UNIVERSITA' DEGLI STUDI DI PAVIA
DIPARTIMENTO DI MEDICINA INTERNA E TERAPIA MEDICA
SEZIONE DI FARMACOLOGIA E TOSSICOLOGIA CELLULARE E MOLECOLARE
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CCIAA MI 1511487 - CAP. SOC. € 10.845,59
C.F. P.IVA 11938080152

Preliminary evaluation of the soothing power of two cosmetic products through a clinical-instrumental test

DOCUCHEM s.l. UNIPERSONAL

DKQ-F-003

DKQ-F-007

Report no. **1201L19F**

Place and date of issue: MILAN – 21st November 2012

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SUMMARY

The objective of this clinical trial is to conduct a comparative pivotalevaluation of the soothing activity of two cosmetic products (DKQ-F-003 and DKQ-F-007), using instrumental measurements of erythema (MEXAMETER) and performing a clinical evaluation of erythema.

The test was conducted by a dermatologist who is a staff member of BioBasic Europe and is organized as follows:

SOOTHING-REPARING TREATMENT

1. Were selected 10 volunteers aged between 18 and 70 years were selected.
2. Three distinct areas of skin on a forearm were identified
3. The colour of the skin was measured at time T0, before irritation to obtain the basal value.
4. Redness was induced with UREA through application for 24 hours of an occlusive patch.
5. The three selected areas on the forearm were treated as follows:
   On one of them no treatment was applied
   The second one was treated with DKQ-F-003
   The third one was treated with DKQ-F-007
7. Measurements of skin colour with Mexameter and clinical evaluation of erythema were taken performed at the following time points after application of product:
   T 0 '(immediately after irritation, after treatment with products)
   T15' (15 minutes),
   T30 '(30 minutes),
   T1H (1 hour),
   T2H (2 hours) after application of product.
8. Photos of red areas were taken at times:

T 0 '(immediately after irritation), T2H (2 hours) after application of product.

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EXPERIMENTAL PART

Report no. 1201L19F

Title

Evaluation of the soothing power of two cosmetic products through a clinical-instrumental test

Scope

The scope of this test is to evaluate whether these products have got a cosmetic soothing power, in particular if can significantly change skin parameters like erythema.

- **Contract information**
- Technical report performed by BIO BASIC EUROPE s.r.l. and Università degli Studi di Pavia.

Final technical report written by BIO BASIC EUROPE s.r.l. on behalf of DOCUCHEM s.l. UNIPERSONAL

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Test subjects

10 female and males subjects, with an age between 18 and 70 years, have been selected for the test, following the undermentioned inclusion criteria:

good state of general health
no dermatopathies
no pharmacological treatment in progress
promise not to change the usual daily routine
no atopy reported in the anamnesis

Preparation of the samples

Samples of the products have been applied following their usual use: as they are.

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EXPERIMENTAL PROTOCOL

Test is executed on three area on panellists forearms.

1. 10 volunteers aged between 18 and 70 years were selected.
2. Three distinct areas of skin were identified in the forearm
3. The colour of the skin at time t0 (before irritation) was detected with Mexameter to assign basal value of erythema.
4. Redness was induced with urea through application for 24 hours of an occlusive patch.
5. On the three selected areas in the forearm the following treatments were applied respectively: DKQ-F-003, DKQ-F-007 and the third area was not treated.
6. .Measurements with Mexameter of erythema were taken at times:
T0 before irritation (basal value of erythema)
T 0 '(immediately after removal of the patch)
T15' (15 minutes) after application of product.
T30 '(30 minutes) after application of product.
T1H (1 hour) after application of product.
T2H (2 hours) after application of product.

7.Clinical evaluation of erythema were taken at times:
T 0 '(immediately after irritation)
T15' (15 minutes) after application of product.
T30 '(30 minutes) after application of product.
T1H (1 hour) after application of product.
T2H (2 hours) after application of product

8. Photos of red areas were taken at times:
T 0 '(immediately after irritation)
T2H (2 hours) after application of product

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EXECUTION OF THE TEST

INSTRUMENTAL PARAMETERS

The **erythema*** is measured with MEXAMETER® MX 18

*The Mexameter® MX 18 is a tool to measure the components responsible for the colour of the skin: in this case the haemoglobin (erythema). The measurement is based on absorption/reflection.
The probe of the Mexameter® MX 18 emits 3 specific light wavelengths. A receiver measures the light reflected by the skin. As the quantity of emitted light is defined, the quantity of light absorbed by the skin can be calculated. For the erythema measurement two different wavelengths are used to measure the absorption peak of haemoglobin. The other wavelength has been chosen to avoid other color influences (e. g. bilirubin). The results are shown within 1 second as aindex numbers (0-999).

