Available online on www.ijcpr.com
International Journal of Current Pharmaceutical Review and Research 2014, 5(1), 14-30

ISSN: 0976-822X

Review Article

Overview of Herbal Dermatological Products and its Regulatory Perspective

*Birje S.S.[1], Kshirsagar A.D.[1], Ziyaurrahman A.R.[2]

[1]*Padmashree Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune*

[2]*Allana College of Pharmacy, 2390-B, K.B., Hidayatullah Road, Azam Campus, Camp, Pune*

Available online: 1st February 2014

ABSTRACT

The current review focuses on Herbal Dermatological Products (HDP) and its related regulatory concern. The demand for HDP is increasing day by day considering that they are safe and concern about their safety is also increased due to risk associated with use of large number of population and their raised possibilities of adverse reactions. There are various guidelines used for the testing of dermatogical products, but they need to be upgraded to include herbal OTC (Over the Counter) and Non-OTC products for their safety testing. Thus, the present review makes an attempt to overview the need of harmonizing existing guidelines of the toxicity testing for HDP.

Key words: Dermatology, Toxicity, Herbal products.

INTRODUCTION

Herbal Dermatological Products (HDP) are classified, according to the dosage forms as solutions, suspension, lotion, gel, ointments, paste,[1] and according to the purpose these could be classified as medicinal and cosmetic products. In recent years, there has been great demand for plant derived products in developed countries. These products are increasingly being sought out as medicinal products, nutraceuticals and cosmetics. There are around 6000

*Author for correspondence: E-mail: smitabss@yahoo.co

herbal manufacturers in India and more than 4000 units producing Ayurvedic medicines[2]. For a wide variety of reasons herbal OTC (Over the counter or non- prescription advertised medicines) products are used. It may be for medicinal purpose or for cosmetic purpose. The products are used unknowing or knowing the toxic effects**.** Due to the increased use of herbal OTC products it is essential to provide safety and efficacy data[3]. The Ayurveda treatise like Bhavaprakasha and Charak Samhita provide various herbs and formulations for the treatment of acne and claim to be safe and efficacious, but claim has not been supported with controlled clinical trial[4]. In 2008, herbal safety news of MHRA (Medicinal Healthcare products Regulatory Agency) banned the use of OSAS (intensive body lotion with aloevera) which was found to contain steroids. It was an unlicensed product and was supplied over the internet and Asian and African beauty shops for the treatment of eczema and psoriasis[5]. Therefore, to avoid the unintentional adverse effect of the herbal dermatological OTC products it is essential to perform the safety testing before it is being introduced in the market. As alternative and complimentary medicines in Western settings continue to gain popularity 62% of Americans used Complimentary and Alternative Medicines (CAM) therapies in 2002 contributing to a US$ 20 billion industry, the use of traditional plant-based remedies remains entrenched in the healing practices of developing countries[6]. India is currently ranked 11th in the global OTC market in size, with an estimate that it will reach 9th position within five years[7]. Currently the Indian OTC market (i.e. non-prescription advertised medicines) is estimated to represent approximately Rs.104 Billion growing at about 8-9%[8].

According to the World Health Organization (WHO)**,** because of poverty and lack of access to modern medicine, about 65-80% of the world's population which lives in developing countries depends essentially on plants for primary health care[9]. There are various guidelines for the testing of chemicals, their ingredients, but there no detail regulatory guideline for the testing of herbal dermatological OTC products. Hence, the available guidelines can be revised for the testing of herbal dematological OTC products. The present review is an attempt to overview regulatory perspective of herbal dermatological OTC products. By considering the widespread utility of said products need of its toxicity evaluation and limitations of the existing guidelines, the review suggests some upgradation in regulatory guidelines and extends scope of substantiating guidelines for the toxicological evaluation of HDP to its fullest.

Why dermal testing? Cosmetic products are widely used and are directly applied to human skin. While the skin provides a protective barrier, certain ingredients may penetrate the skin and become systemically available. Some cosmetic products are applied to mucous

membranes which may enhance availability or, in case of lip products, provide the opportunity for oral ingestion. As such, an evaluation of their safety is of utmost importance. Safety assessment requires knowledge of both the intrinsic hazard of ingredients contained in the product as well as data on exposure levels. Published or otherwise readily available exposure data for cosmetic products are limited at present[10, 11].

