



# **TREBALL DE FINAL DE GRAU**

University of Barcelona

## **COSMETICS: TOXICITY EVALUATION AND LEGAL FRAMEWORK**

Main scope: Toxicology

Secondary scopes: Legislation and Public Health

Ines Fernandez de Mir

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Faculty of Pharmacy



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## **1- ABSTRACT**

The European Regulation (EC 1223/2009) on cosmetic products, that repeals the previous Council Directive (76/768/ECC), presents the legal framework that cosmetics have to comply in order to be in the European Union (EU) market.

The bases of this Regulation are an electronic and single database that contains all the commercialised products and the figure of a responsible person. That person has the obligation to do a Product Information File containing all the important information including the toxicological assays; and those cannot be longer done on animals. The main goal of this Regulation is to guarantee the safety of the consumer and ensure the functioning of an internal market within the EU.

The methods used are: an evaluation through inquiries to Technical Directors of various labs, interviews with experts and an exhaustive review of the previous and actual Regulations. The aims are to assess: the opinion of the cosmetic sector, the ban on animal testing, the implications of the new Regulation on the market and its implementation.

To conclude, this Regulation is still under a process of implementation but with the effort of all the involved parts in a near future it will be very beneficial. The main purpose of it all is the marketing of safe cosmetic products that do not endanger human health.

## **RESUM**

El reglament europeu (CE 1223/2009) de productes cosmètics i que va derogar l'anterior directiva comunitària (76/768/CEE), mostra el marc legal que han de complir tots els cosmètics per ser comercialitzats a la Unió Europea (UE).

Els pilars del reglament són una base de dades electrònica i única on es recullen tots els productes comercialitzats i, per una altra banda, una persona responsable amb la obligació d'elaborar l'Expedient d'Informació del Producte. Aquest darrer, és un dossier on ha de constar tota la informació rellevant inclosos els assaigs toxicològics, que ja no es poden fer en animals. La finalitat principal de la legislació actual és garantir la seguretat del consumidor i permetre el funcionament d'un mercat interior dins la UE.

La metodologia del treball consta d'una avaluació amb enquestes als Directors Tècnics de varis laboratoris, una entrevista a experts i una revisió exhaustiva de la legislació actual i prèvia. Els objectius són veure la opinió del sector, les implicacions de la nova llei al mercat, la implementació d'aquesta i la prohibició d'experimentar amb animals per fer assaigs en cosmètics.

Per concloure, la regulació s'està encara implementant a nivell del sector i amb l'esforç de totes les parts implicades en un futur serà molt beneficiosa. Sempre tenint en compte que, l'objectiu principal de la indústria cosmètica és la comercialització de productes que no posin en perill la salut humana.

## **2- INTEGRATION OF THE DIFFERENT SCOPES**

This project includes three different study fields, but they are all closely related. The new European Cosmetics Regulation (EC N°1223/2009) brings up a series of new aspects that cosmetic companies have to take into account in order to place in the market their products. The main change is the animal testing ban, since the implementation of the Regulation; cosmetics are not allowed to be tested on animals. In their place, new alternative testing methods are to be used. This is the reason why, the main scope of my project is Toxicology.

Being a Regulation what has brought all the changes, it is logical that, another important scope of my research is Legislation. Cosmetic labs have to understand the Regulation in order to apply it correctly.

The third scope in which my project is based is Public Health, because the new Regulation includes an important chapter on Market Vigilance. This means that cosmetics have to follow a study while in the market, like drugs, in order to find, notify and take off the market cosmetics with new found adverse effects.

### 3- INTRODUCTION

#### 3.1- The concept of cosmetics

In the European Regulation EC N°1223/2009 a very accurate definition of cosmetics and the products involved is found.

Cosmetic products are substances or mixture of substances intended to be placed in contact with the external parts of the human body, with teeth or mucous membranes of the oral cavity with the purpose of cleaning, perfuming, changing the appearance, protecting, keeping them in good condition or correcting body odours. [1]

These products include: [1]

- Creams, emulsions, lotions, gels and oils for the skin.
- Face masks, tinted bases (liquids, pastes or powders), make-up powders, after-bath powders, hygienic powders.
- Soaps: toilet, deodorant.
- Perfumes, toilet waters and Eau de Cologne.
- Bath and shower preparations: salts, foams, oils or gels.
- Depilatories, deodorants and anti-perspirants.
- Hair colorants, products for waving/ straightening/ fixing hair, hair-setting products, hair-cleansing products (lotions, powders or shampoos), hairdressing products (lotions, lacquers or brilliantines) and hair-conditioning products (lotions, creams or oils).
- Shaving products, make- up products and removing make-up products.
- Products for the lips, teeth and mouth.
- Products for nail care.
- Products for external intimate hygiene.
- Sunbathing products, products for tanning without sun and skin-whitening.
- Anti-wrinkle products.

They are not considered as cosmetic products those substances or mixtures destined to be inhaled, ingested, injected or implanted into the human body. [1]



Image 1: Different types of make-up which are very popular among women [2]

### 3.2- History of cosmetics

The cosmetics have a history of thousands of years and they are present in almost every society on earth in one way or another. The word cosmetic comes from *cosmetae* and it was first used to describe the Roman slaves who worked bathing people in perfume. [3]

In Egypt, around 10.000 BC, products such as oils, creams, perfumes, ointments, dyes and paints were used. Their most used product was Kohl, a dark-coloured powder made of a combination of antimony, almonds, lead, copper or ash among others. Cosmetics were an important part of their hygiene and health and both men and women regardless of their age wore makeup. Beautiful smells were believed to be godliness and therefore they learnt the science of perfumery. Its goal was to achieve spiritual rather than physical perfection. [3][4]



Image 2: An Egyptian woman applying on make-up [5]

In China, around 3.000 BC, perfume was thought to have six aesthetic moods. The fragrances were very important and so they imported products from Persia, India or Indonesia to elaborate them. [3]

In Persia, cosmetics were used after the Arab tribes were converted to Islam because it was seen as a sign of purity and cleanliness. They considered cosmetics as a part of medicine called it Medicine of Beauty. They used products such as perfumes, lipstick or solid deodorants. [3]

In India, around the 4<sup>th</sup>-5<sup>th</sup> centuries, the most important product was Henna usually used to dye hair. Other products were: turmeric germicidal cream, special bathing cosmetics, Kohl and Itra that was a mixture of concentrated scents. Whereas in Japan, they used

lipsticks to paint their eyebrows, eyes and lips and rice powder to colour their faces and backs. [3][4]

In the middle ages, white powder or other products like lead paint were used to lighten their skin colour because dark skin was a sign of lower class; it meant that they worked outdoors. Then, Native Americans and Australian tribes painted their faces for ceremonies or battles. [3]

The new era of cosmetics started in the 19<sup>th</sup> century; in 1888 the cosmetic deodorant was invented. During the beginning of the 20<sup>th</sup> century, makeup became fashionable thanks to ballet, theatre and movie stars. Also, the first hair treatments appeared and, after the First World War, the eye liner, red lipstick, red nail polish and suntan became fashionable. Other inventions were the sunscreen in 1936 or the aerosols for hair spray in 1941. [4]



Image 3: The first deodorant commercially produced in the 1880s, its name was MUM [6]

From the beginning of this century, the cosmetic market has started rising and nowadays beauty products are available everywhere. They are used mainly by women, although their use is increasing among men. The cosmetic's market has a different dynamic from last century, and the countries that are leading it are: India, Japan, Russia, USA (United States of America) and some countries in Europe. [3] At the moment, the EU has the biggest cosmetics' market with the highest Retail Sales Prizes (71.000 million euros/year) and is employing around 1.500.000 people; followed by the USA and China. The "Asociación Nacional de Perfumería y Cosmética" (STANPA) places Spain as one of the top 5 markets within the EU; with this panorama it is understandable that the regulatory authorities in the EU felt the need to elaborate a stricter and unified Regulation for all its Member States, with the main goal to protect the consumers. [7][26]



## **4-AIM AND HYPOTHESIS**

### **4.1. AIM AND OBJECTIVES**

The aim of this project is, on view of the answers to the interviews distributed among several cosmetic laboratories, to analyse the actual European Commission (EC) Regulation for cosmetics (EC N°1223/2009) and to identify the main novelties in comparison with the repealed Council Directive.

So the main objectives are:

- To critically assess the use of alternative methods to test cosmetics.
- To develop an opinion on the animal testing ban.
- To collect information on the Product Information File and the market surveillance for cosmetics as they are both key points of the Regulation.

### **4.2. HYPOTHESIS**

The ban on animal testing is being applied probably too soon as there are not enough alternative methods validated to do the toxicity evaluation of cosmetics. So, the new cosmetic products might be more risky than before because they cannot be tested on animals and, therefore, there is not enough safety data.

## 5-MATERIALS AND METHODS

I interviewed several professionals of the cosmetic industry, from big and small companies, on how the changes of the cosmetics' Regulation have affected them. I contacted them in two congresses held in Barcelona this year: In-Cosmetics and INFARMA. In these visits I also got through information on different matters.

Secondly, I did an exhaustive bibliographic search of the main novelties that the valid European Commission Regulation for cosmetics includes. This search included the complete review of the Regulation (EC N°1223/2009) and of the repealed Council Directive 76/768/EEC.