Instrumental measurements of erythema (MEXAMETER® MX 18) are taken as follow:

- at the time [t0] (basal value),
- at the time [T0 ']: T0' (after 24 h after induction of stress)
- at the time [T15 ']: after 15 minutes after the application of products on the irritated area
- at the time [T30 ']: after 30 minutes after the application of products on the irritated area
- at the time [T1h ']: after 1 hour after the application of products on the irritated area
- at the time [T2h ']: after 2 hours after the application of products on the irritated area

Clinical evaluation of erythema were performed based on the table below:

VERY SLIGHT ERYTHEMA	+
VISIBLE ERYTHEMA	++
STRONG ERYTHEMA	+++

Clinical evaluation of erythema are taken as follow:

- at the time [T0 ']: T0' (after 24 h after induction of stress)
- at the time [T15 ']: after 15 minutes after the application of products on the irritated area
- at the time [T30 ']: after 30 minutes after the application of products on the irritated area
- at the time [T1h ']: after 1 hour after the application of products on the irritated area
- at the time [T2h ']: after 2 hours after the application of products on the irritated area

The values are measured in the study by the investigator, then processed and displayed graphically.

Photos of red areas were taken at times:
T 0 '(immediately after irritation)
T2H (2 hours) after application of product

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Summarizing Tables of the Values

INSTRUMENTAL AND CLINICAL PARAMETERS

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Evaluation of erythema (Mexameter and clinical evaluation) on treated area with DKQ-F-003

	T0 (basal value)	T0'	IRR	15 min	IRR	30 min	IRR	1 hour	IRR	2 hours	IRR
01EE	100,0	203,0	+++	138,0	++	121,0	+	115,0	+	106,0	
02PL	114,0	225,0	++	167,0	++	135,0	++	112,0	+	109,0	
03EL	106,0	195,0	++	177,0	++	123,0	+	108,0	+	97,0	
04ME	98,0	187,0	++	153,0	++	116,0		99,0		97,0	
05ST	88,0	169,0	++	159,0	++	108,0		91,0		89,0	
06MS	95,0	196,0	+++	153,0	++	127,0	+	104,0	+	99,0	
07LS	89,0	194,0	++	165,0	++	122,0	+	109,0		105,0	
08MC	101,0	197,0	++	165,0	++	116,0		97,0		97,0	
09AG	118,0	245,0	+++	181,0	++	155,0	++	143,0	+	135,0	+
10GD	88,0	202,0	++	176,0	++	120,0	+	95,0		95,0	
MEDIA	99,7	201,3		163,4		124,3		107,3		102,9	

Mexameter values of erythema measured at time T0'(immediately after irritation) -T15'-T30'-T1h-T2h are normalized on basal values of erythema at T0.

Normalized Mexameter values

	T0'	T15'	T30'	T1H	T2H
01EE	103	38	21	15	6
02PL	111	53	21	-2	-5
03EL	89	71	17	2	-9
04ME	89	55	18	1	-1
05ST	81	71	20	3	1
06MS	101	58	32	9	4
07LS	105	76	33	20	16
08MC	96	64	15	-4	-4
09AG	127	63	37	25	17
10GD	114	88	32	7	7

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Evaluation of erythema (Mexameter and clinical evaluation) on treated area with **DKQ-F-007**

	T0 (basal value)	T0'	IRR	15 min	IRR	30 min	IRR	1 hour	IRR	2 hours	IRR
01EE	97,0	202,0	+++	199,0	+++	188,0	++	176,0	++	156,0	++
02PL	119,0	222,0	+++	214,0	+++	223,0	+++	174,0	++	159,0	++
03EL	107,0	190,0	++	188,0	++	182,0	++	167,0	++	147,0	++
04ME	100,0	194,0	++	183,0	++	177,0	++	171,0	++	150,0	++
05ST	83,0	172,0	++	174,0	++	175,0	++	158,0	++	129,0	+
06MS	99,0	199,0	+++	187,0	+++	183,0	++	175,0	++	165,0	++
07LS	87,0	196,0	++	191,0	++	185,0	++	177,0	++	165,0	++
08MC	98,0	190,0	++	188,0	++	175,0	++	171,0	++	145,0	++
09AG	117,0	249,0	+++	249,0	+++	248,0	+++	212,0	+++	169,0	++
10GD	88,0	188,0	++	187,0	++	186,0	++	178,0	++	161,0	++
MEDIA	99,5	200,2		196,0		192,2		175,9		154,6	

Mexameter values of erythema measured at time T0'(immediately after irritation) -T15'-T30'-T1h-T2h are normalized on basal values of erythema at T0.

