Chapter 7
Safety and Efficacy Testing of Topical Products; Practical Considerations

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7.1 Introduction

Skin has always been looked upon as our external natural gear which protects the body from environmental factors like sun, pollution, extreme temperatures, etc. Like our attire, the skin too is supposed to describe one's looks and make a firm statement about one's personality. This external organ of our body which we see more often that the hidden complexities of other vital organs has, thus, been nearer and dearer to all of us. No wonder then that the safety of skin has been of paramount importance to all.

In spite of this, the scientific community started considering systematic safety evaluation of skin products relatively late in the day. It was probably in the year 1966 that Prof. Kligman first proposed the standardized method for detecting the contact allergens in a scientific way [1]. Our knowledge of skin safety testing has evolved several folds since then with the use of standardized protocols, techniques, and availability of newer noninvasive biomedical instruments. However, when it comes to skin safety testing, there is no single method that will be apt for a particular study. As Prof. Maibach puts it after his years of deep experience in the field, "It all depends" on a variety of factors.

The practical aspect related to safety and efficacy will always hold the key in defining the successful evaluation of any topical product. In this chapter, I have tried to capture few such points related to the evaluation of cosmetic products and topical drug formulations. Not all of them are technical.

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7.2 Consumer Habits and Its Importance in Designing Safety and Efficacy Studies of Cosmetic Products

The importance of "Consumer habits" cannot be overlooked in designing safety and efficacy studies of cosmetic products. In fact, the variations in patch testing methodologies such as occluded, open, repeat application open, or occluded are all acceptable precisely for the same reason. While selecting any of these approaches, the product knowledge and its intended use by the consumer must be given paramount importance. An overdesigned unrealistic safety protocol may result in rejecting a product/formulation whereas a lenient unthoughtful theoretical approach may put the consumer at undue risk. The role of the principal investigator and his team, who monitor the trial, is to select an appropriate study design, may be slightly stringent and exaggerated than the actual use conditions, so as to provide an adequate safety margin to protect the end-consumer.

The same holds true while designing efficacy studies as well. For example, imagine a study protocol for the evaluation of an antidandruff shampoo among Asian consumers. The Asian consumers on an average shampoo their hair two to three times a week as against their counterparts in western countries who have a habit of shampooing their hair daily. The Asian consumer also applies hair oil before shampooing which has been a traditional habit in this part of the world. A study design wherein a daily hair wash with antidandruff shampoo and restricting the participants with the use of hair oil will result in larger dropouts due to noncompliance. Also, the outcome of this study, even if positive, will have little relevance in the real-life situation in that market.

It is precisely for this reason that the revalidation of safety and efficacy data is necessary when launching a cosmetic product in new markets. It can be done through short but well-designed safety and efficacy trials which are controlled and supervised by experts followed by in-use consumer trials. It will be irrational to assume that the product will do well in new markets since it has done well in the past in other markets.

7.3 Mindset Issues: Testing for Claims vis-à-vis Claiming "What Tested"

The central theme in testing a topical product for safety and efficacy has to be "the patient" who is finally going to use the product or "the end-consumer" in case of cosmetic formulations. The channel partners such as the medical fraternity, domain experts, and others come thereafter. Today, the whole purpose of testing the product has become that of compliance with the regulatory requirements, often country specific, and outsmarting competition to succeed in the market place. While these are crucial considering business imperatives, they by no means can be the main reasons for evaluating the products. This mindset has taken away the inquisitiveness which

is needed in product testing and makes product evaluation a mere ritual. While the ethical guidelines in conducting clinical evaluation do address participant's safety, it does not and cannot address passion needed by the sponsor, principal investigator and other associated members involved in the trial to make it more holistic and prevent it from being a mere ritual.

In the cosmetic industry, very often the need for product evaluation is triggered by marketing needs for product's preconceived claim. The claim thus drives cosmetic product safety and efficacy evaluation rather than the product's safety and efficacy evaluation driving claims. This is not to take away the credit for the efforts being put in by many cosmetic companies doing basic research and by specialty ingredient manufacturers to find new actives. The point being made here is that these efforts often get diluted so as to pass on the real benefit to the end-consumer.

Also, what we see today are the claims from cosmetic companies which are aimed at outsmarting competitor's claims rather than the claims addressing consumer needs. How many such claims help to build credibility of these products in consumer's mind is anybody's guess.

