COSMETICS EUROPE:

GUIDELINES ON THE MANAGEMENT OF UNDESIRABLE EVENT REPORTS

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Table of Contents:

Section I – Introduction

1. Introduction

The management of reports of genuine undesirable events can be defined as the activities related to their reporting, assessment, understanding and prevention. For companies, these reports play an important role in the post-marketing surveillance of cosmetic products safety.

Article 7 a (1) (f) of the modified Council Directive 76/768/EEC (Cosmetics Directive), requires that **"Existing data on undesirable effects on human health resulting from use of the cosmetic product"** shall be easily accessible to the competent authorities.

Directive 2003/15/EC, the 7th Amendment to the Cosmetics Directive, requires in addition that these data shall also be made easily accessible to the public in accordance with article 7a (1) (h) of the modified Directive 76/768/EEC ("Without prejudice to the protection, in particular, of commercial secrecy and of intellectual property rights, Member States shall ensure that the information required under (f) shall be made easily accessible to the public by any appropriate means, including electronic means").

Colipa issues the following guidelines on the "Management of undesirable event reports " with an aim of minimizing variations in the implementation of the current regulation by giving broad instructions to the cosmetic industry on receiving, centralizing, recording, and analyzing genuine undesirable event reports.

Consistent generation of high quality and reliable data will further demonstrate the high level of product safety and help the surveillance of cosmetic products placed on the EU market, as well as aid in the process of safety evaluation. Compliance with these guidelines will provide the public and national competent authorities with re-assurance that the data presented are accurate, credible and will respect the consumer and healthcare professional privacy protection.

Implementation of these guidelines should be supported by the senior management of the company and requires the participation and commitment of personnel in all departments. The senior management at all levels within the company should communicate the principles developed in these guidelines.

These guidelines shall be revised, as necessary, to take into account the technical/ scientific progress and regulatory developments in this area.

2. Definition of terms

For the purpose of these guidelines the following definitions shall apply.

2.1. Undesirable event

Any human adverse health event which is:

- voluntarily reported by consumers, healthcare professionals, national competent authorities, to have occurred during or after normal or reasonably foreseeable use of a cosmetic product,
- not necessarily related to the product.

At the beginning, every reported event is to be considered as an alleged undesirable event. It will only become a genuine undesirable event when there is evidence that the event has indeed happened. The following are examples of information which should be considered as evidence: consumer or health care professional identity and contact details, description of the reaction (symptoms and delay of onset), complete product identification, etc.

An alleged undesirable event is clearly defined as quite distinct from anecdotal consumer complaints of a non specific nature or reports of sensorial perceptions which can be generally expected from the normal and reasonably foreseeable use of a specific cosmetic product.

2.2. Undesirable effect

Any genuine undesirable event reasonably attributable to the normal or foreseeable use of a given cosmetic product in consistence with Article 7a(1)(f) of the Cosmetics Directive.

Undesirable effects include but are not limited to irritant or allergic reactions that can affect the skin or eyes (2). In very rare cases an undesirable effect could be serious. The term serious is not synonymous with severe. Severe is used to describe the intensity (severity) of the effect as in mild, moderate or severe. Seriousness is used to describe the patient/ event outcome or action (see Annex 1).

2.3. Causality assessment

Analysis of causal association, on a case by case basis, in an attempt to determine the probability that a well identified product used by a consumer is responsible for a genuine undesirable event.

The causality assessment is therefore strictly individual and relates to the effect on individual consumers. It does not give any evaluation of the risk of a product to the general population. The likelihood of causality is obtained from the use of a standardized method for causality assessment (see Annex 2).

Section II – Undesirable events

1. Management

Each company should ensure that an appropriate management system of alleged undesirable event reports is in place, in order to ensure:

- responsibility and accountability for its cosmetic products,
- and that appropriate action can be taken, when necessary.