Normalized Mexameter values

	T0'	T15'	T30'	T1H	T2H
01EE	105	102	91	79	59
02PL	103	95	104	55	40
03EL	83	81	75	60	40
04ME	94	83	77	71	50
05ST	89	91	92	75	46
06MS	100	88	84	76	66
07LS	109	104	98	90	78
08MC	92	90	77	73	47
09AG	132	132	131	95	52
10GD	100	99	98	90	73

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Evaluation of erythema (Mexameter and clinical evaluation) on not treated area

	T0 (basal value)	T0'	IRR	15 min	IRR	30 min	IRR	1 hour	IRR	2 hours	IRR
01EE	98,0	210,0	+++	197,0	+++	192,0	++	185,0	++	166,0	++
02PL	116,0	220,0	++	211,0	+++	218,0	+++	181,0	++	164,0	++
03EL	105,0	193,0	++	185,0	++	196,0	++	187,0	++	167,0	++
04ME	98,0	186,0	++	183,0	++	185,0	++	178,0	++	165,0	++
05ST	86,0	173,0	++	171,0	++	163,0	++	148,0	++	139,0	++
06MS	97,0	206,0	+++	197,0	+++	194,0	++	185,0	++	165,0	++
07LS	90,0	198,0	++	191,0	++	199,0	++	184,0	++	155,0	++
08MC	96,0	200,0	++	195,0	++	179,0	++	185,0	++	172,0	++
09AG	117,0	242,0	+++	249,0	+++	247,0	+++	212,0	+++	167,0	++
10GD	87,0	191,0	++	187,0	++	183,0	++	178,0	++	161,0	++
MEDIA	**99,0**	**201,9**		**196,6**		**195,6**		**182,3**		**162,1**	

Mexameter values of erythema measured at time T0'(immediately after irritation) -T15'-T30'-T1h-T2h are normalized on basal values of erythema at T0.

Normalized Mexameter values

	T0'	T15'	T30'	T1H	T2H
01EE	112	99	94	87	68
02PL	104	95	102	65	48
03EL	88	80	91	82	62
04ME	88	85	87	80	67
05ST	87	85	77	62	53
06MS	109	100	97	88	68
07LS	108	101	109	94	65
08MC	104	99	83	89	76
09AG	125	132	130	95	50
10GD	104	100	96	91	74

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% Reduction of Erithema (instrumental value of Mexameter)

treated area with DKQ-F-003

	T15'	T30'	T1H	T2H
01EE	63,11%	79,61%	85,44%	94,17%
02PL	52,25%	81,08%	101,80%	104,50%
03EL	20,22%	80,90%	97,75%	110,11%
04ME	38,20%	79,78%	98,88%	101,12%
05ST	12,35%	75,31%	96,30%	98,77%
06MS	42,57%	68,32%	91,09%	96,04%
07LS	27,62%	68,57%	80,95%	84,76%
08MC	33,33%	84,38%	104,17%	104,17%
09AG	50,39%	70,87%	80,31%	86,61%
10GD	22,81%	71,93%	93,86%	93,86%
Average	36,3%	76,1%	93,1%	97,4%
Std.Dev	0,2	0,1	0,1	0,1
RSD%	44,18%	7,65%	9,05%	8,20%

treated area with DKQ-F-007

	T15'	T30'	T1H	T2H
01EE	2,86%	13,33%	24,76%	43,81%
02PL	7,77%	-0,97%	46,60%	61,17%
03EL	2,41%	9,64%	27,71%	51,81%
04ME	11,70%	18,09%	24,47%	46,81%
05ST	-2,25%	-3,37%	15,73%	48,31%
06MS	12,00%	16,00%	24,00%	34,00%
07LS	4,59%	10,09%	17,43%	28,44%
08MC	2,17%	16,30%	20,65%	48,91%
09AG	0,00%	0,76%	28,03%	60,61%
10GD	1,00%	2,00%	10,00%	27,00%
Average	4,2%	8,2%	23,9%	45,1%
Std.Dev	0,0	0,1	0,1	0,1
RSD%	113,94%	97,04%	40,84%	26,67%

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Not treated area

	T15'	T30'	T1H	T2H
01EE	11,61%	16,07%	22,32%	39,29%
02PL	8,65%	1,92%	37,50%	53,85%
03EL	9,09%	-3,41%	6,82%	29,55%
04ME	3,41%	1,14%	9,09%	23,86%
05ST	2,30%	11,49%	28,74%	39,08%
06MS	8,26%	11,01%	19,27%	37,61%
07LS	6,48%	-0,93%	12,96%	39,81%
08MC	4,81%	20,19%	14,42%	26,92%
09AG	-5,60%	-4,00%	24,00%	60,00%
10GD	3,85%	7,69%	12,50%	28,85%
Average	5,3%	6,1%	18,8%	37,9%
Std.Dev	0,0	0,1	0,1	0,1
RSD%	91,24%	137,57%	50,84%	30,72%