Apart from these, I also went through numerous scientific articles and official websites from Associations and Organisms involved in the subject:

- *Asociación Española de Toxicología (AETOX)* [8]
- BUSCA-TOX [9]
- *Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)* [10]
- Organization for Economic Co-operation and Development (OECD) [11]
- *Busca Alternativas* [12]
- European Commission (EC) [13]
- European Union Reference Laboratory for the Validation of Alternatives Methods to animal testing (EURL- ECVAM) [14]
- *Red Española para el Desarrollo de Métodos Alternativos a la Experimentación Animal (REMA)* [15]

Finally, I got in contact with two experts on the field, one from the European Commission and one from the AETOX, to get their point of view on the cosmetic's Regulation. They advised and gave me information about the development and validation of alternative methods.

## **6- RESULTS**

### **6.1. LEGISLATION: EC N°1223/2009**

The Council Directive 76/768/EEC [16] and the Community Regulation EC N°1223/2009 [1] are the pillars of this part.

#### **6.1.1- Introduction**

A European Regulation is a legal instrument used to impose clear and detailed rules, which do not give room for diverging transposition by its Member States. What is more, it ensures that the requirements are implemented at the same time in all the States.

The Council Directive 76/768/EEC of July 1976 had been so modified and had gone through so many amendments throughout the time, that in December 2009 it was replaced by a new Community Regulation (EC N°1223/2009). The actual cosmetic's Regulation applies totally in Spain since July 11<sup>th</sup> 2013, after a transition period of three years, and repeals the Council Directive. This new Regulation for the cosmetic industry is the same for all the Member States and establishes a centralized system and a single market. Its aims are to repeal all the different national legislations, make the sector evolve and deepen on some aspects from the last directive with the goal of having a uniform interpretation of it in all European countries.

The main pillars of the actual Regulation are: the safety of all products and a single data base for the entire EU. But its application has not been perfect. There have been problems in different countries with its applicability, it has caused difficulties to the free movement within the UE and the text can be complex to understand.

#### **6.1.2- Structure of the Regulation**

The EC Regulation is divided into ten chapters and ten annexes, so that the information is organized in a clear and simple way. The organization has the following order:

### Chapter I: Scope and definitions

The main difference with the late Council Directive in this chapter is the inclusion of new definitions; they are very specific and have an easy interpretation.

### Chapter II: Safety, responsibility and free movement

The concept of Responsible Person appears, it existed before, but now it has defined responsibilities. This person is the one whose name appears on the label and must ensure the compliance of the obligations set out in this Regulation. Also, new responsibilities for the distributors appear and new aspects are added in the identification within the supply chain, in order to simplify it and make it easier. Another new development is that now the Good Manufacturing Practices (GMP) are compulsory, harmonized and the authorities are in charge of their fulfilment.

### Chapter III: Safety Assessment, Product Information File and Notification

The safety assessment must be done by the responsible person who is in charge of the safety evaluation and the elaboration of the cosmetic product safety report. In order to do it, this person must have a certified qualification in pharmacy, medicine, toxicology or a similar discipline. Since the implementation of this Regulation hundreds of people have been trained to become experts in the cosmetics' safety evaluation. The safety report has an established structure and it is divided into two parts.

As for the Product Information File, it has to be written by the responsible person and it is made of four parts:

- Description of the cosmetic product.
- Cosmetic product safety report.
- Description of the manufacturing method and a statement on compliance.
- Data on animal tests.

This type of file was already being used but since the actual Regulation came into effect it has a defined structure and therefore all the old Product Information Files must be reviewed and if necessary retyped.

Another new aspect of the Regulation is the notification. This notification is the same for all the Member States and is electronic. The responsible person must notify the European Commission in the following cases:

- Before the cosmetic is placed on the market.
- The product is already on the market; in this case, the responsible person must notify the original label.
- The product is placed on the market of a Member State by the distributor but it is already on the market of another country. In such case, the distributor translates the label on its own initiative.

All cosmetics must follow the same notification system and fill in the same Product Information File but the versions can vary depending on the type or case.

#### Chapter IV: Restrictions for certain substances

A cosmetic product cannot contain any of the following categories:

- Prohibited substances listed on Annex II.
- Restricted substances other than in the circumstances listed on Annex III.
- Colorants that do not appear on the list of Annex IV.
- Preservatives that do not appear on the list of Annex V.
- UV-filters except for the ones that appear on the list of Annex VI.

These substances were already listed on the Annexes of the last Council Directive (1976) but have been updated ever since and will continue to be updated in the future.

The substances known as Carcinogenic, Mutagenic or toxic for Reproduction (CMR), can be used under very specific and strict circumstances detailed on the Article 15 of the Regulation. The CMR substances are divided into different categories, for example CMR2 are allowed if there is a previous satisfactory evaluation by the Scientific Committee for Consumer Safety (SCCS). These requirements are the same as in the last Directive, but this Regulation also brings new requirements that such substances have to fulfil in the counted exceptions when they may be used. For instance, CMR 1A and B are generally prohibited but are allowed when:

- They comply with food safety requirements.
- No alternative substances are available.

- There is a previous satisfactory evaluation by the SCCS.
- The use is known.

When used, the products must have a special labelling in order to avoid misuse. New additions of this Regulation are the nanomaterials. They must ensure the health protection and because of their nature, a special notification is needed six months prior to their placement on the market. The requirements of the notification are found in Article 16(3).

#### Chapter V: Animal testing

There is a ban on animal testing when used in the following scenarios:

- The final formulation has been tested on animals.
- The ingredient or combinations of ingredients have been tested on animals.
- Animal testing of finished cosmetic products.

The main difference between the actual Regulation and the last Directive is that, the last gave a period for implementation until 2009 for the scenarios described above and until 2013 for the tests concerning repeated-dose toxicity, reproductive toxicity and toxicokinetics, because fewer alternative methods were known. Since then, any testing method that involves animals is forbidden; there are only a few exceptions when a serious concern arises about an ingredient and the Member State can ask the Commission to derogate the law. The commission with the SCCS can authorise the derogation in the following scenarios:

- A widely used and unreplaceable ingredient.
- An important health problem in which case the need to test with animals is justified but it has to follow a detailed research protocol.

#### Chapter VI: Consumer Information

The information on this chapter has suffered minor modifications; the compulsory data are still the same with the addition of the information about the responsible person. Another change is that now the language is set by the law of the State Member and that there is a new declaration for perfumes and aromatic compositions along with new requirements for them.

## Chapter VII: Market Surveillance

The market surveillance is a new concept and consists of controls of the products that are available on the market. The controls are a series of checks of cosmetic products and economic operators through the Product Information File. Also, the Member States must monitor through the market surveillance authorities that the labs follow the GMP and they shall review and assess every four years that their methods work properly.

In the case that an undesirable effect is found the responsible person, distributor, consumer or health care professional should notify it as quickly as possible to the surveillance authorities and, if the case, to the responsible person. And such authority has the obligation to notify it to the rest of Member States through a data base that enables the exchange of information: RAPEX. At the same time, corrective measures have to be placed and the authorities can ask for a list of cosmetics with risk substances.

## Chapter VIII: Non-compliance and safeguard clause

The novelty is that now the authorities must ensure that the responsible person and the distributors comply with their obligations.

## Chapter IX: Administrative cooperation

This chapter establishes the cooperation between the authorities of the different Member States. Besides, because of the new Product Information File, there is a new article in this chapter that describes the cooperation that must exist between the authorities in order to provide each other with the necessary information to ensure that the product is safe for its use.

## Chapter X: Implementing measures and final propositions

This is the last chapter of the Regulation, it describes:

- The reasons that can cause a modification of the annexes (e.g.: potential health risk) always after a discussion with the SCCS.
- The committee procedures, which always assists the Commission.
- The designation by the Member States of their national authorities, poison control centres and other entities.

- The annual report on animal testing which is presented every year by the Commission to the European Parliament and the Council. It reports the progress that is being made, in particular the legalization of the alternative methods of testing that do not use live animals and the different needs of small and medium enterprises.
- The process of a formal objection of a Member State or the Commission against the harmonized standards of the Regulation, to which the Committee must give its opinion. And after that, the Commission shall act accordingly and inform the Member States.
- The penalties that apply for infringing the Regulation and the dates established for the repeal of the Council Directive 76/768/EEC.

### **6.1.3- Annexes**

#### Annex I: Cosmetic product safety report

This annex represents an important change in comparison with the previous Council Directive. It is divided into two parts:

PART A: Cosmetic product safety information

PART B: Cosmetic product safety assessment

#### Annex II-VI:

The annexes II to VI are actualized constantly and they present some changes since the first amend of the last Directive (1976). They list, in order, the following: list of substances prohibited in cosmetic products, list of substances which cosmetic products must not contain, list of colorants allowed in cosmetic products, list of preservatives allowed in cosmetic products and list of UV filters allowed in cosmetic products.

#### Annex VII: Symbols used in packaging or containers

This annex was also found in the last Directive, but now with greater detail, shows the most important symbols found on the cosmetics' containers.



## Annex VIII: List of validated alternative methods to animal testing

Also found in the repealed Council Directive, it establishes that the alternative methods should be described whether they replace fully or only partially animal tests. Animal testing was not fully replaced by an alternative method that did not use animals until 2013, so this annex was necessary until then.

## Annex IX & X: Correlations

The Annex IX describes the amendments of the repealed Directive and the list of time-limits for the transposition into a national law and its application. Whereas annex X is a correlation table of the Council Directive 76/768/EEC and EC N°1223/2009.