It is in particular the responsibility of each cosmetic company to:

- Record all reports of alleged undesirable events in accordance with the Cosmetics Directive,
- Document, investigate, validate and evaluate each report of a genuine undesirable event.
- Classify these documented reports in terms of causal relationship.
- Store the documentation of each report.
- Evaluate this information in terms of frequency, medical significance and causes.
- Ensure that healthcare professionals and/ or consumers privacy protection is maintained.
- Define corrective action plans when appropriate.
- Include updated and substantiated information into the cosmetic product information.
- Be in position to answer questions addressed by the national competent authorities and/or the public under the requirements of the Cosmetics Directive.

For the establishment and maintenance of this system, companies should appoint a person who is responsible for ensuring that information about all alleged undesirable events, which are reported to the company, are managed according to these guidelines.

This person should have experience in all aspects of such a system and, if not a health care professional herself/himself, should have access to such a professional when necessary.

1.1. Reception

Individual reports from consumers, national competent authorities, or healthcare professionals can be reported to a company by different ways (mail, E.mail, phone, direct contact) and received by different employees.

The company needs to ensure that all these reports are forwarded without delay to the appropriate person.

During this first contact attempts should be made to obtain necessary information required for the opening of a case file.

1.2. Registration - Opening a case file

A file is opened for each report of alleged event received, if four types of information are available:

- the nature of the alleged undesirable event
- the date of onset of event
- an identifiable cosmetic product (e.g. exact name, category, type, batch number),
- an identifiable consumer (e.g., initials, age, sex) or an identifiable reporter, if not the consumer (e.g. name, address),

A specific company reference number should identify each case file. This reference number should be included on all the documents related to the case.

1.3. Case information and documentation

All reports of alleged undesirable events are a valuable source of information and should receive appropriate attention.

However, for the purposes of these guidelines and in the context of the requirements of the Cosmetics Directive, only those undesirable events / effects linked to **normal or reasonably foreseeable** use of a cosmetic product are considered. Reports linked to product abuse or misuse[1], whilst also relevant for cosmetic manufacturers, fall outside the scope of this document and should be classified separately.

- Obtaining relevant information

In recognition of the difficulties posed by the lack of detail in some consumer reports, and to obtain sufficient information, it is important that the person who is responsible exercises judgment in relation to how such reports are recorded, classified and followed up.

A standardized questionnaire can be used in consumer contacts to ensure that the maximum information is obtained at the initial consumer contact(s). An example of the nature of the requested information is presented in Annex 3.

When necessary, the initial consumer contact is followed up by additional contacts with the consumer or the treating healthcare professional in order to complement the information.

All complementary information obtained during the initial or follow up contacts needs to be documented, dated and included into the case file

Additional follow up or medical confirmation may not be necessary for an apparently non-genuine undesirable event. A non-genuine undesirable event would be characterized in particular by the impossibility to obtain information that should be considered as evidence: consumer or health care professional identity and contact

[1] Product use which is not in accordance with the intended purpose and the correct conditions of product use and/or with the directions of use and/or with specific warnings mentioned on the product.

details, description of the reaction (symptoms and delay of onset), complete product identification, etc.

On the other hand, if the undesirable event is considered as genuine, reasonable additional efforts should be made either to obtain voluntary informed consent to contact the treating healthcare professional or to have the consumer provide additional, medically relevant, information.

- Company assistance

When necessary, the consumer should be encouraged by the company to consult a health care professional.

Information should be offered by the company to physicians/dermatologists to aid in the diagnosis in terms of documentation and/or testing. In case of an indication of an allergic reaction, some general recommendations are presented in Annex 4.

1.4. Assessment and classification

The assessment of causality should be applied to cases which are considered as genuine, and for which sufficient relevant information is available regardless of the source of the information (consumer contact reports and healthcare professional reports).

It is possible that the outcome of an initial assessment change at a later stage in the process as a result of additional information obtained from detailed questionnaires or from medical investigation. A causality assessment should only be considered final if it is unlikely that further information will be obtained that could change the assessment.

A qualified person who is experienced in complaint handling and has an appropriate professional background should be responsible for the causality assessment. In certain cases it may be advisable to seek the support of an external or in-house healthcare professional in the causality assessment in order to obtain a high degree of confidence in the result. This should be recorded into the case file documentation and the product information.