There are many past examples of adverse effects occurred due to the application of dermal preparations and cosmetics. The first case of cosmetic allergy was reported in 1983 of cocamidopropyl betaine, which is present in many cosmetic formulations like shampoo, moisturizer etc.[12]. On the other side herbal formulations which are prepared by using various bases can produce toxicity. Salicylates have been proved to be non toxic for the use in cosmetics as fragrance material[13]. To avoid the occurrence of adverse effects, testing of dermal products is essential and in concern to regulatory authority testing of dermal products is mandatory. There are many drugs which are been used with very little data or without any data on its toxicity which may cause harmful effects. Dermal toxicity is performed for assessing the safety profile of the drug for its intended use in humans. The acute dermal toxicity of Pitika Mardini and Esabdamini in male and female Wistar rats showed no mortality in the study under the condition of this test it is concluded that the dermal LD_{50} of Esabdamini and Pitikamardini for wistar rats is more than 2000 mg/kg[14].

Need of HDP safety testing: Traditional medicines offer a rich and largely unexplored source of therapeutic leads for the pharmaceutical industry[15]. Natural products have a wealth of applications. Some of them are used as drugs, while others possess important biological properties or are used as dietary supplements, as dyes, flavoring agents, or ingredients in the cosmetics industry[16]. The need to test HDP arises due to their increased popularity. Although there are many products used without prescription by the public considering that they are safe, but these are the products which may cause harmful effects. For example turmeric which is used for a wide variety of diseases and conditions including skin, pulmonary, and gastrointestinal systems, aches, pains, wounds, sprains, and liver disorders. Toxic effects of turmeric compounds were not studied extensively[17]. However, there are some evidences to suggest that turmeric extracts can be toxic[18, 19, 20].

Regulatory perspective: Regulatory authorities of different countries have their set guidelines for checking various parameters of toxicity of dermal products / applications and also made it mandatory to test the chemicals used for various dermal products / applications. Thus, this toxicity data is required for generation of safety profile for human use before launching new dermal products in the market. Currently alternative *in vitro* dermal testing is preferred, to

avoid the animals use. OECD (Organisation for Economic Co- operation and Development) provides various guidelines for the testing of chemicals. Also, there are guidelines provided by ICH (International Conference on Harmonization) and FDA (Food and Drug Administration) for the testing of dermatological chemicals. US EPA FIFRA (Unitad States Environment Protection Agency Federal Insecticide, Fungicide, and Rodenticide Act) has guidelines related to the toxicity of the dermally exposed chemicals. WHO (World Health Organisation) provides guideline for the testing of HDP (local toxicity test). Besides these there are various guidelines for testing of cosmetics/ Personal Care Products. There are several tests used for the testing of dermatological products as shown in table no.: 01.

OECD guidelines for dermal toxicity testing:

The Organisation for Economic Co-operation and Development (OECD) was established in 1961 with its roots going to the rubble of Europe after world war II. US and Canada also joined the organisation. Other countries like Japan joined in 1964. China, India and Brazil are the new economic giants of OECD. Since, from establishment OECD have provided guidelines related to safety evaluation of chemicals and its preclinical screening. The dermal toxicity guidelines can be summarized as below;

Acute Dermal Toxicity (OECD 402, 1987):[21] In the assessment and evaluation of the toxic characteristics of a substance, determination of acute dermal toxicity is useful where exposure by the dermal route is likely. It provides information on health hazards likely to arise from a short-term exposure by the dermal route. Data from an acute dermal toxicity study may serve as a basis for classification and labeling. It is an initial step in establishing a dosage regimen in subchronic and other studies and may provide information on dermal absorption and the mode of toxic action of a substance by this route.

Acute Dermal Irritation/Corrosion (OECD 404, 2002):[22] Application of the three test patches to the animal in the initial *in vivo* test is recommended in this guideline. This guideline is reviewed taking into consideration the improvements in animal welfare and to the evaluation of all existing information of the test substance in order to avoid unnecessary testing of animals. The testing strategy includes the performance of validated and accepted *in vitro* tests and is provided as a supplement to this guideline. The strategy provides an approach for the evaluation of existing data on the skin irritation/corrosion properties of test substances and a tiered approach for the generation of relevant data on substances for which additional studies are needed, or for which no studies have been performed. It also recommends the performance of validated and accepted *in vitro* or *ex vivo* tests for skin corrosion/irritation