## 6.2- TOXICITY EVALUATION METHODS

The European Union (EU) legislation EC N°1223/2009 banned animal testing for cosmetic purposes in the EU. Before it came into effect in 2009, since the year 2004 an animal testing ban for finished cosmetic products was already in order. Then, as for March 2009, it was prohibited to market products that contained ingredients which had been tested on animals. The last part of the marketing ban came into force on March 2013, when it was banned to test the repeated-dose toxicity, reproductive toxicity and toxicokinetics on animals. [17]

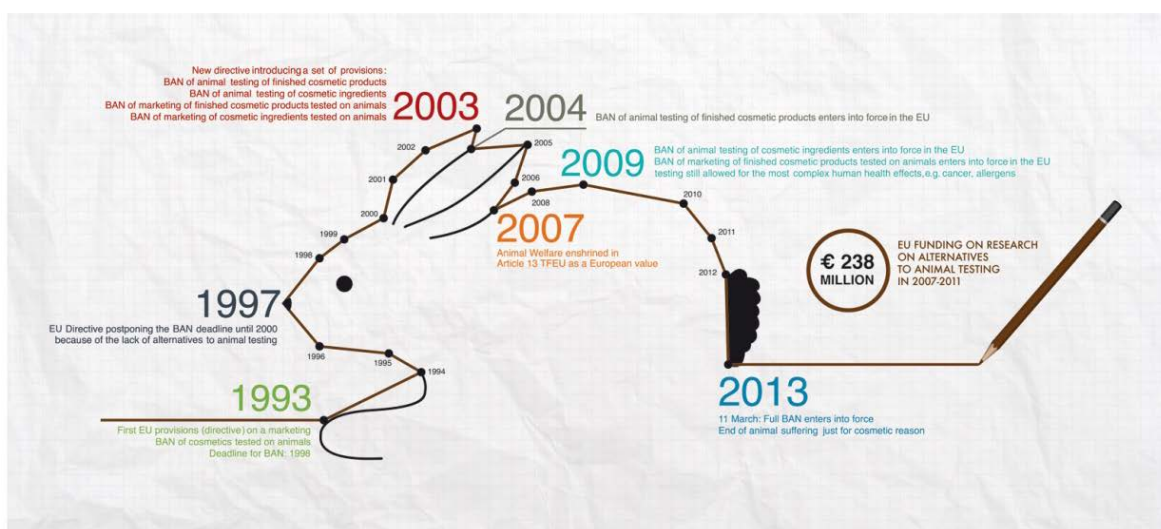


Image 4: History of the EU ban on animal testing for cosmetics [18]

Although testing on animals is forbidden in cosmetics it is still legal in other fields such as toxicological testing and safety evaluation on drugs or food ingredients. In these other fields, in the past few years, the implementation of alternative methods is being done.[17]

What is curious is that Europe is the only continent in the world with an animal testing ban for cosmetics. Other countries like for example China; require animal tests to be done in order to market cosmetic products. The testing ban is also a marketing ban on all cosmetic ingredients or products tested on animals outside the EU after the day the EU legislation came into order. So, nowadays the consumer can be sure that also imported cosmetic products are not tested on animals. Although, this does not mean that many ingredients used in cosmetics have been tested on animals on the past or are being tested, because they are used in other fields (drugs, food, etc.) where its legislation allows it. What is more, cosmetic ingredients might have to be tested on animals to fulfil the REACH (Registration, Evaluation, Authorization and Restriction of Chemicals) requirements, however those are not the same for all legislative domains, and so annexing animal tests for an ingredient to a REACH registration can cause legal problems. [17]

An alternative method is associated with the principles of the 3Rs (Replacement, Reduction and Refinement) of animal testing and are based on either *in vitro* tests or computer based models. The EU made a commitment back in the 1980s to try and replace animals used in experiments, reduce its number and improve the testing process to avoid them unnecessary pain and suffering. The EURL-ECVAM (European Union Reference Laboratory for Alternatives to Animal Testing) is the organism in charge of: promoting the development and use of alternatives, coordinating the validation of test methods, disseminating information on these methods through databases and exchanging information between Member States [17]. The ECVAM has full replacement methods already validated but is still working to improve and it always counts with the validation of the Organization for Economic Co-operation and Development (OECD) [11].

The EURL-ECVAM states that even with the animal testing ban, it is possible to guarantee the harmlessness of the finished cosmetic product because they say there is enough safety data of the ingredients. The European Commission and the authorities of the Member States are making a huge effort to validate enough alternative methods to be able to do a rigorous safety evaluation of the products [19]. The following assays are necessary in order to do a safety evaluation of cosmetic products or ingredients:

CONDITIONS	TOXICOLOGICAL ANALYSIS
Basic assays	Acute toxicity Irritation and corrosivity Skin sensitization Dermal absorption Repeated-dose toxicity Mutagenicity/Genotoxicity
Increased dermal absorption	Carcinogenicity Reproductive toxicity Toxicokinetic studies
Ingredients affected by light	Photo-induced toxicity

Table 1. Toxicity studies to do a risk assessment on cosmetic products [19]

The toxicity studies traditionally done in animals and the actual alternative methods used are to be analysed:

Acute toxicity [19]:

The assays are used to describe possible health adverse effects after a single exposure to a substance through the different routes of administration. This test was originally developed to determine the LD<sub>50</sub> in animals (OECD 401 [11]). Due to the number of animals used this test was replaced originally by three others that used fewer animals, applying the principle of the 3Rs. Those tests were: up and down procedure, fixed dose method and the acute toxic class method. The actual legislation does not allow these kinds of tests and at the moment there are no *in vitro* alternative methods. However, the EURL-ECVAM is developing and optimizing a project called: *EU FP6 ACuteTox project Optimization and pre-validation of an in vitro test strategy for predicting human acute toxicity (EU contract no.LSHB-CT-2004-512051)*. The main goals of it are the compilation, evaluation and generation of high quality *in vitro* and *in vivo* data for comparative analysis [14].

Irritation and corrosion [19]:

This is evaluated in terms of skin irritation, skin corrosion and mucous membrane irritation produced by cosmetic ingredients. The corrosion refers to non-reversible injuries and irritation, on the other hand, refers to reversible injuries. Traditionally, the

method used was the Draize method. The methods were very subjective and the extrapolations of the results to human beings were very complicated. So, numerous alternative methods have been validated; the following are for ocular irritation and corrosion, to tell which products are severely irritating from the ones that are not:

- Bovine Cornea Opacity Permeability (OECD 437)
- Isolated Chicken Eye (OECD 438)
- Fluorescein Leakage Test Method for Identifying Ocular Corrosives and Severe Irritants (OECD 460)



Image 5: A lab rat, an example of the animals used in cosmetic toxicity assays [19]

Apart from the previous, there are also validated alternative methods for dermal irritation and corrosion, such as:

- Transcutaneous Electrical Resistance Test Method (TER- OECD 430)
- Human Skin Model Test (OECD 431)
- Reconstructed Human Epidermis Test Method (OECD 439)

#### Skin sensitization [19]:

This is very important, as it is one of the main adverse reactions of cosmetics. Traditionally, the most popular method was the Local Lymph Node Assay that used mouse or guinea pigs. Some alternative *in vitro* methods are still not validated whereas others have already been developed and validated [9]:

- Peptide Reactivity Assay (DPRA- OECD 442)
- KeratinoSens<sup>TM</sup>

#### Dermal absorption [19]:

Human exposure to cosmetic occurs mainly via skin, so the main goal with these tests is to obtain information of the quantity of ingredients that cross the skin layers and reach the blood. There is an *in vitro* assay described by the OECD 428 [11], which uses human or pig skin and places them into a special chamber with two compartments.

### Repeated dose toxicity [19]:

These assays evaluate the toxic effects that result from the repeated daily dosing with an exposure to a substance for a specific part of the life of an animal. Through the tests, normally 28-day or 90-day tests, one can find the NOAEL (Non-Observed Adverse Effect Level) which is an important parameter to calculate the MoS (Margin of Safety) or MoE (Margin of Exposition) [21].

At the moment there are no alternative tests validated by the ECVAM to replace the animal tests, but there are several under development, for example [14]:

- EU FP6 Predictomics project: short-term models assays for long-term toxicity
- EU FP6 Marie Curie Actions Research Training Network PULMO-NET: Pathogenesis of pulmonary disease.
- EU FP7 SEURAT-1: Towards the replacement of *in vivo* repeated dose systemic toxicity testing.

### Reproductive toxicity [19]:

These studies describe a series of adverse effects caused by a substance, which includes effects on fertility, sexual behaviour, embryonal implementation, foetal development, postnatal adaptation and sexual maturity. There are three validated alternative methods:

- Whole Embryo Culture test (WEC)
- Micro Mass test (MM)
- Embryotoxic Stem cell Test (EST)

### Mutagenicity/Genotoxicity:

Mutagenicity is the induction of permanent transmissible changes in the amount of structure of the genetic material of cells or organisms. Genotoxicity, on the other hand, refers to harmful effects on genetic material that are not necessarily associated with mutagenicity [20]. This is the field with the most validated alternative methods [19]:

- Bacterial reverse mutation (Ames test- OECD 471)
- Mammalian chromosome aberration test (ACT- OECD 473)
- Mammalian cell gene mutation test (MCM- OECD 476)
- Micronucleus test (MNT- OECD 487)

And there are other tests like the Comet Assay and the Genotoxicity Assays that are still under validation from the ECVAM [14].