The causality assessment is obtained using the approach presented in Annex 2. According to this approach, five levels of causality can be obtained: ‘very likely’, ‘likely’, ‘questionable', ‘unlikely' and 'excluded’.

It is possible that a cause other than the cosmetic product is clearly identified through the investigation and causality assessment. In this case the relationship between the undesirable effect and the product is considered as 'excluded'.

Classifications of ‘questionable' and ‘unlikely’ are not considered as sufficiently attributable to the use of a given cosmetic product and thus do not have to be included in the product information according to Article 7 a (1) (f) of the Cosmetics Directive. However, questionable cases can provide useful information and should be carefully analyzed and taken into account as necessary, for further evaluation by the company.

1.5. Closing

As long as the company has reason to believe that it is in the position to obtain additional relevant information which could change the assessment of the case, the case report is considered as not closed.

The company has the possibility to close a report after a minimum of two documented contacts without answer.

Each closed case file should clearly indicate the name of the appropriate company person managing the case, and be dated.

1.6. Data entry

Specific company procedures should be developed for data entry, data coding, control and to ensure the consistency and confidentiality of information.

Some general principles on data entry need to be considered.

- Each case file should be identified with a unique reference number (see 1.2).
- In the case of a specific consumer product return, it should be uniquely identifiable, and linked to a particular case.
- The company should use a standardized medical terminology to describe the undesirable effects.

1.7. Archiving

The company should define clear procedures for archiving and for destruction of very old documents.

It is the responsibility of each company, based on legal requirements of each EU Member State, to specify the retention period for the case files. Retention times for undesirable effects should be longer than retention times for undesirable events.

2. Follow up actions

2.1. Analysis of the data

A human health issue could be identified from one report or, more likely, from several similar reports associated with the same product. As necessary, a trend analysis taking into consideration the nature, severity or frequency of undesirable effects should be performed. Other factors could include possible predisposing factors of the consumers who had experienced the undesirable effect.

When a human health issue is thereby identified, further analyses should be initiated to establish, where possible, the potential mechanism of the undesirable effect.

Concerning the measurement of frequency of undesirable effects, two main indicators are generally used:

- an estimation of the incidence: the number of new cases occurring during a given period of time,
- an estimation of the incidence rate among users to quantify the frequency. The incidence rate of an undesirable effect is the number of new reports occurring during a given period of time, over the total number of cosmetic sales or the total number of users estimated from cosmetic sales (see 3.3).

2.2. Corrective action

As necessary, a number of actions may be undertaken following the assessment of the data. These may include a change in usage instructions, labeling, warnings, formula modification or any further action necessary to protect the health of the consumer.

3. Data reporting

3.1. Internal Company reports

It is the responsibility of each company to define the types of reports provided by the person who is responsible to the relevant company management. For example, a specific and immediate report may be required when a significant safety issue has been identified. In other situations, periodic reports can be provided. These reports should explicitly address any new safety issue.

3.2. Inclusion in the cosmetic product information

All cases classified by the company as ‘very likely’ or ‘likely’ should be considered as sufficiently attributable to the use of a specific product and thus be included into the cosmetic product information, in accordance with Article 7 a (1) (f) of the Cosmetics Directive. These reports should be made accessible to the competent authorities upon request.

It may be useful to make a clear distinction in the presentation between undesirable effects which are documented by a health care professional and those which are based on simple consumer information.

3.3. Consumer information

Following article 7bis (1) (f) of the Cosmetics Directive 76/768/CEE, Colipa has agreed with the Commission and member states that undesirable effects shall be presented in a consistent fashion (2). In most situations the actual number of undesirable effects should be used to compute a value for the number of undesirable effects per 1,000,000 units placed on the market. In situations where the actual volume placed on the market is small (such as a new launch or sale through selective distribution), such a calculation may give a distorted impression. In these situations, the actual number of undesirable effects may be provided.

