

**GENERAL CONDITIONS FOR THE PERFORMANCE OF HUMAN TEST PROJECT**

**EVIC ROMANIA**

**I. REGULATIONS**

The performance of this study, defined as without direct individual (therapeutic) benefit, is based on:

- the general principles of medical ethics in clinical research coming from the Declaration of Helsinki (June 1964) and its successive amendments (Tokyo-Oct 1975, Venice-Oct 1983, Hong-Kong-Sept 1989, Somerset West-Oct 1996, Edinburgh-Oct 2000),
- the recommendations of Colipa-August 1997: "Guidelines for assessment of human skin compatibility",
- the text of the SCCNFP – 23/6/1999 Opinion concerning : Guidelines on the use human volunteers in compatibility testing of finished cosmetic product,
- the general principles of Good Clinical Practices decreed in "Hotararea nr.1/27.02.2004 a Agentiei Nationale a Medicamentului" – official text published in the official bulletin of Romania,
- the international recommendations relating to Good Clinical Practices for conducting clinical trials for drugs ICH E 6, step 4, of 1 May 1996,
- the Directive of the European Parliament and Council 2001/20/EC concerning the harmonization of legislative, statutory and administrative provisions of the member states relating to the application of good clinical practices when conducting clinical trials for drugs for human use – OJ/EC/ of 1/5/2001,
- Law 178/2000 regarding cosmetic products, republished in 2005,
- Law 379/2004 for modifying and completing the law 178/2000 regarding cosmetic products,
- Order 309/729/2001 regarding the inventory of the ingredients used in cosmetic products,
- Order 308/2001- Guidance regarding the principles of good manufacturing practice for cosmetic products,
- Order 1448/2005 regarding the categories of cosmetic products and the lists containing the substances that can be used in the composition of cosmetic products,
- the good laboratory practices (GLP)

The study complies with the law nb 78/17 of 6 January, 1978 related to data processing, files and liberty, and its amendments.

**II. INSURANCE OF THE SPONSOR AND INVESTIGATOR**

The S.C. BIO HIGH TECH SRL is covered by an insurance guaranteeing its civil responsibility towards the volunteers.

Before the beginning of the study, the sponsor certifies he has taken out a public liability insurance guaranteeing the consequences concerning the possible damages resulting from the use of the test product(s) in this study.

**III. INVESTIGATOR CENTRE**

SC Bio High Tech SRL, EVIC ROMANIA located 15, Constantin Bosianu Street, Bucharest, Romania is equipped with material and technical means suitable for the research and compatible with the safety requirements for human subjects and allowed by Trade Registry no J40/13128/13.08.2004 and authorized by Ministry of Health from 15.11.2004.

**IV. TECHNICAL STAFF**

The test is performed on the responsibility of a competent Investigator.

**V. INTERNAL COMMITTEE**

The study must be devoid of any foreseeable serious risk for the safety of the volunteers, the protocol and the information concerning the product(s), particularly that related to its (their) safety are submitted to the of both internal committee of Evic France and Evic Romania, whose constitution and methods of functioning are defined in a procedure.

The committee gets sure that the project meets the conditions of optimal scientific rigour, assesses its general relevance, the suitability between the aims followed and the means implemented and gives an opinion on the protection of the volunteers.

## VI. TEST PRODUCT(S)

### VI.1. Product coding and filing

The sponsor supplies the product(s) in sufficient quantity for the study, if possible in neutral packaging, clearly identified.

The product(s) is (are) coded on delivery.

A sample of the product(s) is taken and kept in the sample library of the investigator centre for 3 years.

### VI.2. Safety

The sponsor certifies:

- that the formulation of the finished test product(s) complies with the law 178/2000 amended with law 508/2002 concerning cosmetic products harmonized with European legislation **Council Directive 76/768/EEC of 27/07/1976** concerning cosmetic products and its successive amendments and particularly the **Directive 93/35/EEC of 14/06/1993** and the **Directive 2003/15/EC of 27/02/2003**,
- the strict conditions of manufacturing of the test finished product(s) guaranteeing chemico-physical and microbiological qualities are in compliance with the specifications,
- the stability of the test finished product(s), within time,
- if possible, its (their) innocuousness and the absence of foreseeable serious risk for the health of the subjects who take part in the study.

If he can not certify this last point the data are analyzed by the safety assessor of Evic Romania in order to start the clinical study without serious foreseeable risk of local intolerance under the experimental conditions adopted.