7.4 Efficacy Results and Interpretations—Instrumental, Clinical, and Consumer Perceptions

With advancements in the area of biomedical instrumentation, objective evaluation has become an integral part of efficacy evaluation of cosmetic products. It has found applications in topical drug product evaluation as well. For example, the vasoconstriction assay for bioequivalence of topical corticosteroids as recommended by the United States Food and Drug Administration (USFDA) guidance mentions use of tristimulus colorimeter such as chromameter for quantification of skin blanching effect [2]. The wide range of skin imaging and bioengineering instruments has provided additional tool for the quantification of various skin parameters.

The use of instrumentation does not undermine the clinical evaluation by experts such as dermatologist/cosmetologist. In fact, a comprehensive protocol for evaluation of efficacy of a topical product be it cosmetic or topical drug formulation, should include clinical evaluation, instrumentation, and self-evaluation by participants to capture the holistic product performance. Very often it has been observed that the instrumentation may capture improvement in certain attributes at an early stage during trial period, followed by clinical improvement as recorded by dermatologist, followed by improvement perceived by the participants. This is understandable. Thus, comprehensive evaluation may take longer time. The practical consideration often limits conducting product trial for such a long duration. An instrumental change observed after 1 month may take several months of product application before the change is seen by the user/participants. The product claims, more in the case of cosmetic products, are made based on earliest significant change as detected by instruments or experts. Thus, we often come across claims like "Within 2 weeks" or "longer lasting for 24 h," etc. In practice, it has been observed at our end that

unless the change as captured by instrumentation for critical parameters exceed 25% compared to initial stage, the effect of product performance will not be perceived at the participants/consumers. This is applicable to cosmetic formulations. This is one way of identifying the critical performance parameters which can be taken forward to make product claim and that will be appreciated by the end-user.

The mere use of instruments does not guaranty correctness of the outcome. As Prof. Albert M. Kligman said, "A Fool with a Tool is still a fool." This is so true. Unless one has taken care and pain to understand, standardize, and calibrate these instruments for regular use, the outcome with such instruments has limited utility. The same is the case while using clinical scales to capture clinical improvement in the skin condition. The periodic training for those who grade clinical improvement and aligning these evaluators in case there are more than one evaluator (often being the case with multicentric trails) becomes of paramount importance.

Finally, the self-evaluation questionnaire to be administered to the participants in the trial can reflect interesting practical concerns/benefits, provided this questionnaire is structured with great care to meet the end objective of the trial.

Obviously then, the collective wisdom of experts and participants supported by objective data from the correct use of instrumentation can give immense insights for practical success of the product in the market place.

7.5 Product Knowledge and Testing Methodology

Mindless testing to comply with internal stake holders in the organization or external stake holders (outside the organization) often creates confusing study requirements. How can someone design a study protocol to prove "Non-irritant" claim for an AHA-based product which is supposed to be a skin peel? How to evaluate primary skin irritation of a topical anti-itch or rubefacient product with patch testing methodology since that is an accepted testing protocol for primary skin irritation?

While many such requests seem ridiculous at the first go, they may provide a trigger for doing something new and innovative either with respect to study design, new techniques or building new skills. But then, a sound and holistic knowledge not only of clinical practices but that of product formulation, new ingredients, newer instrumentation, and emerging new claims is needed.

For example, in one study for a modified topical corticosteroid formulation, the sponsor wanted a "Proof-of-Concept" clinical study by adapting vasoconstriction or blanching study protocol. The existing formulation of the same steroid was modified using skin penetration enhancer. The rationale behind this study is that with penetration enhancer the blanching effect will be more pronounced which presumably relates to the amount of drug entering the skin and hence more bioavailability [3].

The preliminary studies, however, indicated lower blanching effect compared to the formulation without penetration enhancer. The possible explanations could

be systemic absorption of the drug due to enhanced penetration thru the skin. This effect, however, is not desirable.

The conceptualization of a product idea with possible effects and likely enhanced side effects therefore is of paramount importance in designing comprehensive safety and efficacy protocols.

7.6 How to Create a Value Proposition for the Sponsor and Consumer Through Safety and Efficacy Testing?

In a commercial setup, no organization would like to undertake any business activity unless it adds significant value either to its top line (read profitability) or bottom line (read cost structure improvement). Very often, while it is easy to identify value adding activities for the immediate future, it is often difficult to visualize value adding propositions for the strategic long-term period, say over 5–10 years. It is all the more difficult to identify such initiatives in the research and development function of an organization since the function itself by the nature has many "ifs" and "buts" to answer. In spite of this, many organizations have successfully accomplished their strategic objectives by coordinating and meshing activities of various functions within organizations responsible for a new product launch including clinical outcomes and product claims. This success often is the outcome of well planned and thought through set of activities connecting seamlessly across various functions.

