

# Regulation (EC) No 1223/2009 – a recast of the Cosmetic Products Directive 76/768/EEC – in regard to the safety of plant-derived cosmetic product ingredients

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Cosmetic products are regulated at European level to ensure consumer safety. Regardless of the manufacturing processes or the channels of distribution, cosmetic products placed on the EU market must be safe. The manufacturer is responsible for the safety of its products, and must ensure that they undergo an expert scientific safety assessment before they are sold.<sup>1</sup>

To ensure their safety, cosmetic products placed on the market should be produced according to good manufacturing practice [GMP].<sup>2</sup>

GMP is a global standard with origins that can be traced back to the thalidomide tragedy in the 1960s. Thalidomide is a drug that was launched in 1957 as a treatment for nausea of early pregnancy. It was soon found to produce peripheral neuropathy and severe birth defects, problems that had not been picked up during preclinical testing in rats.<sup>3</sup>

Having launched thalidomide in Europe, the drug company William S. Merrell petitioned the US Food and Drug Administration [FDA] in 1960 to be allowed to market the drug in the United States. Troubled by the lack of evidence that the drug was safe for human use, Dr Frances O. Kelsey at the FDA pressed the company for additional research. Her insistence on sufficient safety documentation kept thalidomide off the US market for over a year, time during which the link between thalidomide and birth defects was uncovered. In 1962, the drug was taken off the market.<sup>4</sup>

The consequent requirement of the FDA for more robust safety testing of new drugs spawned the establishment of a number of new contract research organisations [CROs] who would carry out the necessary testing on behalf of companies developing new drugs, agrochemicals, etc. Certain CROs flourished by undercutting responsible laboratories

on price, making a profit by fabricating data and cutting corners on scientific rigour, for example:<sup>5</sup>

- Biometric Testing, Inc.
- Industrial Bio-Test Laboratories

So, in 1976, the FDA implemented its guidelines on good laboratory practice [GLP], a central aspect of which was the need to put in place standard operating procedures, robust process validation, quality control, and quality assurance.

The Good Laboratory Practice for Nonclinical Laboratory Studies (GLP) Regulations, 21 Code of Federal Regulations (CFR) Part 58, were first issued as a draft rule on November 19, 1976 (41 FR 51206), with the final rule issued on December 22, 1978 (43 FR 59986).

FDA promulgated these regulations in response to public concerns that several important studies supporting the safety of FDA-regulated products were seriously flawed due to poor research practices and laboratory misconduct.

These regulations set forth the minimum basic requirements for study conduct, personnel, facilities, equipment, written protocols, operating procedures, study reports, and a system of quality assurance oversight for each study to help assure the safety of FDA-regulated products.<sup>6</sup>

Accordingly, laboratories carrying out safety testing of drugs and pesticides had to be good laboratory practice [GLP]-accredited ... and in turn, for similar reasons, medicinal product manufacturers had to be good manufacturing practice [GMP]-accredited.

In the UK, mandatory compliance with GMP by medicinal product manufacturers followed the Clothier Report (1972) into the “Devonport incident”. FDA regulations mandating GMP in the manufacture of

medical devices came into effect in December 1978. And now, legislation in the US and in Europe requires cosmetic products also to be manufactured to GMP standards to ensure their quality and their safety.

So, Regulation (EC) No 1223/2009 seeks to ensure that cosmetic products are safe to use. It requires cosmetic product manufacturers to comply with good manufacturing practice [GMP]. This means that, in turn, cosmetic product manufacturers have to source raw materials from GMP-compliant sources. This can be a problem with plant-derived cosmetic product ingredients.

Plant-derived cosmetic product ingredients are described by International Nomenclature of Cosmetic Ingredients [INCI] names. INCI names are internationally recognised uniform, systematic names used to identify cosmetic product ingredients, which are allocated by the Personal Care Products Council in the USA, currently at \$200 per name. The Personal Care Products Council has developed nomenclature conventions for “botanicals”. Generally, these ingredients have not undergone chemical modification and include extracts, juices, waters, distillates, powders, oils, waxes, saps, tars, gums, unsaponifiables, and resins. The INCI names for botanicals are based on the latinised binomial identifying the genus and species of the plant. Historically, the primary reference used to establish the latinised binomial names for botanicals was Penso, G., *Index Plantarum Medicinalium Totius Mundi Eorumque Synonymorum*, O.E.M.F., Milano (1983) - ISBN 88-7076-027-8.

This is why many INCI names of “botanicals” refer to what are now out-dated plant names.

Harmonised INCI names for botanicals are designated by the latinised binomial, followed by the common name (where historically used) in parentheses, followed by the plant part (if applicable) and the type of preparation, e.g. *Prunus Persica* (Peach) Leaf Extract.