Table 1: Safety regulatory guidelines for testing of dermatological products

Sr.no.	Organisation	Guidelines
01	OECD	402 Acute Dermal Toxicity 404 Acute Dermal Irritation/Corrosion 406 Skin Sensitisation 410 Repeated Dose Dermal Toxicity: 21/28 days 411 Subchronic Dermal Toxicity: 90 days 427 Skin Adsorption: *In vivo* method 428 Skin Adsorption: *In vitro* method 429 Skin Sensitisation: Local Lymph Node Assay 430 In Vitro Skin Corrosion: Transcutaneous Electrical Resistance Test(TER) 432 In Vitro 3T3 NRU photo toxicity test 435 In Vitro Membrane Barrier Test Method for Skin Corrosion 439 In Vitro Skin Irritation: Reconstructed Human Epidermis Test Method
02	ICH and FDA Guidelines	Photo safety Testing US FDA EU: Skin Sensitisations EU: Skin Corrosion EU: Phototoxicity - In Vitro 3T3 NRU Japan: Guidelines for Screening Toxicity Testing of Chemicals.
03	US EPA FlFRA Toxicology Testing Guidelines	870.1200 Acute dermal toxicity 870.2500 Acute dermal irritation 870.2600 Skin sensitization 870.3200 21/28 dermal toxicity 870.3250 90 dermal toxicity 870.7600 Dermal penetration
04	WHO Guideline for HDP	Local toxicity testing

Table 1: Safety regulatory guidelines for testing of dermatological products

Sr.no.	Organisation	Guidelines
05	Toxicological Testing for Cosmetics / Personal Care Products	Cosmetic, Toiletry and Fragrance Association (CTFA) European Commission: Notes of Guidance for Testing of Cosmetics Ingredients for Their Safety Evaluation European Commission: Understanding the Principles of Safety Evaluation of Finished Cosmetic Products (Considering a Ban on Animal Testing) Japan: Guidance for Cosmetic Safety Evaluation Colipa Guideline: Guidelines for the Safety Assessment of a Cosmetic Product.

under specific circumstances. *In vivo* studies of corrosive substances should be avoided whenever possible.

Skin sensitisation (OECD 406, 1992):[23] Skin sensitisation (allergic contact dermatitis) is an immunologically mediated cutaneous reaction to a substance. In the human, the responses may be characterised by pruritis, erythema, oedema, papules, vesicles, bullae or a combination of these symptoms. In other species the reactions may differ and only erythema and oedema may be seen. This guideline is developed for the testing of the drugs for any skin sensitizing reactions. The guinea pig has been the animal of choice for predictive sensitisation tests for several decades. Two types of tests have been developed: an adjuvant test in which sensitisation is potentiated by the injection of Freunds Complete Adjuvant (FCA), and non-adjuvant.

Repeated Dose Dermal Toxicity: 21/28 days (OECD 410, 1981):[24] In the assessment and evaluation of the toxic characteristics of a chemical the determination of subchronic dermal toxicity may be carried out after initial information on toxicity has been obtained by acute testing. It provides information on possible health hazards likely to arise from repeated exposures by the dermal route over a limited period of time. There is sufficient similarity between the considerations involved in the conduct of a 21-day or 28-day repeated dose dermal study to allow one guideline to cover both test durations. The main difference lies in the time over which dosing takes place.

Subchronic Dermal Toxicity: 90-day Study (OECD 411, 1987):[25] In the assessment and evaluation of the toxic characteristics of a chemical the determination of subchronic dermal toxicity may be carried out after initial information on toxicity has been obtained by acute testing. It provides information on possible health hazards likely to arise from repeated exposure by the dermal route over a limited period of time.

Skin Adsorption: *In vivo* method (OECD 427, 2004):[26] Exposure to many chemicals occurs mainly through skin whilst the majority of toxicological studies performed in laboratory animals use the oral route of administration. The percutaneous absorption study set out in this guideline provides the linkage necessary to extrapolate oral studies when making safety assessments following dermal exposure.

Skin Adsorption: *In vitro* method (OECD 428, 2004):[27] The purpose of the guideline is to study the evaluation of the absorption of a test substance when applied to external skin. The test substance, which may be radiolabelled, is applied to the surface of a skin sample separating the two chambers of a diffusion cell. The chemical remains on the skin for a specified time under specified conditions, before removal by an appropriate cleansing procedure. The receptor fluid is sampled at time points throughout the experiment and analysed for the test chemical and/or metabolites. When metabolically active systems are used, metabolites of the test chemical may be analysed by appropriate methods. At the end of the experiment the distribution of the test chemical and its metabolites are quantified, when appropriate. Using appropriate conditions, absorption of a test substance during a given time period is measured by analysis of the receptor fluid and the treated skin.

Skin Sensitisation: Local Lymph Node Assay (LLNA) (OECD 429, 2010): [28]: The LLNA studies the induction phase and provides quantitative data for dose response evaluation. A reduced LLNA (rLLNA) can be used when there is a regulatory need to confirm the negative prediction of skin sensitizing potential of the test substance.

In Vitro Skin Corrosion: Transcutaneous Electrical Resistance Test (TER)(OECD 430,2004):[29] This guideline provides the assessment of corrosivity of the test material by *in vitro* method. The Assessment of of skin corrosivity in laboratory animals produces pain and suffering of animals. *In vitro* study is also included in test guideline 404 but it lacked in formal independent validation of *in vitro* test. A formal validation was performed for the *in vitro* method.

