Behind the claim

Dermatologically tested, hypoallergenic or clinically tested?

In this column we will talk about the claim on cosmetics and about the most suitable test to support them

This is the first of a series of appointment where we will talk about the claim on cosmetics and about the most suitable test to support them.
One of the most common claims is "dermatologically tested". Despite the familiarity you should have with this statement, are you sure to know exactly what it does mean? According to The EU Guidelines to Commission Regulation (EU) No 655/2013, "*it implies that the product has been tested under the supervision of a dermatologist*". This does not clarify what kind of test it relies upon, but as the guidelines report shortly after "*Depending on the presentation of the claim, it may refer to a specific efficacy or tolerance of the product.*"
The use of the claim "dermatologically tested" for cosmetic products was also assessed by the European Court of Justice (Case C-99/01). The Court clarified that "*the average consumer's expectation of such a claim is that the product underwent tests intended to study its effects on the skin and that the results of those tests were positive and showed that the product was well tolerated*". That said, we should more likely say that the most suitable test will investigate mainly the safety of the product, even if the "dermatologically tested" claim may also embrace a test for effectiveness.
In most cases, the standard test performed to support the claim is a *48h patch test*.
Some ambiguity with the term "clinically tested" may arise. This claim refers to expertise, process or conditions under which the tests were carried out: "*Clinically tested" means that the product was tested on humans under the supervision of a medically qualified professional or another scientifically qualified professional according to a clinical protocol or in a clinical setting.*" Hence, oppositely to what is normally perceived, the claim does not always imply the supervision of a physician, nor the conduction in a clinical institute is mandatory. The most important thing is that the study on human subjects is carried out according to a defined and appropriately designed clinical protocol aimed to investigate safety or effectiveness on a suitable number of subjects in controlled conditions, with a correct statistic and with a preliminary ethical committee evaluation in some situations (i.e. borderline products, children etc.).

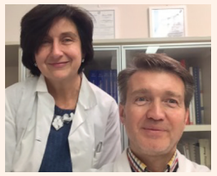
Almost every new formulation developed is normally patch tested before its placing on the market. The cosmetic regulation 1223/09 states that the manufacturer is responsible for the safety of the product and that proof for the product's skin compatibility must be reported in the CPSR (Cosmetic products safety report). Patch tests are carried out on a panel of human subject (at least 20) to check the skin irritation risk. The product is placed on the back of the volunteers, generally with an occlusive patch, for 48h. After patch removal, the skin is inspected at different time-points (15 min, 24h) and the eventual appearance of erythema, edema, vesicles and dryness/desquamation is reported with a score (0-3). The average score is called the MII (Mean Irritation Index). A product is declared as not being an irritant when the MII is < 0.5. What normally is less known, is that I can have a visible reaction in 4 or 5 subject, or a light reaction on 9 out of 20 and still have a MII<0.5 and a "not irritant" judgment despite the very high percentage of reactivity on such a small population. It is true that the product is tested in occlusion and hence under exaggerated conditions of exposure, but the probability of side effects arising in such a case will be very high. What we want to clarify is that the patch test, especially if performed on a small panel, is not a very sensitive mean to predict the product safety on a large population of consumers. That is why many manufacturers prefer to perform an HIRPT (Human Insult Repeat Patch test) on a larger panel of volunteers. In HIRPT the patch test is repeated for several sessions in order to stress the product exposure more and to involve the immune response. In a basic repeated insult patch test, the product application is repeated every day up to 4 times (24h each), on the same skin site. A skin assessment is made every day at patch removal.
This kind of HIRPT may be a more suitable test for products destined to contact with the mucosae or for children of 3 years and lower age, as well as for claiming that a product is "suitable for delicate skin".

Another interesting topic may be how to test products claiming safety "for sensitive skin". In this case the patch test is carried out on selected panel with sensitive skin. Volunteers are screened with a stinging test with 1% lactic acid. Subject who reacts to this reagent when applied in a specific way, are recruited as showing sensitive skin. They are far less in the population than what apparently thought and claimed by simply answering the questionnaires.

For intimate hygiene products often the preferred claim is "gynecologycally tested", that means an in-use test under the supervision of a Gynecologist, even if we recall here that the external genitals are also a dominium of competence of dermatologists . It is not a case if the specialization is called "dermatology and venereology".

Another strategy to investigate the skin compatibility of special products deeper may be to complete the results from a patch test with supplementary *in vitro* tests like skin irritation on 3d epidermis (OECD 439), cytotoxicity on skin-derived cells, or irritation tests on different target epithelia (i.e., oral and vaginal mucosae, corneal epithelia). All these *in vitro* tests are very sensitive, give quantitative and objective results and are very useful to compare formulas and to better identify and trace the level of risk also on a batch-to-batch basis.
In the case of Eye irritation for example, the *in vitro* test on human corneal epithelia (OECD 492) is completely replacing the Draize test on rabbits, gives quantitative results, and allows to perform a test equivalent to the direct instillation in the eye, which is not practicable in human volunteers. The negative side is that this test will just allow you to claim something like "not irritating to the eyes" or "safe for the eye" that is taken for granted by the consumers and is not a marketing issue. That is the reason for the "ophthalmologically tested" claim that is often preferred when dealing with products destined to the periocular area. It is an in-use test on a panel of 20 volunteers, carried out under the supervision of an ophthalmologist, who will check the absence of any inflammation symptoms in the cornea and conjunctive, before and at the end of the use period. The best choice to assess the product safety, in this case, is to also combine this in-use test with the test on human cornea in vitro.

A more sophisticated HIRPT protocol will call for a cycle of 5 weeks of testing, with an induction phase (3 weeks) where repeated insult patch test are applied every 48h, followed by a resting phase (2 weeks) and by an evaluation phase (1 week) with new occlusion patch test for 48 h. The skin readings will be performed after 30', 24 h and 48 h, and a panel of at least 100 subjects is recruited for significance. This is known as Marzulli-Maibach protocol and has been developed with the aim of evaluating the skin sensitization risk of a topical product. This test is typically carried out to support the claim "hypoallergenic". A modification of the protocol, with a pre-treatment with a SLS solution to make the skin more sensitive to aptens, enables to reduce the panel to 50 volunteers and to shorten the induction phase. In any case, this kind of test raises many ethical issues because of the risk to induce a permanent sensitization in a healthy subject. A combination of simpler HIRPT protocols and *in vitro* tests may be a better alternative for testing products to claim low allergy risks.



Elena Bocchietto
Director of the
testing facility - Abich

Stefano Todeschi
Abich

ABICH
Biological and chemical analysis,
research and services
Verbania and Milano, Italy phone
+39 0323 586239 - www.abich.it
Montreal, QB, Canada phone
+1 514 507 9982 - www.abich.ca