## VII. VOLUNTEERS

### VII.1. Constitution of the panel of volunteers and modes of recruitment

SC BIO HIGH TECH SRL has at its disposal a panel of volunteers constantly renewed. These subjects come from all social categories. They either volunteer spontaneously to the Institute or reply to a direct call from the latter.

Prior to their admission they are subjected to a medical examination and a detailed dermatological and cosmetological questionnaire performed by a doctor at the company location.

The volunteers are selected from the general panel of the company on the basis of inclusion criteria and non-inclusion criteria specific to study and on their ability to respect the constraints required by the protocol. They are definitely included in the study after specific questioning and clinical examination.

### VII.2. General inclusion criteria

The following subjects are included in the study:

- using contraceptive method to avoid to be pregnant during the study (for women),
- corresponding to the specific criteria of the protocol,
- certifying not to take part in another biomedical research with or without direct individual benefit in another investigator centre, in accordance with the corresponding procedure,
- giving their written "informed consent", in accordance,
- corresponding to the quality of "healthy volunteer", as defined by BIO HIGH TECH SRL and therefore:
  - exhibiting or declaring no cardiovascular, pulmonary, neurological, genital, urinary, osteoarticular, psychiatric, haematological, immunological or endocrinal pathology which is not stabilized or could interfere directly or indirectly with the study,
  - declaring or exhibiting during examination no cutaneous affection, located on the experimental area or affecting other parts of the body, which could interfere with the study, for example: dermographism, seborrheic dermatitis, eczema, recurrent herpes, pityriasis versicolor, juvenile acne with inflammatory eruption or nodular or cystic acne, psoriasis, important pigmentary disorders (vitiligo, chloasma, multiple lentigines, numerous or congenital nevi), UV light induced dermatitis, urticaria, chronic lupus erythematosus, lichen planus, skin cancer...,
  - declaring no treatment liable to interfere with the interpretation of the results, for example: anti-inflammatory, antihistaminic, desensitization treatment,

- non alcohol dependent,
- non addicted to drugs,
- certifying the truth of the personal information declared to the Investigator.

### **VII.3. General non-inclusion criteria**

The following subjects are not included in the study:

- under 18,
- being of age but protected by law,
- deprived of freedom by administrative or judicial ruling,
- admitted in a medical or social establishment for purposes different from the study,
- hospitalised and ill in situation of emergency,
- pregnant and lactating (women),
- being in exclusion period,
- non liable to respect the constraints of the protocol (living too far from the test facilities, linguistic or intellectual barrier).

### **VII.4. Information of the volunteers and informed consent**

The information is given to the volunteers before the start of the study.

This information, accessible, understandable and suitable for each person, is given orally. Then it is written on a specific document.

The minimal content of this information includes the aim of the study, the methodology, the duration of the study, constraints (obligations, restrictions and troubles), the minor foreseeable risk, the opinion of internal committee and possibly when justified, the expected cosmetic benefits.

This information is completed, if necessary, by the technician or the investigator (or the competent person designated) who answers all the questions asked by the volunteers.

This informed consent form is personal and previous to the study.

It is clear, informed and explicit. It can be checked and is written and given on the same support than the information to avoid any risk of dispute about its content.

The document which enables to collect the written informed consent and to inform the volunteer is signed by the latter and by the Investigator.

The period of exclusion represents the period during which the volunteer is not allowed to take part in another study.

## **VIII. PREMATURE TERMINATION AND SUSPENSION OF THE STUDY**

### **VIII.1. Suspension of the study**

The Investigator can stop the study if the experimentation shows a risk for the health or the integrity of the volunteers, subject to information of the technical manager of Evic Romania the sponsor (case of serious adverse effects).

The sponsor can stop the study at any time for administrative reasons or other ones.

### **VIII. 2. Exclusions**

The investigator can exclude from the study a volunteer:

- non compliant with the protocol (non exploitable results),
- who takes part in another clinical study in another investigator centre,
- who has adverse effect incompatible with a good observance of the protocol,
- in case of adverse event (intercurrent disease requiring a treatment witch could interfere with the study and the interpretation of the results).

### **VIII.3. Withdrawals**

The volunteers who discontinue the study for personal reasons of the study or lose touch the investigator centre, are considered as withdrawals.

The suspension of the study, the exclusions and withdrawals are noted in the Investigator's brochure.