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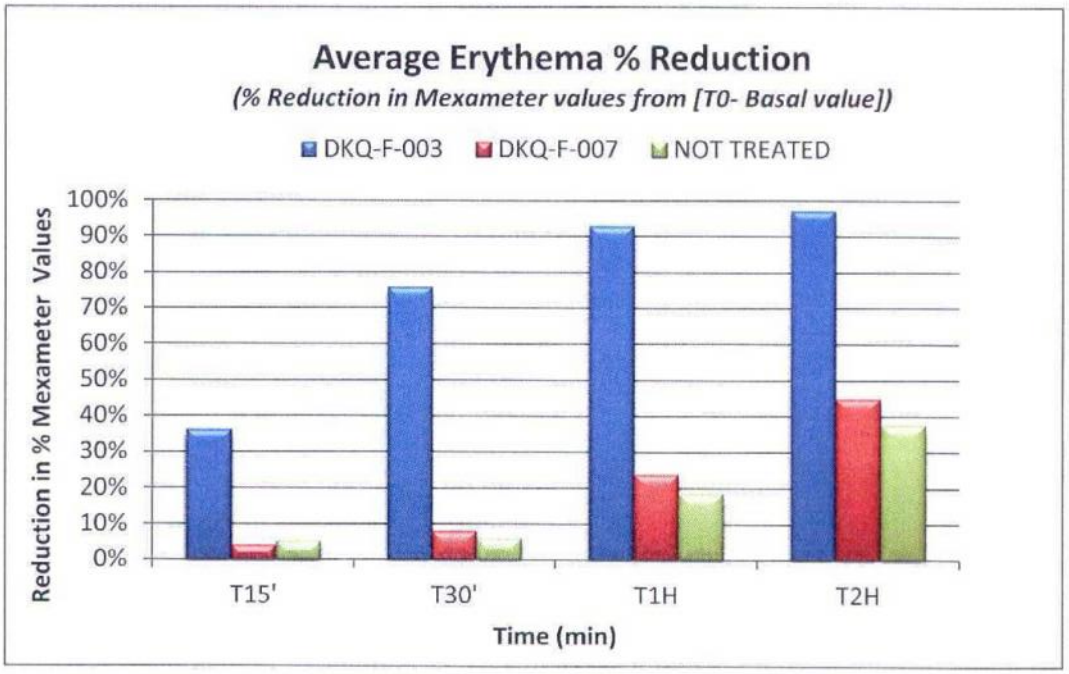
AVERAGE REDUCTION (%) OF ERITHEMA (Mexameter values)

	T15'	T30'	T1H	T2H
DKQ-F-003	36,29%	76,07%	93,05%	97,41%
DKQ-F-007	4,22%	8,19%	23,94%	45,09%
NOT TREATED	5,29%	6,12%	18,76%	37,88%



% of reduction of Mexameter values of erythema on area treated DKQ-F-003 are significantly higher than that of the area treated with DKQ-F-007 and than that of the non treated area.

The product DKQ-F-003 is able to reduce erythema of a percentage equal to 97,5 % after 2 hours of irritation.

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PHOTOGRAPHS

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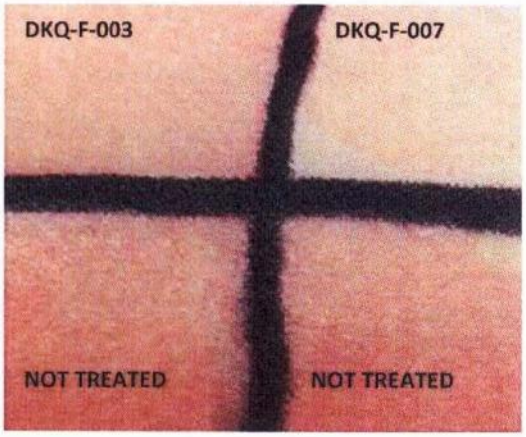
(Immediately after irritation)

T2h (2 Hours after irritation)



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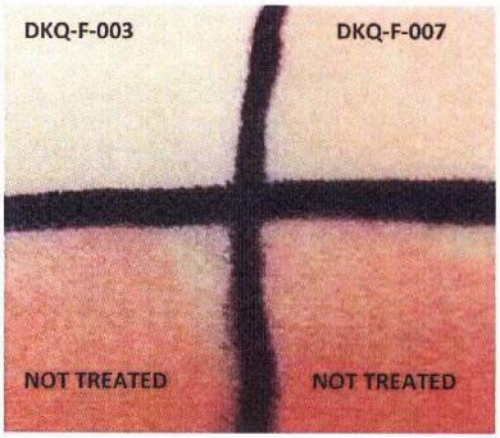
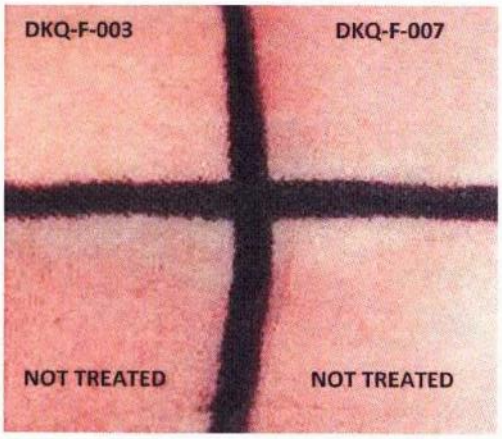


