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ORIGINAL ARTICLE

Stepwise approach of development of dermo-cosmetic products in healthy and atopic dermatitis paediatric population: safety evaluation, clinical development and postmarket surveillance

V. Ribet,[1,*] M. Gurdak,[2] P.-J. Ferret,[3] E. Brinio,[1] F. Giordano Labadie,[4] A.B. Rossi[2,4]

[1]Cosmetovigilance, Pierre Fabre Dermo-Cosmetics, Toulouse, France
[2]Research and Development, Clinical Development Division, Pierre Fabre Dermo-Cosmetics, Toulouse, France
[3]Research and Development, Toxicology Division, Pierre Fabre Dermo-Cosmetics, Toulouse, France
[4]Department of Dermatology, Paul Sabatier University and Larrey Hospital, Toulouse, France
*Correspondence: V. Ribet. E-mail: virginie.ribet@pierre-fabre.com

Abstract

Background/objectives Paediatric skin, considered sensitive, and infant skin, more susceptible to percutaneous toxicity, require specially formulated cosmetic products. As recently shown, early use of emollients in infants "at risk" of developing atopic dermatitis has shown controversial results in reducing the incidence of atopic dermatitis. Development of dermo-cosmetic products for this specific population should especially ensure tolerance and safety. In absence of good clinical practice guideline, we propose here a stepwise approach for the development of paediatric cosmetic skincare products.

Methods Our stepwise methodology for cosmetics aimed at paediatrics, starts with *in vitro* assessment of product's ingredients safety, followed by preclinical and clinical evaluations of the final product, including sequentially: (1) Repeated Open Application Test (ROAT), (2) Human Repeated Insult Patch Test (HRIPT), (3) In-use dermatological and ophthalmological tolerance studies (sequentially in 3a: healthy adults, 3b: healthy paediatric subjects and finally 3c: paediatric patients). We also describe the integrated cosmetovigilance–toxicological surveillance during the clinical development phase and postmarketing.

Results As illustrated with one dermo-cosmetic product intended to be used as a preventative/maintenance treatment for atopic dermatitis in paediatric population, we show that using this stepwise methodology to test a product reduces potential risks of irritation and contact dermatitis in this sensitive population.

Conclusion Standardized ethical stepwise development approach is needed to ensure the commercialization of safe and well-tolerated dermo-cosmetics for paediatrics. The approach described here could potentially serve as guidance for evaluation of new paediatric cosmetic products.

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Conflicts of interest

VR and PJF are employees of Pierre Fabre Dermo-Cosmetics, MG, EB and ABR were employees of Pierre Fabre Dermo-Cosmetics at the time of the study. FGL is a cosmetovigilance consultant for Pierre Fabre Dermo-Cosmetics.

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Introduction

Infant skin differs from adults in terms of structure, function and composition.[1] Although the *Stratum corneum* of infants may appear intact shortly after birth, its water-holding and transport properties become mature only around the 5th year of life,[2–4] while the composition and structure of the SC are critical factors contributing to the quality of the barrier function.[4]

Skin care products safety is thus a critical issue in paediatrics, while the barrier function is immature, and especially in cases of atopic dermatitis (AD),[5] diaper rash[6] or in premature neonates.[7] On another hand, allergic contact dermatitis (ACD) in children was previously considered to be a rare occurrence, but cross-sectional studies through the past decades indicate that ACD is a highly relevant diagnosis in children.[8,9]

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On ethical grounds, it is mandatory that clinical testing in paediatric populations does not cause any harm. Therefore, only products, which have been specially formulated to be applied on damaged/ immature skin, with thorough evaluation from a toxicological perspective and proof of good tolerance should be tested in this population.

Cosmetic products are currently regulated by the European Regulation on cosmetic products CE n°1223/2009.[10] This new text and the Guidelines of the Scientific Committee on Consumer Safety (SCCS)[11] indicate the need to carry out a specific safety evaluation of cosmetic products intended for infants, but do not specify the nature of this evaluation. Interestingly, whereas European health authorities request that cosmetic products bear no risk for the consumer,[12] clinical studies in humans are not mandatory for cosmetics. By contrast with drugs, there is no registration for cosmetics in Europe. Each company is responsible for the safety of their marketed products.