#### Carcinogenicity [19]:

A substance is carcinogenic if it causes a tumour, increases its incidence, malignity or decreases its appearance time when inhaled, ingested, injected or exposed to skin.

The Cell Transformation Assay (CTA) is the only alternative method validated at the moment. However, there is another method which is actually under development and optimization, the carcinoGENOMICS FP6 project [14].

#### Toxicokinetic studies [19]:

These studies describe the process that a substance undergoes, from its absorption until its excretion from the body. There is only one *in vitro* alternative test validated to study dermal absorption (OECD 428 [11]). So, there is a need to develop new *in vitro* and *in silico* tests to predict toxicokinetics of cosmetics. Also, there are other methods for measuring ADME (Absorption, Distribution, Metabolism and Excretion) processes available.

#### Photo-induced toxicity:

These assays are required only for those products that increase their toxicity when exposed to UV light [19]. The first validated alternative test was for phototoxicity, it is called the *in vitro* 3T3 NRU Phototoxicity test (OECD 432 [11]) and it is still under development because it requires the substance to be soluble in water [14].

In general, all these studies are considered as requirements for the toxicological evaluation of all cosmetics ingredients. However, when a considerable oral intake is expected or when the data on dermal absorption indicates a considerable penetration of the ingredients through the skin only carcinogenicity, reproductive toxicity and toxicokinetics studies may become necessary. Also, the photo-induced toxicity data is only required if a product is expected to be used on sunlight-exposed skin. Human data are extremely useful because alternative methods have limited predictability, so to confirm that no harmful effects exist, these kinds of tests should be included whenever available. [21]

On the one side, not testing cosmetics on animals is better because animal and human physiology is very different and the extrapolation of the results was complicated. Also, animal tests were based on the observation of adverse effects and did not really contribute to understand the toxicity or predict it; they took a long time and were very expensive. On the other side, there has to be enough bibliography on the ingredients/products or effective validated alternative methods to be used in cosmetics to make sure the human health is never at risk. So, the development and validation of non- animal methods if they develop correctly would be an important improvement from an ethical point of view and it would also to provide a better safety assessment framework. [17]

The process of finding and validating new alternative methods is a challenge for the administrations and the scientists [22]. The development and validation of alternative methods has improved lately, so it is safe to think that in the mid-term most safe tests, not only in the cosmetic industry, will be done using non-animal testing methods, computer models and other approaches.

### **6.3- THE PRODUCT INFORMATION FILE**

The novelties of the EC N°1223/2009 in comparison with the previous Council Directive is that now there is a defined responsible person that has to guarantee the compliance of the Regulation and, besides that, the Product Information File must contain all the detailed information required.

The Product Information File (PIF) is not only a simple data collection, but it reviews in a critical way all the safety information of a product. It is the dossier that has to be filled when a cosmetic product is placed on the market because it is mandatory for any product marketed in the Community territory; and also for those products on the market before 11th July 2013 [23]. A cosmetic product is an individual and unique combination of ingredients; no ingredients are totally free from potential toxic effects [21]. The person that puts together the file is the responsible person and he/she should keep it for ten years since the date that the last batch went out on the market. In addition, the authorities have to be able to access the file through the responsible person and it has to be accessible in electronic or any other format. The language used has to be understood by the authorities

of the Member State and for each product there has to be a unique notification and only one PIF [23].

The Product Information File must contain [1]:

- A description of the cosmetic product.
- A proof of the effect that the cosmetic product has to accomplish.
- Data on any animal testing performed: as for 11<sup>th</sup> March 2013 no animal testing should be carried on for cosmetic products and their ingredients. The EURL-ECVAM informs that, the industry is forced to use non-animal approaches in order to prove that their products are safe for the consumers. So, there has to be a bibliographic research of previous animal tests in order to get the data needed.
- A description of the method used and an assurance that it complies with the GMP and with the principles of Good Laboratory Practices (GLP).
- The cosmetic product safety report; it is a safety assessment prior to the placement of the product on the market to make sure it is safe for human health when used under normal conditions. The safety report must contain the following key points and all of them have to be carried out, the omission of any of them has to be very justified.

### **The cosmetic product safety report [1]:**

It is divided into two parts; one contains the product information and the other the safety assessment.

#### **PART A- Cosmetic product information**

- 1- Quantitative and qualitative composition of the cosmetic product, including the chemical identity of substances and their function.
- 2- Physical/ Chemical characteristics and stability of the cosmetic product and its ingredients.
- 3- Microbiological quality: it is qualified thanks to the results from the preservation challenge test.
- 4- Impurities, traces and information about the packaging material: the product has to be pure, there has to be evidence of the absence of prohibited substances and the purity and stability of the material have to be stated.
- 5- Normal and reasonably foreseeable use: it has to be justified.



- 6- Exposure to the cosmetic product, there has to be data of: the site of application, the surface area, the amount of product, the duration, the frequency, the exposure routes and the targeted population.
- 7- Exposure to substances: data on substances that can have relevant toxicological effects.
- 8- Toxicological profile of the substances: the methods, which have already been described, that have to be used to find out the toxicological profile have to be detailed. The toxicological routes of absorption, the systemic effects and the margin of safety (MoS) have to be described and, if not present, have to be justified. There are risk factors that have to be calculated [21]:  
 Systemic Exposure Dosage (SED): is the amount of ingredient expected to get to the blood. It can be calculated in percentage or  $\mu\text{g}/\text{cm}$ .  
 Margin of Safety: it is used to extrapolate the results from a group of animals to a human being; it has to be at least a 100 to consider a substance safe for use.  $\text{MoS} = \text{NOAEL}/\text{SED}$
- 9- Undesirable effects: all the related data that involves a cosmetic product(s).
- 10- Information on the cosmetic product: other information like studies on human volunteers or risk assessment in other areas.

#### PART B- Cosmetic product safety assessment

- 1- Assessment conclusion: an statement on the safety of the product.
- 2- Labelled warnings and instructions of use: the label warnings and instructions on the packages.
- 3- Reasoning: an explanation of the scientific conclusion of the risk assessment.
- 4- Assessors' credentials and approval of part B: this person has to be a person in possession of a diploma or other university qualifications recognized by all Member States. This part has to include name, address, a recognised qualification, the date and the signature of the safety assessor.

Besides, a stability test has to be done to ensure that the new cosmetic product or a reformulated product complies with the physical, chemical and microbiological standards and has the quality when stored. The stability test can be positive or negative [24].

A good safety assessment and a good Product Information File ensures the safety of a cosmetic product and it is the best guarantee to place it on the market. All the data needed to elaborate the file can be rearranged according to the possibilities of all the companies ensuring also the safety of the product. The file can always be redeveloped and optimized and the responsible person will always need a team in order to do it properly [21][24].

#### **6.4- MARKET SURVEILLANCE**

The European Cosmetics Regulation EC N°1223/2009 brings up another novelty as it requires a post-marketing system for the detection of undesirable effects caused by cosmetics on human health. A cosmetic placed on the EU market must have high standards of safety and quality as a result of a normal use, so undesirable effects should be rare. [25]

The late Council Directive 76/768/EEC that had been in force in Europe, gave to the cosmetic industry the responsibility to place only safe cosmetics on the market. The data on undesirable effects had to be accessible through the product information and made public upon request. [25]

There is an association called Cosmetics Europe (the European Cosmetic, toiletry and perfumery association) that provides, to the Member States, the guidelines for the assessment of undesirable effects with the aim of minimizing the different interpretations of the legislation.

The actual Regulation (EC 1223/2009) [1] defines an undesirable effect as an adverse reaction for human health attributable to the normal use of a cosmetic. There is a difference between an undesirable effect and a Serious Undesirable Effect (SUE), the latter means that the effect results in a temporary or permanent functional incapacity, disability, anomalies, hospitalization, vital risk or death.

The market surveillance for cosmetics is the process of recruiting, analysing and follow-up studies of the different health adverse effect events within the normal use of a cosmetic product. There has to be an in-market control where checks on the cosmetic products and on economic operators through the PIF are done; and also physical and

laboratory checks of samples when appropriate. Each Member State must have a market surveillance authority to control it. An assessment of their surveillance activities must be carried out every four years and the results have to be communicated to other Member States and to the Commission by e-mail or other means. [1]

The EU countries are responsible of the surveillance of their own markets for cosmetics that involve SUEs. To ensure a common approach there is the Platform of European Market Surveillance Authorities for Cosmetics (PEMSAC) which has representatives of all EU countries and meets twice a year with the following goals [13]:

- Coordinate activities.
- Exchange information.
- Develop and implement joint projects.
- Exchange expertise and best practices in cosmetics market surveillance.

The actual EU cosmetics Regulation created the basis of a common approach for the communication of SUEs. This approach included the notification of SUEs to national authorities and the notification of corrective measures that take place too. All the data on them is part of the cosmetic product safety report and it is mandatory in the EU since July 2013. [13]

In the event of an undesirable serious effect and prior to its communication; the responsible person, distributors or authorities must ensure that it complies with the seriousness criteria [10]. That is followed by a casualty evaluation, an analysis of the cause-effect relation, which aim is to determine the probability to cause a SUE [10]. The responsible person is in charge of doing the casualty evaluation, he/she must have a formal qualification and experience in processing claims [10]. Occasionally, they can count with the assistance of another health professional [10]. In order to guarantee a uniform and structured communication there are three types of prepared forms [10]:

- Form A: for the responsible person or distributor.
- Form B: for the competent authority; it must always enclose a Form A.
- Form C: for the competent authorities in those cases when the SUE has been notified by health professionals and users. It is used to notify them to the responsible person and/or other authorities.