## IX. TREATMENT OF ADVERSE EFFECTS AND ADVERSE EVENTS

### IX.1. Definitions

- **minor reactivity** : any **slight expected or unexpected** local reaction of intolerance or sensation of discomfort **to the test product(s)**, occurring in a volunteer during the study and which should not question the observance of treatment or the good development of the study.
- **adverse effect** : any **annoying and unintended** local reaction of intolerance or sensation of discomfort **to the test product(s)**, occurring in a volunteer during the study or not long after and which could question the observance of treatment or the good development of the study.
- **serious adverse effect** : any adverse effect causing pain or leaving after-effects or inducing an hospitalization or causing a disability or incapacity or questioning the prognosis for survival ..., **leading to suspension of the whole study**.
- **adverse event** : any harmful and unintended event **without relationship with the test product(s)** occurring in a volunteer during the study (change in general state, incurrent disease, accident..) which does not necessarily lead to suspension of the whole study.
- **serious adverse event** : any adverse event whose is fatal or questions the prognosis for survival or induced an hospitalization or causes a disability or incapacity.

### IX.2. Data collection

- **the minor reactivity, adverse effects and adverse events** are noted in the specific section of the investigator's brochure, in accordance with the corresponding procedure.

When one of these phenomena occurs, the Investigator assesses the ascribability of the test product(s) according to the following scale : *none, doubtful, possible, obvious*.

- **the serious adverse effects and the serious adverse events** are noted in an emergency form, in accordance with the corresponding procedure.

### IX.3. Conduct to adopt in case of adverse effect or adverse event

In the face of adverse effect or adverse event, the Investigator defines case by case conduct to be adopted and the suitable steps to ensure the safety of the volunteers taking part in the study.

He can stop the study if the experimentation shows up a risk for the health or the integrity of the volunteers but he must inform promptly (within 24 hours), the technical manager of Evic Romania and the sponsor, by phone or fax.

During the study, the Investigator can exclude (definitively or temporarily) a volunteer:

- in case of adverse effect incompatible with a good observance of the protocol,
- in case of adverse event (intercurrent disease with treatment which could interfere with the study and the interpretation of the results).

The Investigator can modify the protocol or perform additional tests.

He must inform the technical manager of Evic Romania and the sponsor by phone and by fax within 24 hours.

The Investigator can extend the standard period of exclusion or definitively strike the volunteer off the "volunteer" file.

The serious adverse effects or the serious adverse events are notified by the Investigator to the technical manager of Evic Romania then to the sponsor by phone and fax within 24 hours.

In case of serious adverse effects, the possible additional information asked by the sponsor must be supplied within 5 days following the receipt of the form, in order to inform the authorities on time.

## X. DURATION OF THE EXCLUSION PERIOD AT THE END OF THE STUDY

The period of exclusion of the volunteer at the end of the study depends on the reactivity of the latter during the study and on the type of study, in accordance with the corresponding procedure.

### In the case of skin compatibility test:

- when no significant irritation or allergic reaction (skin or mucous membrane intolerance) or sensation of discomfort, justifying a temporary or definitive exclusion, occurs, the period of exclusion last 15 days, except particular derogations related to the of the test.
- when a significant irritation (skin or mucous membrane intolerance) or sensation of discomfort, justifying a temporary or definitive exclusion, occurs, the period of exclusion lasts **15 days at least** and 7 days at least after complete disappearance of the symptoms; when justified by the Investigator, the volunteer can be no more included in tests, whatever their aim, involving products of the same category.

- when a significant allergic reaction (skin or mucous membrane intolerance) or sensation of discomfort, justifying a definitive exclusion, occurs, the period of exclusion last **1 month at least** and 15 days at least after complete disappearance of the symptoms; when justified by the Investigator, the volunteer can be no more included in test, whatever their aim, involving products of the same category (except specific request of a sponsor).

**In the case of skin acceptability and efficacy test**, the period of exclusion lasts **7 days** except in case of reaction of intolerance and in case of particular derogations related to type of effect searched for.

#### **XI. DATA COLLECTION, STUDY REPORT AND FILING**

All the data gathered during the study are recorded legibly and indelibly by the Investigator or the technician responsible for the test, under his control, on the specific document(s) (Investigator's brochures).

Each page of this (these) document(s) is initialed and dated by the Investigator and the technician responsible for the test.

Any missing data is justified and any correction is justified, initialed and dated, without hiding the original recording.

The final report (a report per test product or a report for several test products) is sent to the sponsor, signed and dated by:

- the investigator who certifies that data are valid and comply with GCP,
- the person in charge of the statistical analysis of the result (possibly),
- the person responsible for Evic Romania,

The content of the study report takes into account the recommendations of the Colipa related to the assessment of the efficacy of cosmetic products (August 1997) and the explanatory note related to the structure and the content of the reports of clinical studies – ICH E3, step 4, of 28 November, 1995.

The possible corrections and additions brought to the final report are performed in accordance with the corresponding procedure.