4. General Management and legal compliance

4.1. Quality assurance program

It is preferable, for the management of undesirable events, to have a documented quality assurance program to ensure that the activities developed are in compliance with the principles developed in these guidelines.

4.2. Standard operating procedures

It could be helpful for the people in charge of the management of undesirable events to have written standard operating procedures to define the scope, organization and the management of these activities.

4.3. Outsourcing

When a part or the totality of theses activities are outsourced, the company should inform the subcontractor, in writing, that activities should be performed in accordance with these guidelines.

4.4. Legal compliance

Companies must, in all cases, ensure compliance with applicable national laws and regulations.

In particular, the company and its representatives should be familiar with and discharge obligations to the collection, use and disclosure of personal information in accordance with the national regulations transposing the EU Personal Data Protection Directive (4).

In situations where a consumer explicitly withholds consent to the record of his/her personal data, the person who is responsible should indicate in the case file that it is a consumer report and that the name and contact details have been withheld at the request of the consumer.

Section III – Annexes

Annex 1. Serious undesirable event/ effect

For WHO (6) and ICH (7), a serious adverse drug event/ effect is any event/ effect that:

- is fatal,
- is life-threatening,
- is permanently/ significantly disabling,
- requires or prolongs hospitalization,
- causes congenital anomaly,
- requires intervention to prevent permanent impairment or damage.

Annex 2. Causality assessment method

The aim of this method is to provide a basis for a common understanding and uniform approach to the performance of causality assessments for genuine undesirable events to cosmetic products.

At the beginning, each reported event is to be considered as an alleged undesirable event. It will only become a genuine undesirable event when there is evidence that the event has indeed happened. A non-genuine undesirable event would be characterized, in particular, by the impossibility to obtain information that should be considered as evidence (i.e. consumer or health care professional identity and contact details, description of the reaction, symptoms and delay of onset, complete product identification, etc.) Care must be taken to exclude the possibility of malicious reports by consumers.

Once non-genuine undesirable events have been excluded, the following causality assessment needs to be carried out, regardless of the source of the information (i.e. consumer contact reports and healthcare professional reports). Throughout the gathering of further information, the assessment of whether a reported event is genuine or non-genuine may change. In which case, the reported event may be subsequently excluded from final causality assessment.

It is important to note that a useful causality assessment can only be performed if there is sufficient minimum information on the case history (in particular symptoms and chronology). If this minimum information is not obtained, the case should be considered as not-classifiable. As long as additional information can be reasonably expected to be obtained, which could change the assessability of the case, the case report is considered as not closed. The company has, however, the possibility to close a case report as ‘not-classifiable’ after a minimum of two documented contacts without answer.

The method of causality assessment is based on the analysis of three key parameters:

- Symptoms
- Time sequence of events (chronology)
- Medical investigation or Re-exposure

It is possible that the outcome of an initial assessment of each of these parameters may change at a later stage in the process as a result of additional information obtained from detailed questionnaires or from medical investigation. A causality assessment should only be considered “final” if it is unlikely that further information will be obtained that could change the assessment of the three individual parameters.

The individual parameters may be considered with different weight in the overall causality assessment, depending on the reliability of the source of information. For instance, imprecise description by the consumer of the exact nature of the symptoms or their characteristics (e.g. time sequence) should be balanced carefully against the outcome of a medical investigation or controlled re-exposure to the product by a healthcare professional. However, it needs to be emphasized that all three parameters need to be addressed, and their weight qualified, in the final causality assessment.

A qualified person who is experienced in complaint handling and has an appropriate professional background should be responsible for the causality assessment. In certain cases it may be advisable to seek the support of an external or in-house healthcare professional in the causality assessment in order to obtain a high degree of confidence in the result. This should be recorded into the case file documentation and the product information.

Symptoms

Compatibility of the nature and localization of the symptoms with the reported product use and in terms of possible confounding factors that could on their own have caused the reaction.

- Evocative symptom: a clinical and/or biological symptom which can be "reasonably expected" for this kind of product and is sufficiently specific to suggest a causality.

