clinical trialswithscientificallysound research designs will be determinant for the development of safer and better products. To remain cost-effective, hybrid study designs may be used – that is when phase I and phase II trials as conducted simultaneously as one study such as a phase I/II trial. This is typically done in the pharmaceutical industry with compounds that have a long history of use in the clinic (e.g., testing testosterone + oestrogen as a new therapy against menopause) or with fixed-dose combination products (e.g. Truvada® for HIV composed of already separately approved molecules – i.e., emtricitabine and tenofovir). A comparable approach has been used for the development of a dermatological product called SQINTM for chronic dry skin problems – it underwent a double-blind, randomized, placebo (positive comparator)-controlled phase I/II study in ten (10) patients with spinal cord injury and mobility impairment [25]. Both evidence of safety and efficacy in patients were obtained by the sponsor with less than $100,000 in R&D while clearly showing evidence of superior efficacy compared with the gold-standard.

In conclusion, many recently uncovered control mechanisms (CNS and non-CNS-mediated) are likely to constitute potent targets for the future development of innovative products against various types of skin problems. Adapting regulations that meet the needs of the cosmeceutical industry shall help obtaining valuable safety and efficacy data prior to approval. Safety pharmacology (e.g., vital signs if applicable or relevant side effects – e.g., skin allergy, itching, inflamed, redness, swelling, pain, infection, etc.), stability (shelf-life), bacterial testing, range of effective doses (i.e., MTD may be optional if known-molecules with extensive safety data are used), and proven-efficacy upon repeated use and type of administration (e.g., topical) should constitute some of the pivotal data to be examined by authorities – i.e., as it is already for pharmaceutical products but with longer tests, larger cohorts, and stricter regulations. Shorter and cheaper clinical trials with scientifically sound designs shall be encouraged as well as post-market surveillance (so-called phase IV studies) for cost-effective, long-term monitoring of safety upon repeated use [26].

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