Next, the responsible person should notify it to the competent authority in the time space of maximum twenty natural days. The notification must include: the SUEs, the name of the product and the corrective measures taken. All competent authorities use a common system of identification to avoid duplicity, for example: the OECD codification, the series number or the year of the complaint). When the competent authority receives this information, it should be immediately transmitted to the rest of Member States. Distributors, consumers or health professionals can also report it to the competent authorities and to the responsible person. The authorities use all these information for in-market surveillance activities, market analysis, evaluation and consumer information.[10]

In Spain, the communication of SUEs to professionals is made by the local authority: “Agencia Española de Medicamentos y Productos Sanitarios” (AEMPS). Through their website they issue news and cosmetic security reports that are similar in format to the ones used for drugs. There is also the option of communicating the SUEs by e-mail. [10]

Everybody that participates in the communication process, such as consumers or health professionals, have the guarantee that they cannot be identified. The main aim of this process is to make cosmetics safer for human health, so it should decrease the probability of the SUE repeating itself. The communication of a SUE does not imply it causes a serious risk for human health. [10]

The responsible person has some obligations after the communication of a SUE [10]:

- Analyse all the data.
- Include the data in the cosmetic product safety report.
- Inform the consumers.
- Act accordingly to solve the problem.

The authorities have also some tasks [10]:

- Analyse the trends and signs of detection in the declaration of the SUE comparing them to prior data.
- Provide the consumers with enough information.
- Guarantee the safety of the products in the market.

## 6.5- INTERVIEWS TO COSMETIC PROFESSIONALS

I distributed an interview to twenty-five cosmetic labs with the aim of getting a global idea of what the people that work in the cosmetic's industry think of the actual Regulation. This part of the project was difficult because, first of all, I had to think of the appropriate questions to ask in order to get the correct answers. And, secondly, because I had trouble getting answers from the labs, I understand they are very busy and do not always have the time to do so. Even with these problems, I managed to get eight labs to answer my questions and I am very thankful to them because otherwise this part of my project would not have been possible.

The interview consists of seven questions (see the Annex). The questions were thought so the replies would answer the main topics of the project: the Regulation overview, the animal testing ban, the alternative methods and the market surveillance. The interview was written in Spanish so the interviewees could answer it as easily as possible and it was addressed to the responsible person (Technical Director) or the Product Manager of the lab, all of them professionals that have a deep knowledge of this Regulation and could give a complete answer of the way it has affected their company. As one can see, there are very different kinds of labs included, such as: medical labs that have also a cosmetic line, bigger cosmetic labs but also smaller and local ones. Next, there is the analysis of the answers given to every question:

1. What is your opinion about the late EU Directive (EC N°1223/2009)? What are the benefits that it brings to the sector?

All the interviewees agreed that the Regulation is good or beneficial for the sector. The main benefit named by all was that now the market is unified because the Regulation, the criteria, is the same for all Member States of the EU. This has advantages such as: higher security, simplified registration and commercialization, more quality and control. Some of them also remarked that, in their opinion, the Regulation is very restrictive but always in a rational way. A couple of them, used the answer to also express their opinion about the disadvantages they thought the Regulation has caused, like an increase in the lab's budget or a decrease on the number of approved cosmetics.

2. Product Information File (PIF):

Do you consider it appropriate and easy to implement?

Most of the technical directors considered the PIF appropriate. Three out of eight thought it was easy to implement if one had the necessary data and information. The other five thought it was not an easy task to do, mainly because of the lack of information in some areas.

Do you consider its cost as a factor that makes it harder to apply it correctly?

The majority found that the cost was a disadvantage. It increases, in their opinion, as a result of the resources needed, for example, training courses and human resources. The extra costs make the labs lose competitiveness because they cannot invest a lot of money in other important fields like marketing or research of new products among others. Two of the interviewees, on the other hand, thought the cost had made no difference to their labs.

3. In your lab do animal tests still take place? What is your opinion about the ban on animal testing?

The answer to this question was unanimous; they do not use animals as it is forbidden by the law. Six of the interviewees said that the ban on animal testing is good, whereas the other two thought respectively, that the ban is a bad idea because there is still not enough data from alternative methods and that to experiment in humans only (*in vivo*) is very risky. There is a diversity of opinions on the ban; some think it is good because thanks to the development of alternative methods there is now enough info to avoid animal tests, others think that it is now more ethical and it rationalizes the use of animals. But some, even though they say it is good to ban animal test have named the following disadvantages:

- Extra costs are equal to a decrease on product launches.
- Animal testing was the traditional way to test cosmetics.

4. Alternative methods: Do you think that they can provide toxicological information of the same quality that of animal tests?

The alternative methods are very controversial, so there were very diverse replies to this question. The majority thought it can provide information of the same quality, but that it will be in the long term because in the short term there are not enough alternative methods for everything. Others, that it depends on the product: already commercialized products are easy because there is a lot of information available; but with new products it represents a challenge.

The professionals that answered affirmatively to this question also gave diverse answers, one assured that it is very complicated but at the same time it represents a huge opportunity for the development of the R&D departments. Two stated that there were already enough alternative methods and that they were better than the animal tests.

5. How do the new security instructed professionals contribute to the company? Are they subcontracted?

The majority agreed that they give more security because they have more knowledge on the issue, so they represent an improvement and give prestige to the laboratory. A professional answered that he thought they did not contribute with anything new to their lab and another answered that he had no information on the matter.

Among the interviewed labs, three had these professionals subcontracted; one of them remarked that they did so because it was more objective and that their proposals helped them to improve. The rest had them as part of their staff full or part-time.

6. Cosmetovigilance: Do you think the concept is enough developed to work effectively?

Some said that it has to develop more because, at the moment, there is not enough information and training on the matter. One, in replying so added that the risks of adverse effects had always been low so he did not see the importance of a market surveillance system. One answered that it depended on the resources of the enterprise, so for him, some could make it work effectively whereas others could not. The other three professionals replied that they had it implemented and it worked effectively, they had a department for it. However, they added that the concept is still ambiguous and that it requires a great communication effort and more information.

7. If you had the option, what would you modify of the actual cosmetics Regulation?

The most repeated answer was the lack of agility; that it takes a lot of time to implement changes. Others said that they would make the PIF less exigent, make the Regulation global, add information, simplify/clarify the Regulation and standardize the methods of study.

## **7- RESULTS DISCUSSION:**

The actual cosmetics Regulation (EC N°1223/2009) in opinion of the professionals of the sector (Annex) is beneficial and has supposed a great advance. Some reasons for that could be that it is well organised, very clear and complete in comparison with the previous Council Directive. This simplifies the reading, understanding and implementation by the professionals of the cosmetic industry, even though some parts are very complex. The Regulation is the same for all the Member States within the EU, so it establishes a unified market in a moment when Europe is the continent leading the sector [7]. The Cosmetics Europe Association situates Europe with highest market retail sales prize, so in this context it seems adequate to have a strict Regulation that looks out for the safety of all its consumers [26].

The main drawback of the Regulation according to the interviewees is the lack of bureaucratic agility. The process of updating and modifying of a Regulation is slow and these Regulations once they come into effect are supposed to be subject of updates or modifications. The fact that this Regulation has only modified its annexes II-VI since its implementation in July 2013, shows a lack of bureaucratic agility, which might difficult its optimal implementation [27]. Another delaying fact might be that the Spanish government, through the “Ministerio de Sanidad Servicios Sociales e Igualdad”, has since the 26<sup>th</sup> of December 2013 a paralysed project of “Real Decreto” to regulate cosmetics in Spain [28]. This project should have been out shortly after the Community Regulation came into effect, to control those aspects that the European Commission left to the authorities of the Member States. Some of the aspects that this Regulation project, actually awaiting for approval, should include are: the designation of market surveillance authorities, the measures to protect human health, the procedures for the administrative cooperation, the labelling language and the language of the technical documents, the SUEs process of notification and the establishment of a “Sistema Español de Cosmetovigilancia y Red de alerta de productos cosméticos”. So this supposes an important drawback as it leaves the EC Regulation “kind of” incomplete. [28]

The professionals interviewed stated that alternative test methods would be very beneficial whenever there is enough data, which they hope it will be in the near future. The scenario for the labs is that there is an animal testing ban valid since March 2013, which is also a marketing ban as no cosmetics tested on animals outside the EU can be



marketed here [17]. This presents a problem, as at the moment there are not enough alternative methods validated and accepted to fully replace the animal tests [17]. The ECVAM states that the biggest challenge is to advance on some toxicological areas as nowadays non-animal solutions cannot detect all the possible adverse effects that a chemical could cause to an organism [17]. The European Commission is doing everything in their power to advance in the search and promotion of non-animal methods. They are partnering with organisms such as the SEURAT-1 (Safety Evaluation Ultimately Replacing Animal Testing), COSMOS database and the EPAA (European Partnership for Alternative Approaches to Animal Testing) to join forces in order to achieve it as soon as possible [17]. The use of animals might not have been too ethical in the past; but the implementation in November 2010 of the Directive (2010/63/EU), which spelled out the principles of the 3Rs and introduced measures to facilitate the acceptance and promotion of alternative approaches should have rationalized it [17]. The concerns for the lack of alternative methods and the importance to maintain animal tests for the time being; are being expressed by numerous scientists at the moment, because the European Parliament is debating whether to broaden this ban to the medical research and drug development area [29]. In this direction, sixteen Nobel Prize winners have written a letter to the European Parliament and Commission expressing their concerns about the possible testing ban scenario. In the letter, they express their support to the development of alternative methods to animal testing but add that this area is still under development. So a ban on animal testing, at the moment, would mean a serious step back in the advancing human and animal medical research [30]

Another important improvement in cosmetics safety has been the introduction of the PIF (Product Information File). All the toxicological evaluation tests should be included there, as it is a file that establishes all the information that the laboratories have to provide to their national authorities prior to the launch of a product [1]. The PIF includes the safety assessment; that has to be done by a security professional [1]. All these, provides a greater safety level to the labs but also to the consumers; because when a product is on the market it means it has passed all the evaluations [1].