- Not evocative symptom: a clinical and/or biological symptom which is not "reasonably expected" for this kind of product, which is not sufficiently specific to suggest a causality or which is explained by other factors (e.g. use of other products such as cosmetics, drugs, household products etc. or a current disease).

If the symptoms are not evocative (i.e. not suggestive of the product effect), the final level of causal relationship is decreased by one degree (very likely to likely, likely to questionable, questionable to unlikely).

A number potential contributing factors or alternative causes need to be considered carefully when assessing cases[1].

UVA Sensitivity:

Many individuals are sensitive to UVA exposure, especially in the early part of the year. The condition of UVA polymorphous light eruption can affect up to 14% of females and up 7% of males. The symptoms of a dermal rash can be easily confused with a mild allergic response to a topically applied product. Care should be taken to exclude UVA sensitivity prior to any formal causality assessment.

[1] Useful references:

a) Pao C, et al.(1994).Polymorphic light eruption; prevalence in Australia and England.Br J Dermatol.130(1):62-4.
b) Marzulli FN Maibach HI (1996) Photoirritation, Chapter16 in the book Dermatotoxicology 5th Ed, edited by Marzulli FN & Maibach HI, pub Taylor Francis, Washington DC.231-37.
c) Lane-Brown MM (2000) Photosensitivity associated with herbal preparations of St John's Wort. Med J Austr, 172 (6): 302.
d) Palanisamy A et al. (2003). Photosensitivity reaction in a woman using an herbal supplement containing ginseng, goldenseal and bee pollen. J Toxicol Clin Toxicol, 41(6):865-7

Drugs, Herbs, Foods:

There are many medications and herbal products that are recognized to cause dermal phototoxicity/photoallergy when taken orally. Examples are given below:

- Antibiotics: griseofulvin, nalidixic acid, sulfanilamides, tetracyclines.
- Chemotherapeutics: dacarbazine, 5-fluorouracil, vinblastine.
- Diuretics: hydrochlorothiazide, furosemide.
- Nonsteroidal anti-inflammatories: benoxaprofen, naproxen, piroxicam, tiaprofenic acid, ketoprofen, diclofenac
- Psoralens (as used in uv-chemotherapy): 8-methoxypsoralen, 5-methoxypsoralen.
- Porphyrins: hematoporphyrin
- Other drugs: amiodarone, chlorpromazine, chloroquin, tolbutamide, Calcium antagonist class of drugs,
- Herbal preparations: St John's Wort, ginseng, goldenseal, bee pollen.
- Certain foods: shellfish, fruits (eg tomatoes, strawberries), spices etc.

Concurrent use of other products (incl. household products, cosmetics, etc.):

It is recognized that the consumer may use several products at the same time. The consumer may have an opinion that only one product was the cause of an undesirable event. However this must be carefully evaluated by an appropriate questionnaire. Care must be taken to exclude anecdotal reports where there is doubt or confusion due to the concurrent use of several other cosmetic products.

Time sequence of events (Chronology)

The time sequence of events describes the chronology of product use and undesirable effects, i.e. the time between application of the suspected product and the development of symptoms as well as the time between stopping product use and the clearing up of the symptoms.

- Compatible chronology: the time sequence between product use and the occurrence of symptoms as well as between stopping product use and clearing up of the symptoms is plausible from a medical viewpoint and can be reasonably anticipated for this kind of product use and undesirable effect.

- Incompatible chronology: the time sequence of occurrence and/or clearing up of symptoms is not plausible from a medical viewpoint and can not be reasonably anticipated for this kind of product use and undesirable effect. In this case, the relationship between the undesirable effect and the product is considered as 'excluded'.

- Not clearly compatible chronology: the time sequence of occurrence and/or clearing up of symptoms is not expected from a medical viewpoint and cannot be classically anticipated for this kind of product use and undesirable effect.

