

Editorial

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

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Citation: Guertin PA (2016) The Safety of CNS and Non-CNS Products for Skin Health: Current Status and Emerging Plans for the Future. J Neurol Exp Neural Sci 2016: JNENS-e119. DOI: 10.29011/JNNS-119. 100019

Received Date: 03 December, 2016; **Accepted Date:** 24 December, 2016; **Published Date:** 31 December, 2016

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 pre-clinical 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 laureth sulfate, 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, eczema, 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, vasoconstriction, 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 cellulyarly – 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 trials with scientifically sound 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].

References

1. Ciociola AA, Cohen LB, Kulkarni P (2014) FDA-Related Matters Committee of the American College of Gastroenterology How drugs are developed and approved by the FDA: current process and future directions. *Am J Gastroenterol* 109: 620-623.
2. Handoo S, Arora V, Khera D, Nandi KP, Kumar Sahu SA (2012) comprehensive study on regulatory requirements for development and filing of generic drugs globally. *Int J Pharm Investigig* 2: 99-105.
3. Ciociola AA, Cohen LB, Kulkarni P (2014) FDA-Related Matters Committee of the American College of Gastroenterology How drugs are developed and approved by the FDA: current process and future directions. *Am J Gastroenterol* 109: 620-623.
4. Cutler NR and Sramek JJ (1998) Guidelines for conducting bridging studies in Alzheimer disease. *Alzheimer Dis Assoc Disord* 12: 88-92.
5. DiMasi JA, Grabowski HG, Hansen RW (2016) Innovation in the pharmaceutical industry: New estimates of R&D costs. *J Health Econ* 47:

20-33.

6. Siddiqui M and Rajkumar SV (2012) The high cost of cancer drugs and what we can do about it. *Mayo Clin Proc* 87: 935-943.
7. McGrath JA and Eady RA (2004) Pope, F.M. *Rook's Textbook of Dermatology* (7th ed.). Blackwell Publishing. pp. 3.1-3.6.
8. Bos JD and Meinardi MM (2000) The 500 Dalton rule for the skin penetration of chemical compounds and drugs. *Exp Dermatol* 9: 165-169.
9. Baynes RE and Hodgson E (2004) Absorption and Distribution of Toxicants. in Chapter 6 of *A Textbook of modern toxicology*. 3rd edition. John Wiley & Sons, Inc.
10. Jockenhövel F (2004) Testosterone therapy--what, when and to whom? *Aging Male* 7: 319-324.
11. Pineau A, Fauconneau B, Sappino AP, Deloncle R, Guillard O (2014) If exposure to aluminium in antiperspirants presents health risks, its content should be reduced. *J Trace Elem Med Biol* 28: 147-50.
12. Badenoch-Jones P, Turk JL, Parker D (1978) The effects of some aluminium and zirconium compounds on guinea-pig peritoneal macrophages and skin fibroblasts in culture. *J Pathol* 124: 51-61.
13. Sato H, Takahashi M, Furukawa F, Miyakawa Y, Hasegawa R et al. (1987) Initiating potential of 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (AF-2), butylatedhydroxyanisole (BHA), butylatedhydroxytoluene (BHT) and 3,3',4',5,7-pentahydroxyflavone (quercetin) in two-stage mouse skin carcinogenesis. *Cancer Lett* 38: 49-56.
14. Storer JS, DeLeon I, Millikan LE, Laseter JL, Griffing C (1984) Human absorption of crude coal tar products. *Arch Dermatol* 120: 874-877.
15. Darbre PD and Harvey PW (2008) "Paraben esters: review of recent studies of endocrine toxicity, absorption, esterase and human exposure, and discussion of potential human health risks." *J Appl Toxicol* 5: 561-578.
16. Handa O, Kokura S, Adachi S, Takagi T, Naito Y et al. (2006) Methylparaben potentiates UV-induced damage of skin keratinocytes. *Toxicology* 227: 62-72.
17. Reddy VB, Iuga AO, Shimada SG, LaMotte RH, Lerner EA (2008) Cowhage-evoked itch is mediated by a novel cysteine protease: a ligand of protease-activated receptors. *J Neurosci* 28: 4331-4335.
18. Kirby LG, Pernar L, Valentino RJ, Beck SG (2003) Distinguishing characteristics of serotonin and non-serotonin-containing cells in the dorsal raphe nucleus: electrophysiological and immunohistochemical studies. *Neuroscience* 116: 669-683.
19. Papoiu AD, Tey HL, Coghill RC, Wang H, Yosipovitch G (2011) Cowhage-induced itch as an experimental model for pruritus. A comparative study with histamine-induced itch. *PLoS One* 6: e17786.
20. Wasilewska A, Winiarska M, Olszewska M, Rudnicka L (2016) Interleukin-17 inhibitors. A new era in treatment of psoriasis and other skin diseases. *PostepyDermatolAlergol* 33: 247-252.
21. Keri J (2016) What's new in acne and rosacea? *SeminCutan Med Surg* 35: 103-106.
22. Cevikbas F, Steinhoff M, Ikoma A (2011) Role of spinal neurotransmitter receptors in itch: new insights into therapies and drug development. *CNS Neurosci Ther* 17: 742-749.
23. Blessing WW, Yu YH, Nalivaiko E Raphe (1999) pallidus and paraparapidal neurons regulate ear pinna vascular conductance in the rabbit. *Neurosci Lett* 270: 33-36.
24. Key BJ1, Wigfield CC (1994) The influence of the ventrolateral medulla on thermoregulatory circulations in the rat. See comment in PubMed Commons below *J Auton Nerv Syst* 48: 79-89.
25. Guertin PA (2016) Randomized double-blind study assessing safety and efficacy of SQIN on xerosis in subjects with mobility impairment and paralysis. *J Dermatol Clin Res* 4: 1-5.
26. Resnik DB (2007) Beyond post-marketing research and MedWatch: Long-term studies of drug risks. *Drug Des Devel Ther* 1: 1-5.