Once it is on the market, the process of market surveillance begins; it is a crucial phase of the process because it is the look-out for possible SUEs that could have not been found out during previous evaluations [1]. The interviewees mentioned that this phase was still under development and that there was a lack of information, so the correct application

depended on each company. The ideal scenario would be for the cosmetovigilance to work in the same way as the pharmacovigilance, but that is not possible at the moment, as there is a lack of systems, databases, protocols, etc. in the cosmetovigilance in comparison with the pharmacovigilance [31].

There is yet another drawback in order to implement all these changes. A huge economic inversion is needed, because each of the aspects mentioned above (PIF, security specialists, alternative methods or cosmetovigilance) requires an infrastructure, a group of specialized professionals, equipment and resources. In the interviews, the professionals pointed the extra cost as an important factor that difficult the implementation of the new cosmetics' Regulation. The truth is, that after two years from the deadline for conforming to the Regulation and even with the help given by the EC and national authorities some companies, especially medium and small enterprises, choose to ignore the Regulation, struggle to understand the requirements fully or remain only partially compliant [32]. They do these, because they cannot face the extra costs that a full implementation of the Regulation would cause them [32]. But, by doing so they are risking the consumers' safety and their business as they can be reported to RAPEX (Rapid Alert System for non-food dangerous products) [33] for not conforming to the Regulations. This would mean for the company, important financial losses in sales but also in penalties as well as an important damage to the brand image [32]. It also represents an obvious safety concern for the consumers and the fact that companies are risking human health in order to avoid bankrupt, should be a warning for the national authorities and European Commission [32]. Experts say that there has to be a way to help the enterprises and at the same time continue to provide the high safety standards to the consumers. In addition, the companies should have a more positive view of the regulatory aspects because a Regulation is not something to overcome rather than collaborate with [34]. The laboratories should have a better coordination within itself, especially among the marketing, R&D and Regulatory departments which should help to improve these businesses situation [34]. It is certain that the process might take a time but I personally hope that with the effort from all the parts involved (labs, consumers and the authorities), in a near future it will be beneficial for everybody.

## 8- CONCLUSIONS

- The European cosmetics market is the most important of the world. So, a strict and actual Regulation to replace the old-fashioned Council Directive is appropriate.
- The alternative methods to animal testing, *in vitro* or *in silico*, to assess cosmetic products and ingredients will be very effective in the future. But there is a lot of research and economic investment to be done. At the moment, with the few tests that are fully accepted and validated it might not be enough.
- The Product Information File is one of the main novelties of the actual Regulation. Even if it is strict, it is crucial for the safety and toxicological assessment of cosmetics.
- The market surveillance will represent a huge progress in the safety of cosmetics once the process starts functioning smoothly. To achieve it, suitable infrastructures running are needed and there should be more information and formation for: laboratories, pharmacies, consumers or shops.
- The authorities should help the companies, especially small and medium enterprises, financially and with training courses. They should also work together to make the European market stronger and to ensure the high safety standards for the consumers.
- There is still a lot of research and work to do, but all will be in benefit of the human health.

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## **10-ANNEX: INTERVIEWS TO COSMETIC PROFESSIONALS**

This annex contains the complete interviews answered by different professionals of the cosmetic's industry.

**Nombre del laboratorio: AMENITIES PACK NOVOTECNIC**

1. ¿Qué opinión tiene usted sobre la última directiva de la UE [Reglamento (CE) N° 1223/2009]? ¿Qué aporta la normativa de beneficioso al sector?

Como cualquier Directiva es buena al unificar el mercado en Europa y, además, incrementa la calidad percibida por los consumidores sobre los productos cosméticos.

Pienso que es más fácil de cumplir para las medianas y grandes empresas que para las pequeñas que carecen de la estructura de personal y medios económicos para implementarla. En el sector hay muchas empresas de este tamaño para las que la excesiva regulación es un lastre.

2. Expediente de Información del Producto:

¿Lo considera adecuado para el sector y fácil de implementar?

Si, en general, es adecuado. No es fácil de implementarla, por eso se hacen cursos sobre cómo hacerlo

¿Considera su coste como un factor que hace complicado su correcta aplicación?

Sí. Especialmente para las pequeñas empresas o emprendedores

3. ¿En su laboratorio experimentan aun con animales? ¿Cuál es su opinión sobre la prohibición de experimentar con animales?

No experimentamos con animales. La prohibición por un lado es buena porque lograra un desarrollo de métodos alternativos eficaces. Por otro lado, los animales han sido una forma tradicional de testar cosméticos y productos farmacéuticos.

4. Métodos alternativos: ¿Piensa que con su uso se puede obtener información toxicológica de la misma calidad que con los ensayos en animales?

A corto plazo no. A largo plazo espero que se puedan desarrollar ensayos eficaces a un precio razonable.

5. ¿Qué aportan los nuevos profesionales formados en seguridad en cosmética a la empresa?

Un valor añadido de seguridad cara a los consumidores



¿Tiene subcontratados dichos trabajos?

No

6. Cosmetovigilancia. ¿Le parece que el concepto está suficientemente desarrollado cómo para llevarla a cabo con eficacia?

Se está en ello. Pero creo que hacen falta cursos de formación y un poco de normalización a nivel europeo sobre cómo llevarla a cabo en forma eficaz y que por lo tanto sea realmente útil y no se quede en un documento más a tener en cuenta.

7. Si tuviera la opción, ¿que modificaría de la actual normativa de cosméticos?

Modificaría la agilidad. La normativa se publicó hace ya años y el sector es muy dinámico. Por lo que, no solo hace falta actualizar los anexos sino otros temas. Se debería actualizar a un nivel más global, no solo europeo, teniendo en cuenta especialmente los grandes lugares de producción, como por ejemplo China.

### **Nombre del laboratorio: CINFA**

1. ¿Qué opinión tiene usted sobre la última directiva de la UE [Reglamento (CE) N° 1223/2009]? ¿Qué aporta la normativa de beneficioso al sector?

En mi opinión es bueno que exista por fin una regulación en el tema de los cosméticos, que haya unas restricciones y un control. Esto es, a mi parecer, los beneficios de la normativa respecto a la anterior.

2. Expediente de Información del Producto:

¿Lo considera adecuado para el sector y fácil de implementar?

Es adecuado y bueno para el sector ya que permite una regulación más fácil e igual para todos.

Para los laboratorios grandes, como el nuestro, no ha requerido mucho esfuerzo implementar este punto de la nueva normativa. No sé cómo ha sido para los laboratorios más pequeños.

¿Considera su coste como un factor que hace complicado su correcta aplicación?

Para nuestro laboratorio, el coste no ha sido un factor en contra para la correcta aplicación. No ha habido ningún inconveniente.

3. ¿En su laboratorio experimentan aun con animales? ¿Cuál es su opinión sobre la prohibición de experimentar con animales?

No experimentamos con animales vivos. Pienso que está bien que se prohíba experimentar con animales, ya que, a veces la experimentación superaba unos límites éticos.

4. Métodos alternativos: ¿Piensa que con su uso se puede obtener información toxicológica de la misma calidad que con los ensayos en animales?

Los métodos alternativos son mejores que la experimentación con animales.

5. ¿Qué aportan los nuevos profesionales formados en seguridad en cosmética a la empresa?

Más seguridad. Además la ley lo obliga, por lo que es necesario para lanzar el producto al mercado.

¿Tiene subcontratados dichos trabajos?

Sí. Son externos al laboratorio.

6. Cosmetovigilancia. ¿Le parece que el concepto está suficientemente desarrollado cómo para llevarla a cabo con eficacia?

En nuestro laboratorio, existe desde hace tres años, un departamento exclusivo dedicado a esto (departamento de Cosmetovigilancia). Por lo tanto, nosotros lo tenemos desarrollado, desde antes de que fuera obligatorio por ley y es eficaz.

7. Si tuviera la opción, ¿que modificaría de la actual normativa de cosméticos?

No modificaría nada, me parece que por fin, está bien regulado.

### **Nombre del laboratorio: FERRER**

1. ¿Qué opinión tiene usted sobre la última directiva de la UE [Reglamento (CE) N° 1223/2009]? ¿Qué aporta la normativa de beneficioso al sector?