In absence of good clinical practice (GCP) guidelines for the assessment of cosmetic product safety and efficacy, we propose a rigorous, stepwise approach for the development and assessment of dermo-cosmetics intended to be used in the paediatric population, including: (1) in vitro toxicology assessment of ingredients and (2) of formulation, (3) clinical evaluation in adults, followed by clinical evaluation in healthy paediatric subjects and in atopic paediatric patients, with detailed cosmetovigilance (CV) assessment during the full development, (4) Other analyses and (5) and postmarket surveillance. We also provide an example of this methodology for one dermo-cosmetic intended to be used in maintenance treatment in atopic dermatitis.

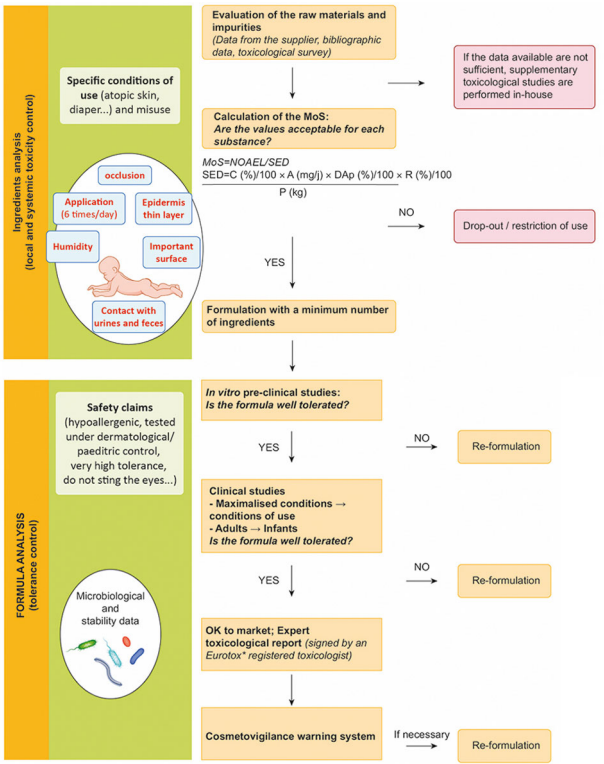

Figure 1 Evaluation steps of a baby cosmetic product. MoS, Margin of Safety. *Eurotox: Federation of European Toxicologists & European Societies of Toxicology, http://www.eurotox.com/.

Methods

Internal guidelines for the development of paediatric dermo-cosmetics

This internal guideline has been elaborated jointly by pharmacists, toxicologists and dermatologists of the clinical, toxicology, regulatory and cosmetovigilance departments of Pierre Fabre Dermo-Cosmetics Laboratories.

Step 1: Toxicological profile of the ingredients and formula prevalidation Because cosmetic product combines several ingredients, the first step consists in analysing the toxicological profile of each ingredient and their impurities and calculating their safety margin (MoS), according to the last revision of the Guidelines of the SCCS (Fig. 1).[11] This margin takes into account the physiological characteristics (surface area/weight ratio), dermal/percutaneous absorption under specific exposure conditions (i.e. large surface area of intended application in infants, skin barrier disruption such as atopic skin and buttocks area under occlusion with inflammation and erosions in the case of diaper rash) and conditions of use of the final product (quantity, frequency, whether the product is rinsed off or left on). Generally, the raw materials used are widely known materials benefiting from a robust history of use without observed side effects. Fragrances and preservatives, the most common allergens in the paediatric population, are minimized or preferentially avoided.[8,9,13,14]

Step 2: Preclinical local toxicity tests of the formula This step consists in evaluation of the formula tolerance in *in vitro* models simulating realistic conditions of use of the product. These evaluations include the following:

- Local cutaneous irritant potential, using an internal model of Reconstructed Human Epidermis (RHE);
- Local ocular irritant potential, using the neutral red release test,[15] the Hen's Egg Test-Chorioallantoïc Membrane Het Cam test,[16] and the model of reconstructed Human Corneal Epithelium (HCE, OECD TG 432 guideline).
- Phototoxicity by treating RHE with UVA;
- Urine-like assay using Reconstructed Human Epidermis.[17]

Step 3: Clinical evaluations associated with the premarketing cosmetovigilance The first evaluation in humans, Repeated