In Vitro Skin Irritation: Reconstructed Human Epidermis Test Method (OECD 439, 2010):[30]
This test guideline represents the human health endpoint skin irritation. It is mainly based on reconstructed human *epidermis* (RhE), which in its overall design (the use of human derived

non-transformed *epidermis* keratinocytes as cell source and use of representative tissue and cytoarchitecture) closely mimics the biochemical and physiological properties of the upper parts of the human skin, *i.e.* the *epidermis*. This test guideline also includes a set of Performance Standards (PS) for the assessment of similar and modified RhE-based test methods developed by EC-ECVAM (8). A three-dimensional RhE model, which is cultured to form a multilayered, highly differentiated model of the human *epidermis* is used for performing the test.

In Vitro 3T3 NRU photo toxicity test (OECD 432, 2004):[31] The test is established with the view of testing chemicals or test substances that may produce phototoxic effect when applied to the body. The test evaluates the photo - cytotoxicity effect by the relative reduction in viability of cells exposed to chemicals in the presence versus absence of light. Substances tested using this test may show phototoxic effect *in vivo* after systemic application and distribution to the skin, or by topical application. The test is based upon comparison of the cytotoxicity of a chemical when tested in the presence and in the absence of exposure to a non-cytotoxic dose of simulated solar light.

In Vitro Membrane Barrier Test Method for Skin Corrosion (OECD 435, 2006):[32] The guideline is based upon testing the chemicals which have potential to produce irreversible skin damage, in which visible necrosis through the epidermis and within the dermis can be observed**.** It is proposed with the aim of testing the skin corrosive substances. Artificial membrane is used to see the response of the corrosive substances in a similar manner like in animal in vivo test. Validation studies have been completed for an *in vitro* membrane barrier test method. The commercially available test method is Corrositex®. This guideline also provides the categorization or classification of the corrosive substances according to the Global Harmonization System (GHS) The test includes two components: synthetic macromolecular bio-barrier and a CDS (Chemical Detection System). The test is based upon the detection of the barrier damage by corrosive test substance after application of the test substance to the artificial membrane barrier most probably by the same mechanism of corrosion that operate on living skin. The penetration of the test substance through membrane barrier can be measured by a number of procedures, including a change in the color of a pH indicator dye or in some other property of the indicator solution below the barrier.

EU: The European Medicines Agency (EMEA) was established in the mid-1990s to administer the multitude of EU laws developed by the EC's Directorate General for Enterprise in relation to the evaluation and authorization of pharmaceutical products and biologics destined for human and/or veterinary use.

EU: Phototoxicity – In Vitro 3T3 NRU: [33] The test gives excellent effects compared to *in vivo* test. This test helps to identify the phototoxic potential of the test substance in association with the UV and visible light exposure.The test is based upon the cell damage by the test substance which can occur by four different mechanisms. The test is based upon the comparison of the cytotoxicity of the chemical in the presence and absence of exposure to non-cytotoxic dose of UV / visible light. Cytotoxicity is expressed as reduction of the uptake of the Neutral red dye 24 hrs after treatment with the test chemical and irradiation.

US EPA FIFRA: These guideline are series of test guidelines that have been developed by the Office of Prevention, Pesticides and Toxic Substances, United States Environmental Protection Agency for use in the testing of pesticides and toxic substances, and the development of test data that must be submitted to the Agency for review under Federal regulations.

870.1200 Acute dermal toxicity:[34] Acute dermal toxicity determination is useful where exposure by the dermal route is likely in the assessment and evaluation of toxic characteristic of the test substance. Acute dermal toxicity provides information on health hazards likely to arise from short-term exposure of the substance by the dermal route. Data from an acute study may serve as a basis for classification and labeling. It is an initial step in establishing a dosage regimen in subchronic and other studies and may provide information on dermal absorption and the mode of toxic action of a substance by this route. An evaluation of acute toxicity data should include the relationship, if any, between the exposure of animals to the test substance and the incidence and severity of all abnormalities, including behavioral and clinical abnormalities, the reversibility of observed abnormalities, gross lesions, body weight changes, effects on mortality, and any other toxic effects. This test is useful to study the test in either rats, rabbits, or guinea pigs or other species adapted for study. Dosing test substances known to cause marked pain and distress due to corrosive or irritating properties need not be carried out.

870.2500 Acute dermal irritation:[35] In the assessment and evaluation of the toxic characteristics of a substance where exposure by the dermal route is likely, determination of the irritant and/or corrosive effects on skin of mammals is necessary. Information derived from this test helps to identify the possible hazards likely to arise from exposure of the skin to the test substance. Data on primary dermal irritation are required by 40 CFR part 158 to support the registration of each manufacturing-use product and end-use product.