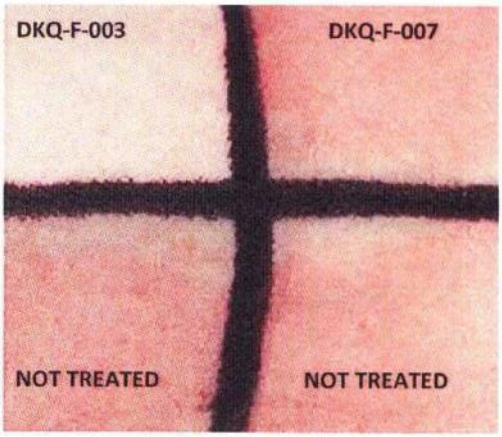
01EE

T0' (Immediately after irritation)

T2h (2 Hours after irritation)



02PL



02PL

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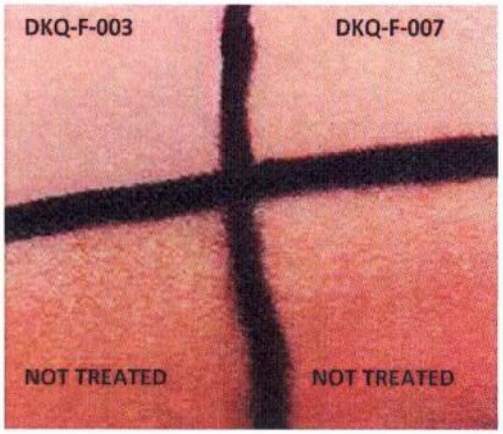
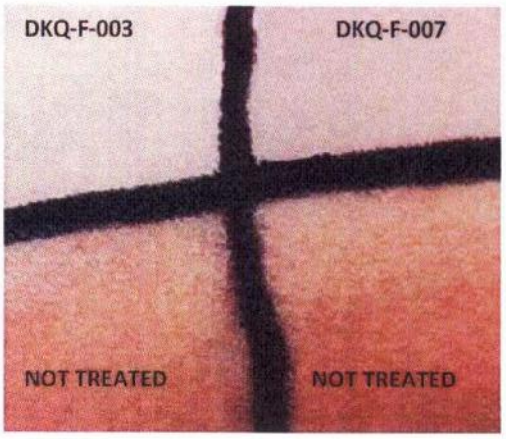
T0' (Immediately after irritation)



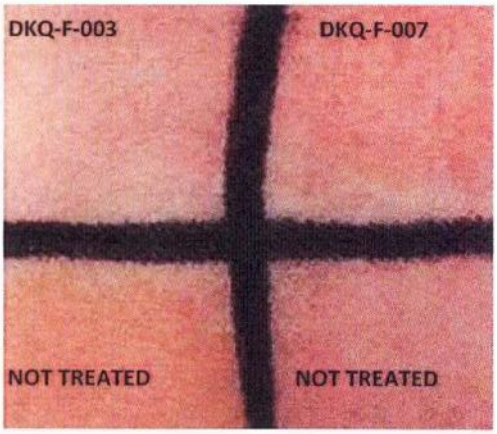
03EL

T2h (2 Hours after irritation)



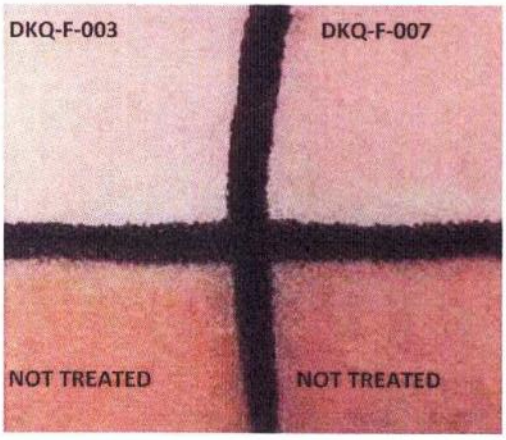
03EL

T0' (Immediately after irritation)