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Open Application Test (ROAT)[18] is conducted in a panel of at least 15 healthy adults. The product is applied on a limited area of the healthy skin, usually an hemiface and the antecubital crease, as this is one of the thinnest skin in the body and it can be evaluated bilaterally (the contralateral area serves as control). A dermatologist or trained technician evaluates objective signs and the volunteers report any subjective symptoms (discomfort, burning sensation, sensation of warmth, skin tightness, stinging, other) after each application. In the absence of reactions, the product is applied under maximized exposure (stripped skin and under occlusion). The application is repeated daily for 5 consecutive days. The stripping of skin is performed following a standardized protocol (a square of tape is applied six consecutive times and stripped in four different directions). The size of the test area is usually 3 cm by 3 cm to 5 cm by 5 cm, and the amount of test substance should be sufficient to cover the test area.[19]

This standardized exposure mimics 'in-use' situation in patients with skin barrier damage. It aims at eliciting allergic contact dermatitis in the test area. In some cases, contact allergy to a product can only be evidenced with this technique.

The next step is the Human Repeated Insult Patch Test (HRIPT) or Final Clinical Safety Test (FCST), adapted from Marzulli & Maïbach.[20] It evaluates local tolerance after repeated application under occlusion and confirms the absence of potential allergenicity and risk of cumulative exposure. This test is performed in at least 100 adults under an occlusive patch (12 mm Finn Chambers® provided by Smartpratice Canada, Calgary, Alberta, Canada) for 48 h on the back. The product is applied thrice a week for 3 weeks and evaluation is performed at each visit (thrice a week). After a follow-up period of 14 days, a challenge patch applied for 48 h assesses potential sensitization effect. Skin reactions are clinically evaluated by comparison with a negative control (distilled water).

Dermatologic and ophthalmologic tolerance. Dermatologic and ophthalmologic tolerance is evaluated in at least 30–50 adult volunteers with healthy and sensitive skin in normal conditions of use, twice daily, for 21 consecutive days. After 21 days, evaluation is performed by a dermatologist and ophthalmologist (when the product is applied on the face), and volunteers are asked to fill in a questionnaire about the product tolerance and acceptability.

If the product is well-tolerated, the same evaluation is then performed in paediatric subjects with healthy and atopic skin. The average intensity of physical signs (erythema, dryness, roughness, desquamation) on the face and body is rated by dermatologists and paediatricians on a 0–4 scale. Functional symptoms (pruritus, irritation) are recorded by parents in a diary. In order to evaluate compliance and systemic exposure,[21,22] the investigational product is weighed before the first application and after 3 weeks of use and undesirable events have to be reported.

Studies in atopic dermatitis patients include only patients with mild disease, and the efficacy of the product is also assessed by measuring SCORAD index, a European validated score of AD severity[23] and PO-SCORAD.[24]

Premarketing cosmetovigilance. During the clinical programme, if any sign of intolerance is reported, the investigators should identify and report the following details: time of onset, duration, intensity, area affected, temporal relation to application, whether the application was terminated, if any treatment was needed, and follow-up time until the reaction was resolved.

Any undesirable effect occurring during all clinical evaluations should be reported, analysed and discussed by the internal safety committee, including toxicologists, pharmacists and dermatologists. All cases of intolerance are reported descriptively and analysed by the sponsor safety committee during the consolidated analyses of safety. Depending on the frequency and/or severity of reactions, the clinical programme can be terminated and formulation changes implemented. Cosmetovigilance database on other dermo-cosmetic products and specific ingredients are taken into account in these evaluations.

Step 4: Other analyses The physico-chemical, microbiological and compatibility characteristics of the product and its packaging are also evaluated.

Step 5: Postmarketing surveillance The Pierre Fabre cosmetovigilance department ensures systematic collection, recording and analysis of undesirable events (serious and non-serious) spontaneously reported by customers or physicians, which occurred during or after normal or reasonably foreseeable use of a cosmetic product in all the countries where the product is marketed. A cosmetovigilance index (CVI) is calculated according to the Pierre Fabre worldwide Cosmetovigilance System. The CVI, categories are the following: class I: very good tolerance, class II: good tolerance, class III: medium tolerance and class IV: poor tolerance. Based on the CVI and analysis of data collected from various sources (toxicological, clinical etc.), a 'safety signal' can be issued. Concerned products/ingredients are then placed on 'safety watch', i.e. detailed monitoring with a shorter period of follow-up. If the safety signal is confirmed during 'safety watch' surveillance, a cosmetovigilance alert is emitted and corrective actions are undertaken, such as changes in the packaging, usage instructions, or eventually product retraction. The impact of corrective actions is monitored to ensure their effectiveness.