870.2600 Skin sensitisation:[36] The purpose of the test guideline is to identify test substances with skin sensitisation potential. The determination of the potential to cause or elicit skin

sensitisation reactions (allergic contact dermatitis) is an important factor in evaluating the toxicity of substance. The information derived from skin sensitisation tests aids in recognizing the possible hazards to a population exposed repeatedly to a test substance. Testing of the test substance is not required if the test material is a known skin sensitizer. The methods used for testing of substance are: Local Lymph Node Assay (LLNA) test, or Guinea-pig Maximization Test (GPMT), or Buehler test. These tests are based upon the skin sensitisation reaction study.

870.3200 21/28 dermal toxicity:[37] This study provides information on possible health hazards which are likely to be produced during repeated (21/28 days) dermal exposure to the test substance. It provides information on the intensity of the percutaneous absorption, target organs, possibility of accumulation of the test substance. The information obtained can be used in selecting dose levels for long-term studies and for establishing safety regimen for human exposure. The study is not helpful in determining the effects which have a long latency period. The information obtained to humans from this study is valid only for a limited degree. This test serves as a preliminary test to the 90 days study. The test substance is applied in a repeated dose to the skin of several experimental animals; for 21/28 days. In this study three test dose levels are used and one control. An additional satellite group is included which consist of animals dosed with higher dose and kept for observation for further 14 days after completion of the 21/28 days study. The degree of irritation of the substance is interpreted and scored at specified intervals and is further described to provide a complete evaluation of the effects. The duration of the study should be sufficient to permit a full evaluation of the reversibility or irreversibility of the effects observed but need not exceed 21/28 days. When testing solids (which may be pulverized if considered necessary), the test substance should be moistened sufficiently with water or, where necessary, a suitable vehicle, to ensure good contact with the skin. When vehicles are used, the influence of the vehicle on irritation of skin by the test substance should be taken into account. Liquid test substances are generally used undiluted.

870.3250 90- day dermal toxicity:[38] The subchronic dermal toxicity (90 days study) is carried out based on the information obtained from acute and sub-acute toxicity testing of a chemical. The 90- day dermal toxicity study has been designed to allow the determination of the no-observed-effect level (NOEL) and toxic effects associated with continuous or repeated exposure to a test substance for a period of 90 days. It provides useful information on the test substance degree of percutaneous absorption, target organs, the possibilities of accumulation. It is also useful in selecting dose levels for chronic studies and for establishing safety regimen

for the human exposure. This test serves as a preliminary test to the chronic dermal toxicity study. The test substance is applied in a repeated dose to the skin of several experimental animals; for 90 days. In this study three test dose levels are used and one control. An additional satellite group is included which consist of animals dosed with higher dose and kept for observation for further 14 days after completion of the 90 days study. The degree of irritation of the substance is interpreted and scored at specified intervals and is further described to provide a complete evaluation of the effects. The duration of the study should be sufficient to permit a full evaluation of the reversibility or irreversibility of the effects observed but need not exceed 90 days. When testing solids (which may be pulverized if considered necessary), the test substance should be moistened sufficiently with water or, where necessary, a suitable vehicle, to ensure good contact with the skin. When vehicles are used, the influence of the vehicle on irritation of skin by the test substance should be taken into account. Liquid test substances are generally used undiluted

870.7600 Dermal penetration[39]: The information from dermal absorption study permits to determine the risk in case where the oral or inhalation route has shown toxic effects in experimental animals and the test substance is used by humans through dermal route. A complete kinetic analysis essentially enables an investigator to convert oral or inhalation low-effect and no-effect doses into dermal low-effect and no-effect doses, thus allowing the calculation of an margin of exposure or risk for systemic toxic effects which have not been or cannot be tested practically by the dermal route .The complete kinetic analysis can be performed in two ways. The first entails calculating the maximum systemic doses produced by the oral (or inhalation) no-effect and low-effect doses and calculating the dermal doses which will produce the same maximum systemic doses. The calculated dermal no-effect and low-effect values are then compared with the dermal exposures from the risk assessment. In a second method the dermal exposure is converted to a maximum systemic dose which is compared with the maximum systemic doses equivalent to the oral no-effect and low-effect doses. Information on dermal exposure is necessary in order to determine doses and durations of exposure to be evaluated in the dermal absorption study. It is expected that this information will have been gathered in order to perform the risk assessment and to make the basic decision as to whether the study is required. The test substance to be tested should be of known chemical purity and radio labeled. The information derived from skin sensitisation tests aids in recognizing the possible hazards to humans exposed repeatedly to a test substance.