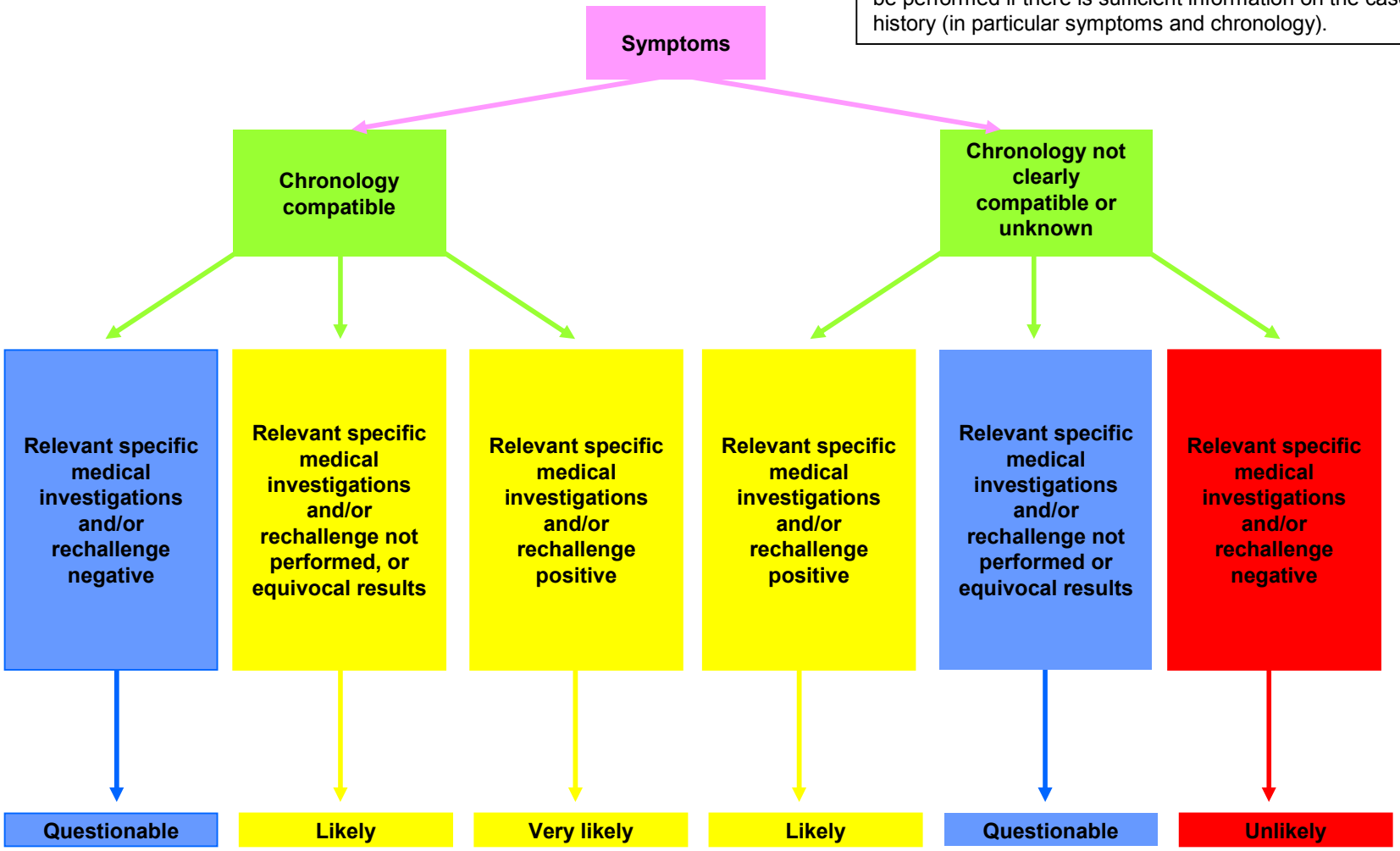
Medical investigation, re-exposure

Results of specific medical investigations and/or the result of a controlled re-exposure with the suspected product. The result of these investigations or the re-exposure can be supportive of a causal link, equivocal or non-supportive. It is possible that a cause other than the cosmetic product is clearly identified through such an investigation. In this case, the relationship between the undesirable effect and the product is considered as 'excluded'.

Rechallenge: controlled re-exposure to the product, considering the exposure conditions of the time when the event occurred.