Results

Clinical development: individual studies in the clinical programme for one range of products intended to be used in atopic dermatitis in paediatrics

We present the results of studies in the development programme for the skin care range of emollients designed for paediatric patients with AD, with a focus on the safety/tolerability results.

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All the studies were carried in accordance with the most recent recommendations of the World Medical Association (Helsinki Declaration of 1964, and its successive updates) and locally applicable regulatory requirements, and informed consent of the adults or, for paediatric studies, of the two parents or legal guardians was obtained.

ROAT test Repeated open application test was performed in 15 adult volunteers with self-declared sensitive skin receiving application of the undiluted product (4 mg/cm^2) on intact sensitive skin (hemiface, $n = 15$) and stripped skin (elbow crease, 4.5 cm^2, $n = 12$) twice a day during 5 consecutive days. There were no clinical signs observed at the elbow crease, nor on the hemiface, and no discomfort was reported by the subjects.

HRIPT Human repeated insult patch test was performed in 101 adults. No visible cutaneous reactions at induction or challenge phase were observed, nor any serious adverse event related to the study cream.

Dermatological and ophthalmological tolerance in adults with sensitive skin In 31 adults with sensitive skin (mean age: 52 years), no cutaneous or ocular reactions potentially related to the study cream were reported by the dermatologist and ophthalmologist, nor any intolerance reported by the volunteers after 3 consecutive weeks of use of the product twice a day on the face and the body (arms and legs).

Dermatological tolerance in children with sensitive skin In 32 healthy volunteers aged 5 months to 6 years inclusive (mean ± SD = 44.9 ± 19.4 months), all with self-reported sensitive skin, there was no undesirable event, nor significant clinical manifestation of intolerance or allergy leading to premature withdrawal from the study. The use of the investigational product did not induce any dermatological, ocular or mucous physical signs (erythema, dryness, roughness, desquamation) and/or functional sign of irritation (Table 1). The average quantity of cream used for 3 weeks was 58.8 ± 10.5 g (range: 42.2–82.1 g), i.e. 2.0 g, i.e. per application and per subject.

Dermatological tolerance in atopic adults and children In six infants (6–19 months) and 26 children (2–5 years old) having sensitive healthy skin (G1, $n = 16$), or mild AD (G2, $n = 16$, SCORAD range: 15–25) and 10 adults (G3, 19–38 years old) with mild AD (SCORAD range: 15–25), the product was applied for 21 days, at least twice daily on face and body. No objective or subjective reaction was observed in any group on the face or on the body. The cutaneous tolerance was classified as very good. For G2 and G3 subjects, the skin improved significantly throughout the study ($P < 0.05$) and from the

Table 1 Functional and physical signs before (T0) and after 3 weeks of use (W3) of the cold cream-based moisturizing study cream in children with sensitive skin. Bold values highlight the decrease in occurrences of symptoms and signs

Type of sign	Nb. of occurrences (% of subjects)		Average intensity (Grade 1/2/3/4)		Changes in % of occurrences		
	T0	W3	T0	W3	↑	↓	→
Face							
Functional signs†							
Pruritus	5 (15.6)	0 (0.0)	1.00 (5/0/0/0)	0.00 (0/0/0/0)	0.0	**100.0**	0.0
Physical signs‡							
Erythema	12 (37.5)	8 (25.0)	1.25 (9/3/0/0)	1.13 (7/1/0/0)	0.0	**50.0**	50.0
Dryness	21 (65.6)	10 (31.3)	1.33 (14/7/0/0)	1.10 (9/1/0/0)	4.8	**81.0**	14.3
Roughness	3 (9.4)	2 (6.3)	1.33 (2/1/0/0)	1.00 (2/0/0/0)	0.0	**66.7**	33.3
Desquamation	1 (3.1)	0 (0.0)	1.00 (1/0/0/0)	0.00 (0/0/0/0)	0.0	**100.0**	0.0
Body							
Functional signs§							
Pruritus	9 (28.1)	0 (0.0)	1.22 (7/2/0/0)	0.00 (0/0/0/0)	0.0	**100.0**	0.0
Physical signs¶							
Dryness	25 (78.1)	15 (46.9)	1.84 (9/11/5/0)	1.20 (12/3/0/0)	0.0	**92.0**	8.0
Roughness	8 (25.0)	6 (18.8)	1.88 (1/7/0/0)	1.33 (4/2/0/0)	0.0	**75.0**	25.0
Desquamation	5 (15.6)	0 (0.0)	1.00 (5/0/0/0)	0.00 (0/0/0/0)	0.0	**100.0**	0.0