Alongside the INCI names, these botanicals are also assigned CAS Registry Numbers.<sup>7</sup> A CAS Registry Number is “a globally accepted identifier of a chemical substance”.<sup>8</sup> Further, a CAS Registry Number is supposed to refer to a “unique organic and inorganic substance”<sup>9</sup> and “designates only one substance”.<sup>10</sup> However, in the case of botanical extracts, they refer to mixtures of unspecified composition. Typically, all the various botanical extracts prepared from a particular plant species (whether from seeds, leaves, roots, etc; and irrespective of the solvent and method used to prepare the extract) are assigned the same CAS Registry Number. Clearly, when applied to botanical extracts, CAS Registry Numbers do NOT refer to unique chemical substances.

So, when applied to botanicals used as cosmetic product ingredients, CAS Registry Numbers at best identify just the plant source and certainly NOT the chemical composition.

Similarly, INCI names do not imply a particular chemical composition nor indeed a particular standard or grade of purity. It follows that INCI name and CAS Registry Number designations tell us nothing about whether a botanical extract is safe for use as a cosmetic ingredient, nor does the INCI name or CAS Registry Number indicate that the use of the botanical extract as a cosmetic ingredient complies with the laws and regulations of the United States, Europe, or any other jurisdiction.

Indeed, the Personal Care Products Council acknowledges that the assignment of an INCI name does not imply that the ingredient is “approved,” “certified,” or “endorsed” by the Personal Care Products Council or by any other organisation or governmental body,<sup>11</sup> as does Regulation (EC) No 1223/2009.<sup>12</sup>

Conversely, if an ingredient does not have an INCI name, it does not mean that the ingredient may not or should not be used in finished cosmetic and personal care products. The suitability for use of any ingredient as a component of a finished cosmetic product is solely the responsibility of the finished product manufacturer. And the suitability of an existing INCI name to describe a raw material is a business decision that ultimately must be made by the finished product manufacturer.<sup>11</sup>

Regulation (EC) No 1223/2009 provides an extensive list of materials / ingredients that are not allowed to be used in cosmetic products,<sup>13</sup> but passes responsibility for all other ingredients to the toxicologist who prepares the cosmetic product safety report that is required as part of the product information file.

When putting together a cosmetic product safety report (as is required by Regulation (EC) No 1223/2009), toxicologists CANNOT rely on an INCI name or a CAS Registry Number as an indicator of the composition of a plant-derived cosmetic product ingredient. However, on the basis of cosmetic product safety reports I have seen, they [sometimes] do. And it follows from this observation that the cosmetic product manufacturer in question is probably not complying with GMP in the sourcing of the botanical extract(s) in question.

The toxicologist really should inspect not only the Technical Data Sheet for each ingredient but also a Certificate of Analysis for each batch of each ingredient. A Technical Data Sheet shows what the material should and should not contain. A Certificate of Analysis certifies that a particular batch of that product complies with the Technical Data Sheet (or with a recognised standard) as regards what it should and should not contain.

For a plant-derived cosmetic product ingredient, the least I would expect to see in the Certificate of Analysis is the kind of information that is included in a pharmacopoeial monograph, including:

- a declaration that the cosmetic product ingredient has been prepared from properly-authenticated plant material of suitable quality
- an indication that it contains the stated quantity of the relevant chemical material(s);
- an indication that it does not contain unwanted contaminants.

The growers of plant material for the cosmetic product industry should be complying with good agricultural and collection practice [GACP].<sup>14</sup>

The manufacturers of botanical extracts for use in cosmetic products should be complying with good manufacturing practice [GMP] to ensure the quality and safety of raw materials.

Certificates of Analysis for botanical extracts should be produced by laboratories that comply with good laboratory practice [GLP].

“Raw material related issues continue to be one of the most common findings during GMP inspections and most FDA warning letters to GMP facilities cite violations in raw material management. FDA’s GMP inspectors pay special attention to the way raw materials are sourced, handled, controlled, used, and accounted for at a given facility. [...] The real challenge in raw material management lies in the fact that it is mostly based on the performance of independent vendors out of direct control of the GMP facility. Hence it is important for all GMP manufacturers to implement robust methods for raw material risk management.”<sup>15</sup>

#### **Summary points:**

Regulation (EC) No 1223/2009 has been a culture shock for [some] cosmetic product manufacturers and for [some] toxicologists who prepare cosmetic product safety reports.

When investigating a suspected case of cosmetic-product-associated dermatitis, infection, respiratory distress, etc, question the identity and purity of declared ingredients and especially any botanical extracts. INCI names and CAS Registry Numbers tell us very little about the composition of botanical extracts.

If testing is to be carried out as part of a consumer safety-related incident, insist on receiving ingredients from the same batches as those used in the manufacture of the offending batch of cosmetic product. ■

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#### **References**

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