Me parece muy bien que por fin exista una legislación específica para cosméticos.

En mi opinión la nueva normativa no aporta nada de bueno al que la cumple rigurosamente, más bien les empeora, ya que, hará disminuir el número de cosméticos nuevos aprobados.

2. Expediente de Información del Producto:

¿Lo considera adecuado para el sector y fácil de implementar?

El expediente de Información del producto es bueno para el sector cosmético, es adecuado, ya que permite tener toda la información del producto junta.

En cuanto a la implementación, requiere unos costes extras, por lo tanto, aumenta el coste de producción de los cosméticos.

¿Considera su coste como un factor que hace complicado su correcta aplicación?

El coste se incrementa, lo que supone siempre una desventaja en el momento de la aplicación, tanto para las grandes como las pequeñas empresas.

3. ¿En su laboratorio experimentan aun con animales? ¿Cuál es su opinión sobre la prohibición de experimentar con animales?

No experimentamos con animales ya, pues seguimos estrictamente la normativa. En mi opinión, sería mejor experimentar con animales, ya que, probar los cosméticos por primera vez en humanos es un poco arriesgado. Si los medicamentos se prueban antes de en humanos en animales, por qué los cosméticos lo tienen prohibido no tiene mucho sentido.

4. Métodos alternativos: ¿Piensa que con su uso se puede obtener información toxicológica de la misma calidad que con los ensayos en animales?

De momento no se puede obtener información de la misma calidad, esperemos que en un futuro sea posible.

5. ¿Qué aportan los nuevos profesionales formados en seguridad en cosmética a la empresa?

Aportan prestigio, seguridad, cache, mejora continua tanto para la marca como para el consumidor.

¿Tiene subcontratados dichos trabajos?

No. Son propios del laboratorio, pertenecen a un departamento especializado.

6. Cosmetovigilancia. ¿Le parece que el concepto está suficientemente desarrollado cómo para llevarla a cabo con eficacia?

A mi parecer, falta conocimiento a nivel de oficina de farmacia, tanto el farmacéutico como el consumidor. A diferencia de los medicamentos donde el

concepto de farmacovigilancia ya se encuentra muy desarrollado, también gracias al tiempo; la cosmetovigilancia a este nivel le faltaría aun información para que con el conocimiento se pueda llevar a cabo con eficacia.

7. Si tuviera la opción, ¿que modificaría de la actual normativa de cosméticos?

La agilidad, en mi opinión, el tiempo que se necesita para llevar a cabo un cambio, es demasiado lento. En general, todo el tema burocrático que requiere la normativa para llevarse a cabo es demasiado lento.

**Nombre del laboratorio: IDESA PARFUMS**

1. ¿Qué opinión tiene usted sobre la última directiva de la UE [Reglamento (CE) N° 1223/2009]? ¿Qué aporta la normativa de beneficioso al sector?

El Reglamento Cosmético CE n° 1223/2009 sienta las bases de una Normativa común para los fabricantes de productos cosméticos, a nivel europeo, lo cual creo que es beneficioso tanto para las marcas locales / nacionales como las de importación (europeas o no) ya que todas se rigen por el mismo criterio y exigencia para su comercialización en el Mercado Europeo.

2. Expediente de Información del Producto:

¿Lo considera adecuado para el sector y fácil de implementar?

Al principio, como todo cambio, no es fácil de implementar.

De hecho, en el antiguo Real Decreto de Cosmética, el Expediente de Producto ya contemplaba la realización de un Dossier para cada producto con la formulación, información técnica, y todos los datos del producto, materias primas y test,...pero el contenido quizás no estaba tan bien especificado como se detalla en el Reglamento actual 1223/2009.

Tal y como se detalla en el Reglamento actual, hay que recopilar un montón de información, lo cual es muy laborioso.

Aún y así, existen muchas herramientas informáticas que facilitan este trabajo, y su mantenimiento al día.

Al final y gracias al sentido común de los profesionales técnicos se puede conseguir un sistema más o menos ágil para mantener la información actualizada y al día.

En definitiva es un proceso laborioso y que requiere de muchos recursos.

¿Considera su coste como un factor que hace complicado su correcta aplicación?

Por supuesto que este sistema sistemático de recopilación y actualización de los Expedientes de Información de todo Producto que se lanza al mercado supone un coste notable para las empresas. Este coste es tanto de recursos profesionales (mano de obra y tiempo) como de ejecución de tests para soportar la Inocuidad, Tolerancia y Eficacia de los productos cosméticos.

3. ¿En su laboratorio experimentan aun con animales? ¿Cuál es su opinión sobre la prohibición de experimentar con animales?

Desde hace muchos años las empresas medianas y grandes del sector ya no experimentan en animales. Considero que es una buena opción ya que hay que racionalizar el uso de la experimentación animal y reservarla a proyectos médicos y farmacéuticos, donde el riesgo humano es superior.

En cosmética hay que asegurar que los productos que empleamos sean inocuos y seguros, y cuya composición química no vaya más allá de la mera funcionalidad cosmética. No hay que emplear materias primas raras o que incluyan en su composición cierto riesgo para la salud humana.

En cierta forma este coste adicional supone una evaluación previa de las empresas antes de lanzar multitud de productos al mercado. Esto de una forma natural limita el número de lanzamientos y éstos a su vez deben ser mejor evaluados y analizados.

4. Métodos alternativos: ¿Piensa que con su uso se puede obtener información toxicológica de la misma calidad que con los ensayos en animales?

Con los métodos alternativos no siempre se obtiene toda la información deseada, pero hay miles de bases de datos con información anterior a la prohibición en animales, a partir de las cuales se obtiene muchísima información de seguridad, y que nos permite hacer la elección correcta de materias primas nuevas (a veces por similitud de estructura química).

Aparte los fabricantes/proveedores de materias primas están destinando muchos recursos a garantizar la buena tolerancia de los nuevos activos y materias,... con lo cual debemos confiar en los datos que aportan.

5. ¿Qué aportan los nuevos profesionales formados en seguridad en cosmética a la empresa?

Bajo mi criterio el soporte de los profesionales especializados en temas de seguridad aportan mucho más conocimiento a las empresas a la hora de seleccionar las materias empleadas en los nuevos desarrollos, poniendo un criterio previo de selección que quizás antes del Reglamento no se aplicaba.

¿Tiene subcontratados dichos trabajos?

Por supuesto subcontratamos dichos trabajos porque llega un momento que se requiere de muchísima especialización en las diversas materias involucradas en un producto cosmético. Además que creemos que la existencia de estos profesionales toxicológicos que trabajan no sólo para nosotros, sino que para varias empresas, la casuística es tan grande, que nos llega a beneficiar.

Otra razón de confiar en los profesionales expertos externos es que no somos juez y parte en el desarrollo, y sus propuestas de mejora y optimización nos ayudan a implementar cambios de mejora en nuestros productos.

6. Cosmetovigilancia. ¿Le parece que el concepto está suficientemente desarrollado cómo para llevarla a cabo con eficacia?

Como todo sistema dentro de una empresa se puede explicar con mayor o menor grado de exigencia. Esto dependerá de los recursos que cada empresa quiera destinar a desarrollar en mayor o menor grado el propio sistema de cosmetovigilancia.

7. Si tuviera la opción, ¿que modificaría de la actual normativa de cosméticos?

Intentaría desarrollar la Normativa de una forma más clara, al igual como es el caso de los medicamentos.

Por ejemplo, estandarizar cómo deben hacerse los estudios de estabilidad

Simplificar el sistema de recolección de datos y evaluación. Por ejemplo en Farmacia las materias primas se basan en un cumplimiento de Farmacopea, y si las materias empleadas están certificadas no hay que hacer tantos estudios de evaluación de la toxicidad. En Cosmética exigiría que toda materia prima que se registrase y salga al mercado, debiera cumplir unos estándares y también registrarse en algún libro similar al de la farmacopea, de esta forma no deberíamos preocupar de la evaluación de seguridad los fabricantes de productos cosméticos.

**Nombre del laboratorio: IDONEA PERSONAL COSMETICS**

1. ¿Qué opinión tiene usted sobre la última directiva de la UE [Reglamento (CE) N° 1223/2009]? ¿Qué aporta la normativa de beneficioso al sector?

Es una normativa basada en el sentido común, pero quizás demasiado restrictiva para el escaso histórico de incidencias de salud provocadas por productos cosméticos.

Aporta agilidad, seguridad y mayor facilidad para la internacionalización.

2. Expediente de Información del Producto:

¿Lo considera adecuado para el sector y fácil de implementar?

Es adecuado aunque excesivamente denso.

No es difícil de implementar, aunque todavía falta que los proveedores de materias primas faciliten la información necesaria de forma más ágil.

¿Considera su coste como un factor que hace complicado su correcta aplicación?

No.

3. ¿En su laboratorio experimentan aun con animales? ¿Cuál es su opinión sobre la prohibición de experimentar con animales?

No disponemos de laboratorio propio. Pero nuestro partner de fabricación no lo hace y estamos de acuerdo con esta medida.

4. Métodos alternativos: ¿Piensa que con su uso se puede obtener información toxicológica de la misma calidad que con los ensayos en animales?

Es más complejo pero puede hacerse. En este sentido hay una gran oportunidad para el I+D de los laboratorios de ensayos.