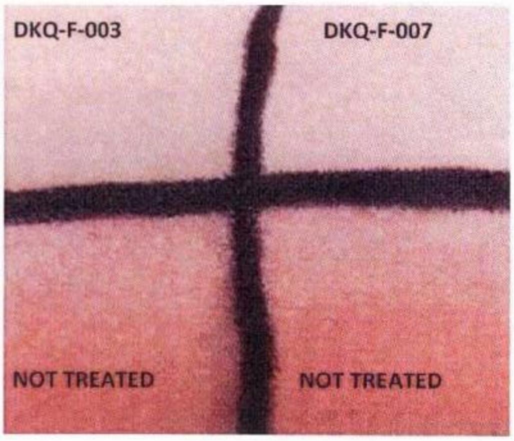
04ME

T2h (2 Hours after irritation)



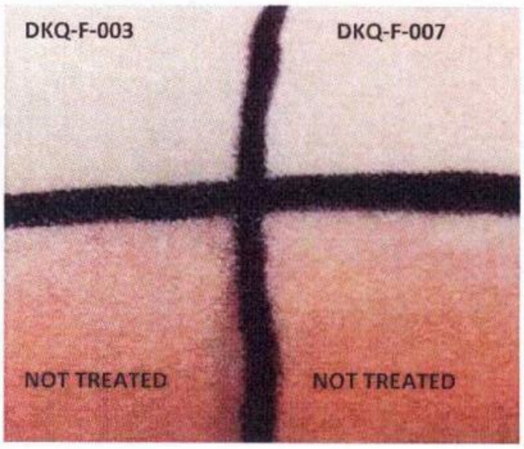
04ME

T0' (Immediately after irritation)



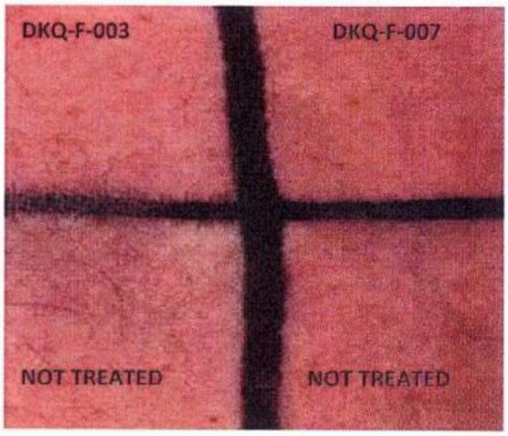
05EL

T2h (2 Hours after irritation)



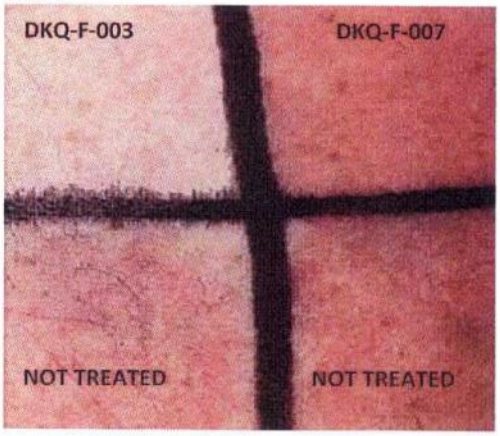
05EL

T0' (Immediately after irritation)



06MS

T2h (2 Hours after irritation)



06MS

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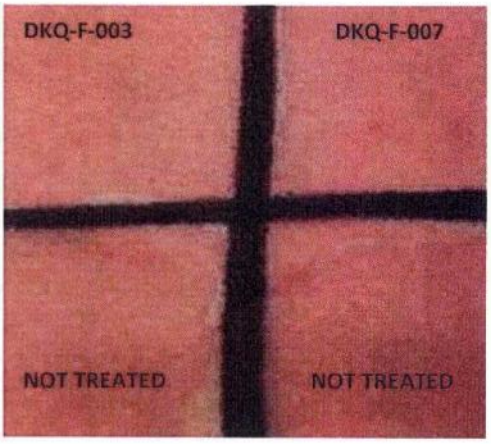
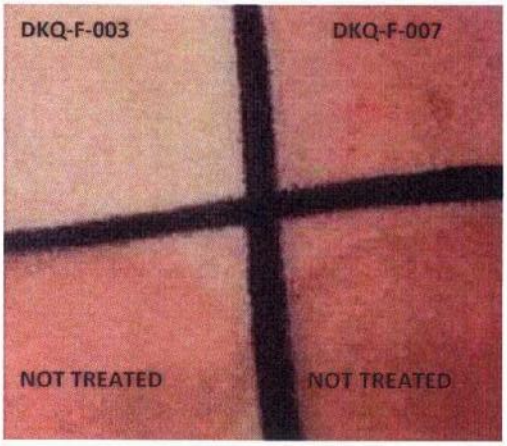
T0' (Immediately after irritation)