If a rechallenge is appropriate, it should preferably be by protocol-controlled specific tests under medical supervision. Results from consumer-reported re-application may be accepted by the company expert as equivalent to a re-challenge, if they are sufficiently reported and controlled.

It is important to note that a causality assessment can only be performed if there is sufficient information on the case history (in particular symptoms and chronology).



Symptoms : if the symptoms are not evocative (i.e. not suggestive of the product effect) the final level of causal relationship is decreased by one degree (very likely to likely, likely to questionable ,questionable to unlikely)

Compatible chronology : A time sequence between product use and the occurrence of symptoms as well as between stopping product use and clearing up of the symptoms which is plausible from a medical viewpoint and can be reasonably anticipated for this kind of product use and undesirable event. If the chronology is not compatible the causal relationship is **excluded**.

Rechallenge : Controlled re-exposure to the product, considering the exposure conditions of the time when the event occurred.

Annex 3. Example of typical case information

Date of contact

Consumer[2]

- Name or initials
- Contact details
- Sex
- Age (in particular if a child is involved)
- Baseline characteristics, including relevant medical history and relevant past cosmetic product use (e.g. history of allergy, a previous reaction with a cosmetic product).

Reporting person, if different from the consumer:

- Name,
- Contact details
- Qualification (e.g. physician, dentist, pharmacist, nurse, consumer or other non-healthcare professional).
- As far as information can be shared[2]: baseline characteristics of the consumer, including relevant medical history and relevant past cosmetic product use (e.g. history of allergy, a previous reaction with a cosmetic product).

Suspected product

- Product category
- Exact name,
- Batch number (if possible)

Conditions of use

- Duration of application
- In case of an error in the product use (e.g. misuse), the sequence of events leading up to the error.

Undesirable event

- Signs/symptoms
- Chronology (date of start of event, the time to onset/clearing of signs or symptoms)
- Seriousness of the event
- Diagnosis made by a health-care professional, if available.
- Results of medical investigation and/or re-exposure
- Clinical course of the event, including medical treatment, if any

[2] *Important : Consumer related information needs to respect privacy and data protection, see reference (4)*

Annex 4. Example of information to be provided for a medical investigation of a reported (allergic) skin reaction

The dermatologist/allergologist should first examine the reproducibility of the reported skin reaction, where appropriate, by testing the finished product as it is or in a suitable dilution (recommended or mildly exaggerated use conditions).

In case of an indication of an allergic reaction, the dermatologist treating the consumer should be provided with the various individual substance samples in suitable (ready-to-test) solutions. When diluting the test substance, care should be taken to ensure that the concentrations remain below the irritation threshold of the respective cosmetic ingredients.

On the other hand, the concentration should be sufficient to trigger an allergic reaction beyond any doubt.

A suitable vehicle (e.g. petrolatum, water, alcohol, etc.) may be used as dilution medium, depending on the solubility of the individual substance.

The ingredients should be described according to INCI with details of the dilution concentration and actual pH. Vehicle substance(s) should be also submitted for control reason in the used form and concentration. Raw materials, i.e. commercial concentrations, should only be sent out on request since it is often extremely difficult for the dermatologist to dissolve raw materials at the necessary test concentration in adequate vehicles; testing with the neat material could put the patient at risk for a severe skin reaction.

Annex 5. Legal references & bibliography

1. Council Directive 76/768/EEC on the approximation of laws of the Members States relating to cosmetic products.

2. Colipa. 7th Amendment of the Cosmetic Directive/ Technical Guidance Document on its implementation. Explanatory Memorandum (1st July 2004).

3. Directive 2001/95/EC of the European Parliament and of the Council of 3 December 2001, on general product safety.

4. Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995, on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

5. Commission Guidelines on the Implementation of Article 7a.1.(h) of the Council Directive 76/768/EEC.

6. WHO/EDM/QSM/2002.2 Safety of medicines. A guide to detecting and reporting adverse drug reactions.

7. ICH Guideline (E2A), CPMP/ICH/377/95

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