5. ¿Qué aportan los nuevos profesionales formados en seguridad en cosmética a la empresa?

No lo sé porque esta tarea la tenemos subcontratada.

¿Tiene subcontratados dichos trabajos?

Si

6. Cosmetovigilancia. ¿Le parece que el concepto está suficientemente desarrollado cómo para llevarla a cabo con eficacia?

Si está desarrollado, pero hace falta mayor esfuerzo en la comunicación e información a todos los agentes implicados, principalmente a las nuevas figuras recogidas en esta nueva normativa.

7. Si tuviera la opción, ¿que modificaría de la actual normativa de cosméticos?

Que los gobiernos estatales estuvieran obligados a complementar los contenidos que les competen en un plazo corto. En el caso de España aún no han publicado la regulación que les corresponde y por tanto hay muchos aspectos de la norma europea en estado de indefinición.

**Nombre del laboratorio: Laboratorio Marti Tor. Marca MARTIDERM**

1. ¿Qué opinión tiene usted sobre la última directiva de la UE [Reglamento (CE) N° 1223/2009]? ¿Qué aporta la normativa de beneficioso al sector?

En general pienso que es una Norma que ha beneficiado al sector cosmético porque garantiza la calidad y la seguridad de los cosméticos que se ponen en el mercado además de unificar criterios para todos los países miembros de la UE. Es una normativa exigente pero muy racional en la mayor parte de sus apartados.

2. Expediente de Información del Producto:

¿Lo considera adecuado para el sector y fácil de implementar?

Es difícil contestar si es adecuado o no. En ciertos aspectos es un poco exagerado y a veces exento de lógica. No tiene mucho sentido evaluar el riesgo toxicológico que pueda existir con la aplicación tópica de muchos ingredientes que ingerimos todos los días sin cuidado alguno. Con respecto a la facilidad de implementación, lo más importante es tener formación suficiente para su elaboración y aplicar mucho sentido común en muchos de sus contenidos. ¿Considera su coste como un factor que hace complicado su correcta aplicación?

En este sentido se ha especulado mucho y los costes pueden oscilar mucho dependiendo de si lo elaboras dentro del mismo laboratorio o lo subcontratas a una empresa de servicios que también ofrecen tarifas muy dispares.



3. ¿En su laboratorio experimentan aun con animales? ¿Cuál es su opinión sobre la prohibición de experimentar con animales?

No experimentamos con animales entre otras cosas porque está prohibido y se han desarrollado muchos métodos alternativos in vitro en su lugar para evaluar productos cosméticos. Paradójicamente lo que si hacemos es experimentar con humanos mediante los test in vivo de evaluación de eficacia y tolerancia de productos cosméticos. De todos modos, hablamos de experimentar con productos cosméticos, no con fármacos.

4. Métodos alternativos: ¿Piensa que con su uso se puede obtener información toxicológica de la misma calidad que con los ensayos en animales?

Pienso que sí. Actualmente se ha avanzado mucho en este sentido y hay muchas alternativas.

5. ¿Qué aportan los nuevos profesionales formados en seguridad en cosmética a la empresa?

Una ayuda importante para garantizar la seguridad de los productos que se introducen en el mercado europeo.

¿Tiene subcontratados dichos trabajos?

No, lo hacemos internamente con la participación del responsable de Regulatory y del responsable de calidad. Ambos elaboran el dossier recopilando toda la información de cada producto y yo misma realizo la evaluación de seguridad.

6. Cosmetovigilancia. ¿Le parece que el concepto está suficientemente desarrollado cómo para llevarla a cabo con eficacia?

El concepto en sí es algo ambiguo. Sin embargo, nosotros si que lo llevamos a cabo con bastante eficacia y buen seguimiento gracias a la participación del Departamento de Atención al cliente que recoge esta información mediante un formulario que tenemos destinado para este fin. Contamos además con la ayuda de un Dpto. médico que realiza el seguimiento de las incidencias informando de las posibles causas de las reacciones adversas al tiempo que aconseja para un buen uso de los productos.

7. Si tuviera la opción, ¿que modificaría de la actual normativa de cosméticos?

Reduciría la exigencia en cuanto a toxicología del dossier de información.

**Nombre del laboratorio: PHARMA PARFUMS**

1. ¿Qué opinión tiene usted sobre la última directiva de la UE [Reglamento (CE) N° 1223/2009]? ¿Qué aporta la normativa de beneficioso al sector?

Lo más beneficioso es que es un marco común para todos los estados miembros de aplicación igual para todos, lo cual facilita bastante la tramitación y comercialización de los productos en la comunidad económica.

2. Expediente de Información del Producto:

¿Lo considera adecuado para el sector y fácil de implementar?

Es adecuado pero no fácil de implementar principalmente porque la información que solicita de materiales no es fácil de conseguir de los proveedores pero es necesario para asegurar el producto.

¿Considera su coste como un factor que hace complicado su correcta aplicación?

Indudablemente este tipo de costes añadidos no ayudan a mejorar la competitividad del producto en cuanto a precio. Pero como es obligado para todos, todos nos vemos afectados por igual.

3. ¿En su laboratorio experimentan aun con animales? ¿Cuál es su opinión sobre la prohibición de experimentar con animales?

Obviamente ni en el mío ni en ninguno se debería hacer, en nuestro caso hay suficiente información toxicológica sobre el producto para no ser necesario hacer este tipo de pruebas.

En mi opinión personal siempre es mejor no experimentar con animales.

4. Métodos alternativos: ¿Piensa que con su uso se puede obtener información toxicológica de la misma calidad que con los ensayos en animales?

Dependiendo del riesgo y del método puede ser viable, en otros casos no. Realmente esto sólo afecta a productos de innovación; de los productos viejos ya tenemos suficiente información bibliográfica. En cualquier caso entiendo que en riesgos como cáncer, mutaciones o riesgo en el feto el límite no es tan claro.

5. ¿Qué aportan los nuevos profesionales formados en seguridad en cosmética a la empresa?

Nada nuevo, más trabajo y más exhaustivo pero entiendo que las buenas empresas ya tenían este tipo de profesionales antes de la aplicación del reglamento sólo que ahora está mucho más reglado cómo efectuar ese control y cómo registrarlo.

¿Tiene subcontratados dichos trabajos?

Algunas pruebas del producto final se realizan en laboratorios externos pero el informe se realiza con nuestro personal.

6. Cosmetovigilancia. ¿Le parece que el concepto está suficientemente desarrollado cómo para llevarla a cabo con eficacia?

Entiendo que es un concepto válido en farmacia y que por ello se quiere trasladar a nuestro sector pero no ha tenido en cuenta muchos factores diferentes del sector medicamento respecto al cosmético. Supongo que al final se irá matizando y puede llegar a ser efectivo, el tiempo lo dirá.

7. Si tuviera la opción, ¿que modificaría de la actual normativa de cosméticos?

En principio nada excepto que para aplicarlo la gestión de tiempo y energía inicial es muy elevada y esto me gustaría cambiarlo pero nunca es viable en legislaciones nuevas, necesitan su tiempo de implantación y de conseguir máxima efectividad.

### **Nombre del laboratorio: SESDERMA**

1. ¿Qué opinión tiene usted sobre la última directiva de la UE [Reglamento (CE) N° 1223/2009]? ¿Qué aporta la normativa de beneficioso al sector?

Me parece muy importante que dispongamos de un reglamento Europeo común, que facilite el registro de productos cosméticos, y con ellos su comercialización.

Aporta cierta unanimidad de criterios y mayor control y seguridad de los cosméticos para el usuario.

2. Expediente de Información del Producto:

¿Lo considera adecuado para el sector y fácil de implementar?

Adecuado: Si.

Fácil de implementar no tanto, los criterios para el cálculo del Mos han ido cambiando conforme se veía la falta de información de los ingredientes.

¿Considera su coste como un factor que hace complicado su correcta aplicación?

El coste material es elevado cuando solicitas la evaluación a un externo, una vez implementado de forma interna no cuesta tanto a nivel material pero si de recursos humanos.

3. ¿En su laboratorio experimentan aun con animales? ¿Cuál es su opinión sobre la prohibición de experimentar con animales?

No experimentamos con animales, pero a veces no se dispone de los ensayos alternativos validados suficientes.

4. Métodos alternativos: ¿Piensa que con su uso se puede obtener información toxicológica de la misma calidad que con los ensayos en animales?

Creo que en este momento no

5. ¿Qué aportan los nuevos profesionales formados en seguridad en cosmética a la empresa?

Tenemos más información sobre los productos que antes, lo cual es importante para el sector y para el consumidor

¿Tiene subcontratados dichos trabajos?

Parte subcontratamos y los nuevos desarrollos se hacen en el propio laboratorio

6. Cosmetovigilancia. ¿Le parece que el concepto está suficientemente desarrollado cómo para llevarla a cabo con eficacia?

Se va implementando poco a poco, también tendremos en cuenta que en general los riesgos son bajos.

7. Si tuviera la opción, ¿que modificaría de la actual normativa de cosméticos?

Es una pregunta difícil, pero los 2 problemas mayores para la empresa son:

- Cálculo de Mos, por la falta de información, luego sería interesante disponer de bases de datos toxicológicos de los ingredientes cosméticos.
- La falta de unanimidad en cuanto de los “Productos de cuidado personal”, solo España mantiene su “disposición adicional segunda” sin crear un criterio común Europeo.