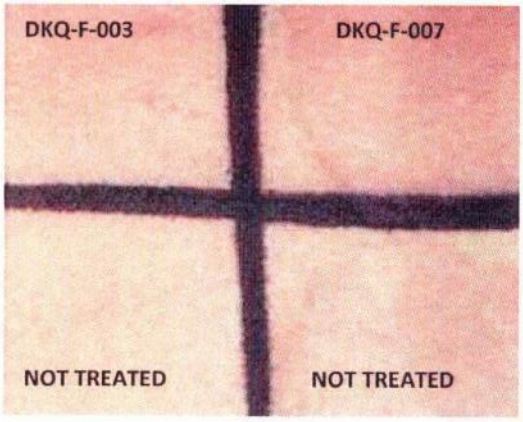
07LS

T2h (2 Hours after irritation)



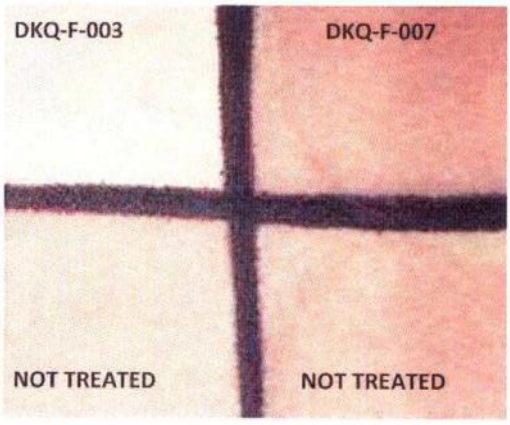
07LS

T0' (Immediately after irritation)



08MS

T2h (2 Hours after irritation)



08MS

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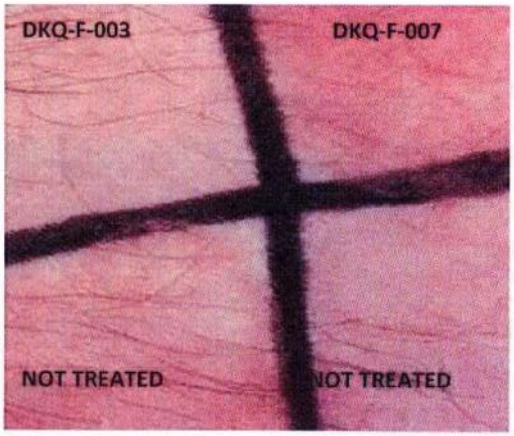
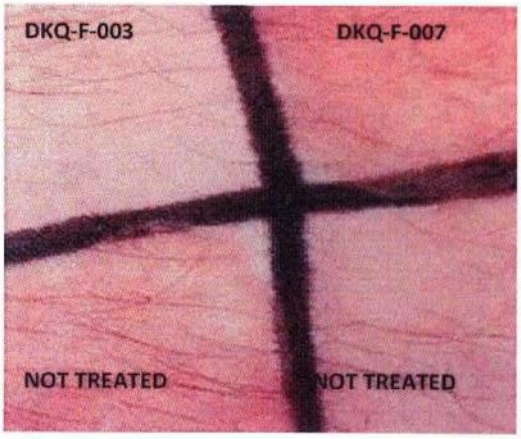
C.F. e P.IVA 11910080159

T0' (Immediately after irritation)



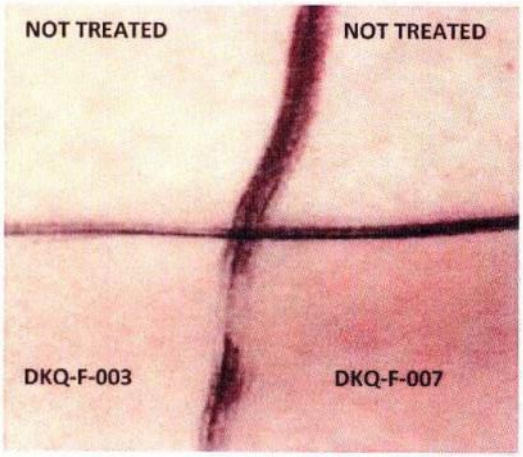
09AG

T2h (2 Hours after irritation)



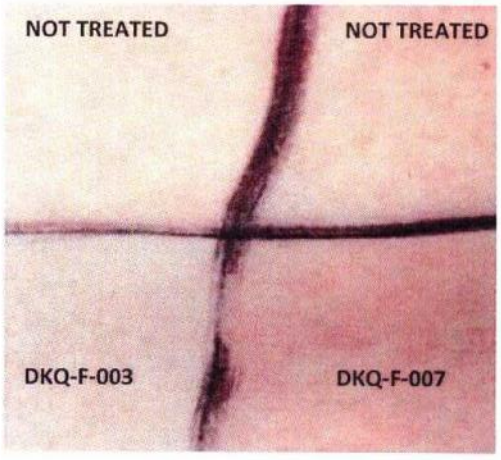
09AG

T0' (Immediately after irritation)