WHO: WHO is the authority responsible for public health within the system of United Nations. WHO/Europe collaborates with a range of public health stakeholders in the Region and globally, to ensure that coordinated action is taken to develop and implement efficient health policies and to strengthen health systems

Local Toxicity Test[40]: According to WHO guideline, local toxicity testing of dermatological preparations is performed with a view of observing dermatological reactions after application of the preparation. Local toxicity testing of herbal drugs is performed by various tests which include; skin sensitisation test, adjuvant and patch test, buehler test, draize test, freund's complete adjuvant test, maximization test, open epicutaneous test, optimization test, split adjuvant test etc. If the preparation is solid preparation, then it is to be made wet with water or a suitable solvent to provide a uniform application; if the preparations are semi-solid preparations, then to be tested as undiluted preparations. If preparations are liquid preparations then to be tested as undiluted preparations However, an aerosol agent can be diluted if necessary. Guinea-pigs are considered the most suitable experimental animals due to their high susceptibility. It is recognized that the above-mentioned methods differ in their probability and degree of response to sensitizing substances. However, it is generally accepted that the use of freund's complete adjuvant increases sensitivity and therefore the possibility of detecting substances with weak sensitizing potential. The skin reaction of each animal should be evaluated according to the assessment standard of the particular test method used. Other local toxicity tests may be conducted if the herbal medicine is intended for such use i.e. vaginal, rectal, respiratory, etc. irritations tests.

Cosmetics / Personal Care Products was founded in 1894 as the Manufacturing Perfumers' Association and was renamed to the American Manufacturers of Toilet Articles (AMTA) in 1922; in 1970 the association adopted the name Cosmetic, Toiletry, and Fragrance Association. In November 2007, the name was changed to the Personal Care Products Council.

Toxicological testing for Cosmetics / Personal Care Products: Cosmetic, Toiletry and Fragrance Association (CTFA): This is an association formed for the safety evaluation of products manufactured in New Zealand. This mainly focuses on the evaluation of safety of cosmetic and toiletry preparations.

The European Commission is the executive body of the European Union. The body is responsible for proposing legislation, implementing decisions, upholding the Union's treaties and the general day-to-day running of the Union.

European Commission: Notes of Guidance for Testing of Cosmetics Ingredients and for Their Safety Evaluation: [41] The "Notes of Guidance for Testing of Cosmetic Ingredients and Their Safety Evaluation by the SCCP" is a document assembled by the members of the Scientific Committee on Consumer Products (SCCP, replacing the former SCCNFP and SCC). The document is prepared such that it contains appropriate information on the different aspects of testing and safety evaluation of cosmetic ingredients. This document provides guidance for testing of cosmetic ingredients and for the safety assessment of finished product. This guideline is applicable to both the competent authority of the member states, and to the persons who are manufacturing cosmetics and introducing them into the market. This guideline is based upon testing of cosmetic ingredients by various methods, like acute toxicity testing, subchronic toxicity testing, chronic toxicity study photo toxicity testing, skin absorption, percutaneous absorption, skin irritation, skin corrosion testing etc.

There are many other guidelines provided by different regulated countries for the dermal testing of the drug. EU (European Union): skin sensitisation test, skin corrosion test, Japanese guidelines for screening toxicity testing of chemicals. The main principle behind this guideline is to provide relevant data on the safety profile of a test substance before its human exposure to avoid accidents. OECD guidelines are the guidelines which are followed basically for testing of chemicals.

For dermal testing currently there are many *in vitro* test procedures introduced in relation to in vivo studies in animals. The *in vivo* test are been replaced by *in vitro* test due the more specificity of the results. Test like skin sensitisation, skin corrosion are replaced by *in vitro* tests. Considering the ban on animal study for the safety evaluation of cosmetic products several new *in vitro* procedures are being introduced and authorized by the regulatory authority.

To facilitate the replacement of existing procedures with new one there are processes developed nationally and internationally, considering test method development, regulatory acceptance consideration of the method at national and international level.[42] European commission for cosmetic ingredients has banned the use of animals for the testing of animals and using the alternative method instead, contending that the ban is for the test meeting the EU regulatory outline for cosmetics.[43] Computer or mathematical modeling is becoming a strategy for replacing the animal experimentation. QSAR (Quantitative Structure Activity Relationships) is one of the mathematical method of screening which is developed to predict the skin and ocular irritancy. A concept known as Threshold of Toxicological Concern (TTC) was introduced. Briefly, the TTC is a concept that is based on the assumption that for all

substances there is a level of human exposure below which there is a negligible probability of an appreciable risk to human health with regards to systemic toxicity [44].