The thought process for planning these activities invariably starts from markets to be catered to, users in these markets (end-consumers in case of cosmetic products and patients and dermatologists for dermaceuticals and topical pharmaceutical products). The correct insights into their needs is the most important but equally difficult task, which if done correctly, opens will open the path for successful product launch. This is followed by rating and ranking all the needs and asking the consumer/customers to score their level of satisfaction on a simple scale from 0 to 5 or any other suitable scale. This simple exercise helps in identifying those areas or gaps which can then be filled with the product under consideration. Having identified the gaps, the next step is to verbalize them with an exhaustive and comprehensive product brief which is the first step in the research or developmental activity of a new product. The critical activity thereafter for the R&D team is to convert this product brief into a technical brief wherein each and every customer need is effectively measured by one or more quantifiable technical parameters. This is not simple and needs thorough deliberation within the R&D team. Many of these technical parameters can be measured through systematic safety and efficacy studies. The early identification of safety and efficacy evaluation parameters helps in effective identification of product strengths and weaknesses. The entire product improvement, launch and communication strategy then can be designed around these findings. The process is the adaptation of the quality function deployment (QFD) process which is very successfully followed in various industries such as automobile and many others.

This process helps in connecting a consumer need in the case of cosmetic products and a dermatologist or skin expert's needs for pharmaceutical products to product performance and deliverables.

7.7 Ethical Issues in Study Design

The study design for safety and efficacy evaluation is often conceptualized by the sponsor or the company wanting to conduct these trials. Obviously, their objective is to derive as much information as possible with optimal sample size of participants and at a competitive cost. This is natural from their viewpoint but in this process very often the ethical issues in the conduct of the trial get overlooked. For example, a skin lightening trial for a cosmetic face cream often describes a protocol wherein volunteers/participants would apply the product under evaluation to half the face and the other half will be applied a placebo cream. If one looks at the study hypothesis, it states that the product under evaluation is expected to significantly lighten the skin (statistically significant difference at 95 % confidence interval) in a specific time period compared to placebo cream. The reason for doing half-face trial is to have each individual acting as his own control in the trial thereby eliminating an important variable, i.e., of skin type and individual life style and habits.

If this hypothesis was to come true, the trial would end up with number of participants having one side of their face looking significantly lighter than the other side. While the sponsor will be delighted with these results which prove that their product is efficacious, how is it likely to impact the participants? Is it therefore ethically correct to conduct such a trial?

Here is another example for safety evaluation of topical products. In this case, the regulatory body has recommended a protocol for patch testing wherein 3 % sodium lauryl sulphate (SLS) has been recommended as positive control [4]. The test protocol further suggests that only those volunteers showing combined erythema and edema score of more than 4 (Draize scale) should be included in the patch testing study. This may be because it is difficult to visually grade erythema in participants with darker skin (skin type 4 predominantly) thereby necessitating use of such high levels of SLS. The skin damage which 3 % SLS may evoke serious ethical issues more so when the same volunteers repeatedly participate in these safety studies over a period of time.

So, it is not only the sponsoring organization but sometimes even regulatory authorities who need to be sensitive to ethical issues while drafting guidelines in conduct of a trail.

The Ethics Committee/Institutional Review Board approving such trials has a very important role to play in protecting participant's well being which very often the sponsor and regulators themselves may not be in a position to visualize.

The point being made here is that along with the technical considerations one has to consider social and psychological factors in practice to safe guard the interest of all involved parties.

7.8 Summary and Conclusion

While at a macroscopic level, there are differences between Caucasian, Hispanic, Asian, and African skin, structurally, all skin types have similar qualitative structure. At quantitative levels, they differ from each other. For example, African and Asian skins have greater levels and different dispersion of melanosomes because of different photo-protection needs. Similarly, differences in skin thickness exist for different skin sites. Sex and age may also change biomechanical properties of the skin to a certain extent. These changes may be important for the evaluation of certain types of products while they may not significantly impact others.

The practical consideration and understanding therefore, is of paramount importance in conducting any safety or efficacy trial for topical products. Clear understanding of study objective, product–skin interaction, ethical consideration with respect to participant's safety and benefits, and intrinsic desire to offer value to the patients or end-users is the key to innovate newer products and therapies. This in turn will bring credibility and sustainability to the sponsoring companies to create profitable business propositions.

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