10GD

T2h (2 Hours after irritation)



10GD

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CONCLUSIONS

As one can notice the product:

DKQ-F-003

can change the clinical and instrumental parameters evaluated on the volunteers who underwent the clinical test, therefore the product has proved to have a :

soothing effect (% of reduction of erythema is significantly higher than that of the non treated area)

istead the product:

DKQ-F-007

can not significantly change the clinical and instrumental parameters evaluated on the volunteers who underwent the clinical test, therefore the product has not proved to have any soothing effect (% of reduction of erythema is comparable to that of non treated area)

Experimenter

Dott.ssa Evelyn FALCONI KLEIN

Monitor

Prof. Plinio RICHELMI

Quality Control

Dott. Claudio ANGELINETTA

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[illegible]

Enclosure A : recruitment

Date (d/m/y) : ☐☐ ☐☐ ☐☐

Volunteer no.: ☐☐☐

Consent Form

Volunteer's initials ☐☐☐

Title

PRELIMINARY EVALUATION OF THE SOOTHING AND PROTECTIVE POWER OF TWO COSMETIC PRODUCTS THROUGH A CLINICAL-INSTRUMENTAL TEST

Sponsor
DOCUCHEM s.l. UNIPERSONAL

Report no. 1201L19F

I confirm that the volunteer has read the enclosed informative form. The volunteer has had the opportunity to ask questions to which was given an exhaustive answer. The volunteer was explained the Objective, the method and the features of the clinical survey, benefits and possible discomforts. The volunteer has agreed to take part in the test.

Date: ☐☐ ☐☐ ☐☐

Physician's name
(in block letters) _____

Physician's signature

_____

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[illegible]

.

Allegato B: arruolamento / Enclosure B : recruitment

Date (d/m/y) : ☐☐ ☐☐ ☐☐

Volunteer no. : ☐☐☐

CHECK OF THE INCLUSION AND EXCLUSION CRITERIA

Volunteer's initials	☐☐☐	
Age: between 18 and 70 years	YES	NO
Good state of general health	YES	NO
No dermatophaties	YES	NO
Absence of pharmacological treatment in progress untill the selection	YES	NO
Promise not to change the usual daily routine	YES	NO
no atopy reported in the anamnesis	YES	NO
In compliance with the procedures mentioned in the survey the volunteer, after having been informed, has given his or her consent	YES	NO

ATTENTION: Just one mark indicating "no" is enough to bar the volunteer from the survey

Enclosure C : recruitment

Date (d/m/y) :

Volunteer no. :

INFORMATIVE FORM

Volunteer's initials

Title

PRELIMINARY EVALUATION OF THE SOOTHING AND PROTECTIVE POWER OF TWO COSMETIC PRODUCTS THROUGH A CLINICAL-INSTRUMENTAL TEST

Sponsor
DOCUCHEM s.l. UNIPERSONAL

Report no. 1201L19F

Introduction

All tested cosmetic products do not contain any substance which is forbidden by the EEC legislation as far as the use of cosmetic and personal hygiene products is concerned, the preservatives in the product formula are in the list of accepted components published by the EEC and are used in a concentration provided for by the law and moreover limits and instructions, published in the Enclosures of the 76/768 EEC regulation, are mentioned for those substances for which there is a concentration limit.

Scope

The scope of this test is to evaluate whether this product t has got a cosmetic soothing power, in particular if the product can significantly change skin parameters like skin redness.

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Informative Form (Continuation)

The clinical data are strictly confidential

During or at the end of the test the promoters of the survey or some Health officers may have to examine your case file. The results could also be published . In any case your name will never be mentioned, unless if absolutely necessary and also in this case only to people - who like us - are subject to professional secrecy. All information gathered in the survey will remain strictly confidential and you won't be identified from it.

What happens, if you decide not to take part in the test ?

Your decision to take part in the test must be absolutely voluntary, you must not feel forced to. If you decide not to take part, you will neither run into any inconvenience nor lose any benefit which you enjoy at present. If you decide to interrupt the treatment, you can do it any time and you will neither run into any inconvenience nor lose any benefit you enjoy now. However, if you decide to interrupt it, you should inform your physician promptly and you had better come back for a check up. We ourselves reserve the right to interrupt the test if we feel it isn't any longer good for you.

You can ask questions or you can ask for an explanation any time before, during and after the treatment applying directly to:

Physician _____ Phone _____

who will attend you throughout the treatment.

Enclosure E: Helsinki Declaration

DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.
   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions

(methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

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32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or

    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

MILANO ITALY