Need of upgrading existing guidelines:

Limitation of existing guidelines: The existing guidelines are limited to the safety evaluation of chemicals, cosmetics and their ingredients, but it does not include the testing of HDP (medicinal and cosmetics) which are used by the large population as over the counter products. It constricts to the testing of chemical moiety. There is a need for testing of formulations as there may be any change in its properties when it is formulated with other ingredients.

Up gradation of existing guidelines: There is a need for the up gradation of existing guidelines for the testing of HDP. For testing the HDP newer criteria can be considered. A new concept like reverse pharmacology can also be applied for the evaluation of safety of the products to reduce the cost, time and toxicity. Reverse pharmacology is with a scope to understand the mechanism levels of biology and to optimize safety, efficacy, and acceptability of herbal products. In reverse pharmacology, a reverse path is followed i.e. from clinical to laboratory. There should be well documented clinical case studies to substantiate safety profile of herbal dermal OTC products which can help in drawing some common conclusive observation and parameter applicable for safety testing of HDP. Thus, clinical data can be used to evaluate the safety parameter of the HDP[45]. The database available from post- marketed products can be used for facilitating the concept of reverse pharmacology, so with minimum time we can produce internationally accepted uniform *invivo, invitro* and *exvivo* models which can cover all dermatological and cosmetic product from various areas across globe.

SCOPE: There are various regulations for the safety assessment of chemicals and cosmetics carried out by different regulatory authorities. There is a need to harmonize the testing of cosmetics and herbal medicines globally to avoid unnecessary health hazards. Emphasize should be put on developing international guidelines for the safety assessment of herbal OTC dermatological products as these are taken by the public as self medication without knowing the adverse effects. The use of traditional data of the herbal ingredients and the regulatory guidelines may help in launching the products with its safety profile. Provision of toxicity data will make the consumer aware of its application carefully.

CONCLUSION

The use of herbal medicine is increasing and large number of population uses it believes that they are safe. The need of harmonization of guidelines is essential for the assessment of safety of the herbal OTC dermatological products before they are been launched in the market. The standardisation of herbal drugs is an important factor and taking this into consideration it is necessary to upgrade the available guidelines to include HDP. Inclusion of HDP testing for its safety profile will help to use it on a large scale. Although most of the herbal drugs originate from plants with a history of traditional use, it does not mean that they are safe. The use of all available information through traditional use and its history should be done for the evaluation of the safety and efficacy. Thus, the use of available guidelines and traditional history of herbal drug together may help in evaluating the safety profile of the herbal dermatological OTC products.

REFERENCES

1. Buhse, L., Kolinski., R., Westenberger B., Wokovich, A., Spencer, J., Chenb C.W., Saleh Turujman, S., Basak M.G., Kang G.J., Kibbe A., Heintzelman, B., Wolfgang E, Topical drug classification, International Journal of Pharmaceutics 2005; 295: 101–112.
2. Panchawat, S., Rathore, K.S., Dr. Sisodia, S.S., Dr. Nema R.K. Standardisation and evaluation of Herbal Drug Formulation, Articles base, 2009.
3. Pieter A. Hooyenga, Renger F. Witkamp, Kees Groen Herbal products: Marketing strategies and legislation; International Journal of green pharmacy, 2009; 270-276.
4. Lalla, J.K., Nandedkar, S.Y., Paranjape, M.H., Talreja, N.B, Clinical trials of ayurvedic formulations in the treatment of acne vulgaris, Journal of Ethnopharmacology,2001;78: 99–102.
5. Drug Safety Update, monthly newsletter from Medicinal and Healthcare products Regulatory Agency and Commission on Human medicine, 2008;1: Issue 7.
6. Makunga, N.P., Philander, L.E., Smith, M., Current perspectives on an emerging formal natural products sector in South Africa, Journal of Ethnopharmacology, 2008; 119:365–375.
7. Nicholas Hall and Company, India, DB6 2006.
8. Bhangale,V., OTC Marketing of Drugs, International Marketing Conference on Marketing & Society, IIMK, 2007; 8-10