There was no erythema on the body. ↑: increased; ↓: decreased; →: unchanged.
†All the subjects presenting functional signs on the face at T0 had sensitive dry skin.
‡All the subjects presenting physical signs on the face at T0 and W3 had sensitive dry skin, apart from one subject who had sensitive normal skin.
§All the subjects presenting functional signs on the body at T0 had sensitive dry skin.
¶All the subjects presenting physical signs at T0 and W3 on the body had sensitive dry skin.

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first evaluation (1 week), as shown by the SCORAD results (Fig. 2).

Postmarketing cosmetovigilance The CV index was calculated for the product with data collected since the product commercialization. The CV index calculated on the basis of cosmetovigilance data collected since August 2010 is class I grade (very good tolerance).

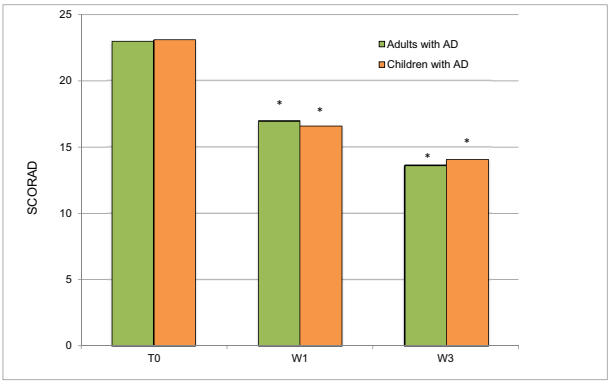

Figure 2 Cold cream-based moisturizing cream. Changes in SCORAD in children and adults with AD at T0 and after 1 week (W1) or 3 weeks (W3) of cold cream-containing moisturizing cream use on the face and body. *$P < 0.05$ vs T0.

Discussion

Infants and young children have an immature skin barrier and potentially risk developing allergic contact dermatitis when using cosmetics, highlighting the need for careful assessment of tolerance during the development of dermo-cosmetics intended for use in this population.[3,25] Clinical studies are not mandatory in the development of cosmetics, and the decision to test the products in clinical studies or not relies on manufacturers. We propose a guideline for the development and surveillance of paediatric skincare products (Fig. 3), the first step is the choice of ingredients for the formulation, including a limited number of ingredients in accordance with the French regulatory authorities[26,27] and low concentrations of actives. Each ingredient is carefully selected to minimize the risk of allergy and preservatives should be avoided.[12] The second step involves a battery of preclinical tests on reconstructed human tissue models, and the results can reveal any potential toxicity before testing in humans. The third step is the clinical evaluation and includes intra-individually controlled clinical evaluation of tolerance during repeated exposure in adults in a localized area, followed by application under maximalized exposure (stripped skin, under