9. Calixto, J.B., Efficacy, safety, quality control, marketing and regulatory guidelines for herbal medicines (phytotherapeutic agents) Brazilian Journal Medical and Biological Research 2000; 33: 179-189
10. European Centre for Ecotoxicology and Toxicology of Chemicals [ECETOC], 1993. Monograph No. 20. Percutaneous Absorption.
11. US Environmental Protection Agency, Consumer products. In: Exposure Factors Handbook, vol. III, 1997; pp.16.1–16.40, Washington, DC 20460.
12. Anton, C. de Groot, Dermatogical drugs, topical agents and cosmetics, Chp. 14, Side effects of drugs, Annual 19, 1996 ; Elsevier Science B.V.
13. Belsito, D., Bickers, D., Bruze, M., Calow, P., Greim H., Hanifin, J.M., Rogers, A.E., J.H. Saurat , I.G. Sipes , H. Tagami, A toxicologic and dermatologic assessment of salicylates when used as fragrance ingredients, Food and Chemical Toxicology, 2007; 45 S318–S361.
14. K. B. Burade, A. R. Chopade & B. S. Kuchekar. Acute Dermal Toxicity Studies of Pitika Mardini and Esabdamini in Rodents, Arch Pharm Sci & Res ,2009; 1 : 2, 171 -174.
15. Corson, T.W., Crews, C.M., Molecular understanding and modern application of traditional medicines: triumphs and trials. Cell, 2007; 130: 769–774.
16. Cordell, G., Natural products in drug discoverys creating a new vision. Phytochem. Rev. 1, 2002; 261–273
17. Aggarwal, B.B., Sundaram, C., Malani, N., Ichikawa, H., 2007. Curcumin: the Indian solid gold. Adv. Exp. Med. Biol. 595, 1–75.
18. Toxicity prediction of compounds from turmeric (Curcuma longa L)S. Balaji, B. Chempakam, Food and Chemical Toxicology 2010; 48: 2951–2959
19. Deshpande, S., Lalitha, V.S., Ingle, A.D., Raste, A.S., Gadre, S.G., Maru, G.B.,.Subchronic oral toxicity of turmeric and ethanolic turmeric extract in femalemice and rats. Toxicol.Lett, 1998; 95:183–193.
20. Kandarkar, S.V., Sawant, S.S., Ingle, A.D., Deshpande, S.S., Maru, G.B.,.Subchronic oral hepatotoxicity of turmeric in mice – histopathological and ultrastructural studies. Indian J. Exp. Biol. 1998; 36: 675–679.
21. Acute Dermal Toxicity (OECD 402, 1987).
22. Acute Dermal Irritation/Corrosion (OECD 404, 2002).
23. Skin Sensitisation (OECD 406, 1992).
24. Repeated Dose Dermal Toxicity: 21/28 days (OECD 410, 1981).
25. Subchronic Dermal Toxicity: 90-day Study (OECD 411, 1987).

26. Skin Adsorption: In vivo method (OECD 427, 2004).
27. Skin Adsorption: In vitro method (OECD 428, 2004).
28. Skin Sensitisation : Local Lymph Node Assay (LLNA) (OECD 429, 2010).
29. In Vitro Skin Corrosion: Transcutaneous Electrical Resistance Test (TER) (OECD 430, 2004).
30. In Vitro Skin Irritation: Reconstructed Human Epidermis Test Method (OECD 439, 2010).
31. In Vitro 3T3 NRU photo toxicity test (OECD 432, 2004).
32. In Vitro Membrane Barrier Test Method for Skin Corrosion (OECD 435, 2006).
33. EU : Phototoxicity – *In Vitro* 3T3 NRU.
34. US EPA FlFRA Toxicology Testing Guidelines, 40 CFR 870.1200 Acute dermal toxicity.
35. US EPA FlFRA Toxicology Testing Guidelines, 40 CFR 870.2500 Acute dermal irritation.
36. US EPA FlFRA Toxicology Testing Guidelines, 40 CFR 870.2600 Skin sensitisation.
37. US EPA FlFRA Toxicology Testing Guidelines, 40 CFR 870.3200 21/28 dermal toxicity.
38. US EPA FlFRA Toxicology Testing Guidelines, 40 CFR 870.3250 90- day dermal toxicity.
39. US EPA FlFRA Toxicology Testing Guidelines, 40 CFR 870.7600 Dermal penetration.
40. Research guideline for evaluating the safety and efficacy of herbal medicines, Local Toxicity Test, WHO guidelines, 1993.
41. European commission: The sccp's notes of guidance for the testing of cosmetic ingredients and their safety evaluation, 6th revision, 2006.
42. 2009 NICEATM-ICCVAM Activity Test Method Validation and Regulatory Acceptance in the US. Last Updated: March 30, 2010.
43. EU Regulation Update: Tackling the Animal Testing Ban By: Annelie Struessman, PhD, CONUSBAT, 2010.
44. Nohynek, G. J., Antignac, E, Thomas R, Toutain H., Safety assessment of personal care products/cosmetics and their ingredients, Toxicology and Applied Pharmacology,2010; 243: 239–259.
45. Patwardhan, B., Ashok, D. B., Vaidya, Chorghade, M., and Joshi, S.P., Reverse Pharmacology and Systems Approaches for Drug Discovery and Development, Current Bioactive Compounds 2008; 4: 000-000.