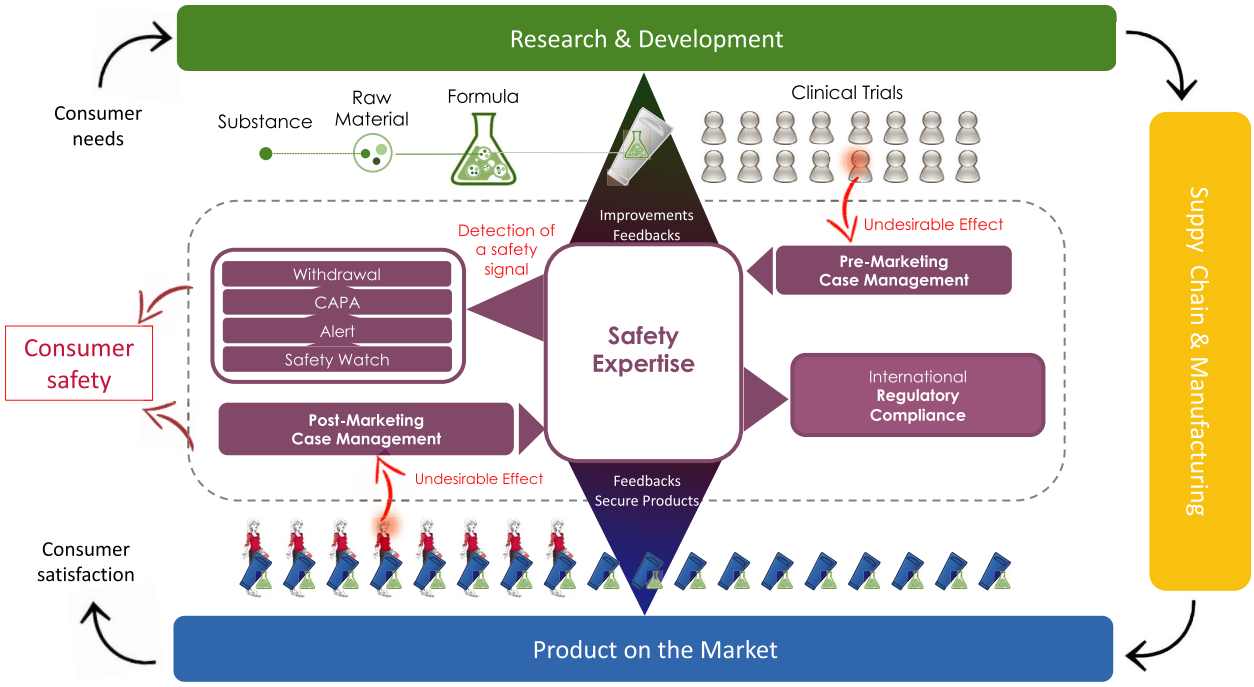

Figure 3 Cosmetovigilance procedures. A "safety signal" refers to new information with the potential to modify the safety assessment of a product or trigger further investigation. A signal usually arises from an unexpected modification of a pre-existing level of reporting in terms of the number of reports or the nature of reported reaction.

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Table 2 Number of subjects (age range) involved in clinical tests in adults and in children for various products of a paediatric skincare line of products

Product	Adults				Children					Total
	1 ROAT	2 ROAT stripped skin	3 HRIPT	4 Dermatological tolerance	1 Patch tests	2 Biometrology	3 Dermatological tolerance	4 Ocular tolerance test	5 International multicentric study[37]	
Cold cream	15[S]	12	101	31[S]	-	-	16[S] (6 months to 5 years) 16 atopic vs. 10 atopic adults	-	-	**201**
Moisturizing cream	14[S]	14[S]	-	20 (50%[SE])	15[S]	II - IH: 12 IH mini regression: 12	29 (3 months to 10 years) vs. Comparator 50% atopic	-	-	**116**
	-	-	-	-	-	-	32 (5–23 months) 50% atopic	-	-	**32**
Cleansing gel	15	-	103	33[S,SE]	-	-	41 (6–12 months) including 26 atopic	31	-	**223**
Diaper rash cream	12	12	112 50% atopic	-	-	-	31 (13.8 months) 55% atopic	-	-	**167**
Cleansing foam	12	21	100	19[S]	-	-	35 (3 months to 6 years) including 17 atopic	-	-	**187**
Cleansing water	12 (19–42 years)	10 (18–35 years)	-	-	-	-	28 (4.3 years) 56% atopic	-	-	**50**
Moisturizing milk	17[S]	19 (26.5 years)	100	31[S, SE]	-	-	15[S] (6 months to 5 years) 15 atopic vs. 11 atopic adults	-	-	**208**
Craddle cap gel	12 stingers*	14 (20–42 years)	51 atopic	14 stingers*	-	15 (46 years) psoriasis model	30 (24.8 months) vs. Comparator	20[SE] (18–45 years)	65 (1–12 months) vs. 62 control	**283**
Total per test	**109**	**102**	**567**	**148**	**15**	**39**	**309**	**51**	**127**	**1467**

S, Sensitive skin; SE, sensitive eyes; *Stingers: Subjects which positively respond to lactic acid test (i.e. with sensitive skin diagnosed not only on the basis of declaration, but objectivized by a test).

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occlusion), then is 'in-use test' in adults with atopic dermatitis. Finally, the last step is the clinical evaluation in the paediatric population, with healthy and atopic skin, sequentially. All subjects included in clinical tests should be evaluated by a board-certified dermatologist, who should investigate and report adequately all reactions and symptoms observed. Ophthalmologic tolerance is evaluated for any product intended to be applied on the face in normal conditions of use. In products without preservative, the sterility of the product after use is also assessed. In the example of a range of products for sensitive and atopic dermatitis skin, the development programme was performed on a large population of 1509 subjects, including 926 adults and 541 paediatric subjects (62 controls; Table 2). The clinical studies in adults with healthy sensitive skin – ROAT, HRIPT, as well as dermatological and ophthalmologic tolerance in normal conditions of use – all showed excellent tolerance of the cream, allowing to proceed further with clinical studies in paediatric population with sensitive skin and atopic dermatitis. However, in another range of products for adults, three failed to pass some of the tests in the last 5 years and had their development interrupted. This rigorous process thus allows commercialization of products with proven and validated safety.

Regular use of emollients is the mainstay of AD treatment and can potentially prevent flares.[27–32] Preliminary data from a cohort study has shown a potential primary prevention interest for emollients,[33] however the results from a larger cohort in two studies did not confirm this hypothesis (European Academy of Allergy and Clinical Immunology (EAACI) 2019 Congress: Session HT 2 (Boyle) and abstract TP0986 (Skjerven). Presented June 2 and 3, 2019). Efficacy assessment for products in AD patients is based on clinical evaluation of signs and symptoms of AD and on the use of SCORAD index.[28] The study cream for baby face and body presented here as an example demonstrated its excellent dermatological tolerability in infants, children and adults with AD. After 3 weeks of use with an average of 2.0 g per day per subject in adult and paediatric patients with mild AD, there was a full improvement of signs (erythema, roughness, dryness, desquamation) and symptoms (pruritus and sleep loss), as measured by SCORAD. The very good cutaneous tolerance observed during the clinical development was confirmed by postmarketing surveillance, with a class I (very good tolerance) rank, attributed based on cosmetovigilance data collected since the market introduction of the product. Other studies recently published by other companies on cosmetic formulations for children with atopic dermatitis also rely on a series of clinical tests in order to demonstrate the safety and efficacy of their product.[34,35]

However, whereas trials for drugs are very strictly controlled, there is no mandatory registration for cosmetic products and thus no established and agreed-on development programme. In the Research and Development division of Pierre Fabre dermo-cosmetics, a multidisciplinary group composed of toxicologists, chemists, pharmacists, pharmacologist and dermatologists, with a recognized clinical expertise defined a stepwise approach for the development of dermo-cosmetics intended to be prescribed by dermatologists for patients with dermatoses, as adjuvant to or maintenance of drug treatments. Additional steps are requested when the product is intended for use by the more sensitive paediatric population.

Nevertheless, even with clinical studies being conducted, there is always a potential risk of intolerance when the product is used in a larger population. Cosmetovigilance is a major asset for detecting early safety signals that were eventually not observed during the development programme. Mandatory cosmetovigilance has been only recently established in Europe. The European Union Cosmetics Regulation (EC) No. 1223/2009[10] requires companies to collect and assess reports of undesirable effects from the cosmetic products they market, and serious undesirable effects should be reported within 20 calendar days to the national competent authorities since 2009.

In 2017, Pierre Fabre dermo-cosmetics, together with members of Cosmetic Europe, have issued guidelines to promote a consistent practical approach for the management of undesirable effects and the notification of serious undesirable effects.[36]

We believe that the development of dermo-cosmetic products for the paediatric population should involve a multidisciplinary team including dermatologists, pharmacists, pharmacologists, toxicologists and chemists and should be based on robust clinical studies performed according to GCP. Besides, assessments should be conducted ethically, and when a product targets a specific population, studies have to be performed in that particular population. In absence of GCP guidelines for the assessment of cosmetic product safety and efficacy, quality processes are approved by clinicians, who wish to make evidence-based choices, relying on toxicological evaluation. Our standardized ethical and GCP approach could potentially serve as guidance for the evaluation of new cosmetics targeting the paediatric population.

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