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Comments

13 September 2017

Italian Decree regulating the use of vegetable substances and preparations in food supplements, replacing the Decree of the Minister for Health of 9 July 2012

Dear Sir or Madam,

the European Commission received a notification by the Italian Republic concerning an Italian decree called "**Decree regulating the use of vegetable substances and preparations in food supplements, replacing the Decree of the Minister for Health of 9 July 2012**" on 28.06.2017 which is currently undergoing the TRIS notification.

The decree is laying down the list of herbal substances and preparations allowed for use in food supplements indicating the requirements to be met to make sure that they are safe. It contains a positive list of herbal substances allowed to be used in food supplements. The list contains certain herbal substances – for example such as *Pelargonium sidoides* - which are to be classified as Novel Food according to Regulation (EU) 2015/2283 or Regulation (EC) 258/97[1] or medicinal products. We kindly ask the European Commission to request from Italy to delete these substances with known pharmacological effects from the notified list since the list is not in compliance with European Union law.

Drawing on 65 years of experience, the German Pharmaceutical Industry Association (BPI) e.V. represents a broad spectrum of the pharmaceutical industry on both national and internationals levels. More than 250 companies with more than 78.000 employees are members of BPI. One focus of the association's activities lies in the area of self-medication with over-the-counter medicinal products, which include phytopharmaceuticals and health products from other regulated areas such as supplements.

We raise concerns regarding the notified list due to following reasons:

[1] The New Novel Food Regulation (Regulation (EU) 2015/2283 will become effective in all parts on 01.01.2018 and will replace Regulation (EC) 258/97.

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- It has to be borne in mind that most EU Member States (including Italy!) classify certain substances included in the Italian positive list for food supplements - such as *Pelargonium sidoides* - as **medicinal products**[2] (see under 1.).

- The notified Italian positive list disregards the decisions taken by the European Medicines Agency (EMA) which has published **European Union herbal monographs**[3] on certain active pharmaceutical ingredients included in the notified list; these monographs include **special warnings and precautions set out in a scientific review process by EMA which are simply ignored in the Italian list**; it would be completely against the objective of consumer protection to simply disregard those special warnings and precautions just because the list deals with food supplements as exactly the same substance is concerned (see under 2.).

- Moreover, the **European Food Safety Authority** (EFSA) has included certain substances - such as *Althaea officinalis* L., *Ginkgo biloba* L., *Hypericum perforatum* L. or *Pelargonium sidoides* - in a **list of botanicals substances** that contain a possible concern for human health when used in food and food supplements[4]; also this list of EFSA is simply ignored by the Italian Republic which cannot be justified from the consumer protection perspective (see under 3.).

- Some substances have been included in an Italian negative list until recently and were restricted from being used in food supplements – they should now be **switched to a positive list without any scientific justification** (see under 4.).

- The Italian Republic might have the competency to enact positive lists of food supplements under EU Law; however, it **must comply with the rules and procedures of the EU Novel Food Regulation** which provides for an exclusive authorisation procedure for Novel Food (see under 5.).

1. The list contains substances Italy itself classifies as medicinal products

[2] See the SmPC of KALOBA® which contains *Pelargonium sidoides*; the product has obtained a marketing authorisation by AIFA: https://farmaci.agenziafarmaco.gov.it/aifa/servlet/PdfDownloadServlet?pdfFileName=footer_001292_038135_RCP.pdf&retry=0&sys=m0b1l3.

[3] Herbal medicine for human use: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/herbal_search.jsp&mid=WC0b01ac058001fa1d

[4] SCIENTIFIC REPORT OF EFSA, Compendium of botanicals reported to contain naturally occurring substances of possible concern for human health when used in food and food supplements, EFSA Journal 2012;10(5):2663; http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2012.2663/epdf.

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Many of the plants listed in Annex I of the Italian Decree are typically used in herbal medicinal products. For example, the following plants:

- *Althaea officinalis* L.
- *Equisetum arvense* L.
- *Ginkgo biloba* L.
- *Primula veris* L.
- *Quercus rubor* L.
- *Sambucus nigra* L.
- *Thymus vulgaris* L.
- *Vitex agnus-castus* L.

In other European countries, e.g. Germany, these plants are marketed as herbal medicinal products. For many of the plants listed here, monographs of the Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency are available, which provides for a medical application of the corresponding plant part or preparation, whereby a pharmacological effect can be assumed in these plants.

Furthermore one of our member company has obtained marketing authorisations and registrations for herbal medicinal products containing *Pelargonium sidoides* in 18 EU Member States, including KALOBA® in Italy. It would be disproportionate if the Italian Republic would now simply turn this opinion on the pharmacological effect of *Pelargonium sidoides* around without giving any (scientific) explanation at all. ***Pelargonium sidoides* is one of the few herbal active ingredients for which the submission of a Periodic Safety Update Report is required** according to the List of European Union (EU) reference dates and frequency of submission of periodic safety update reports (PSURs) (EURD list)[5] of the EMA which shows that **EMA considers the compound an active pharmaceutical ingredient**.

2. Special warnings and precautions set out in EMA monographs are simply ignored

[5] See line 2690 of the list of European Union (EU) reference dates and frequency of submission of periodic safety update reports (PSURs);
http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500133159.

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The substance *Pelargonium sidoides* is also considered by EMA as an active pharmaceutical ingredient as reflected in the European Union herbal monograph[6]. A European Union herbal monograph contains the Committee of Herbal Medicinal Products' (HMPC's) scientific opinion on safety and efficacy data about a herbal substance and its preparations intended for medicinal use. The HMPC evaluates all available information, including non-clinical and clinical data, but also documented long-standing use and experience in the EU. According to EMA[7]:

> *"Final monographs are taken into account by Member States when examining an application. While Member States are not obliged to follow the monographs, any decision not to accept the content of a monograph as adopted by the HMPC should be duly justified taking into account their* ***important role in bringing harmonisation*** *to this field and to facilitate the use of the simplified registration procedure."*

It can be concluded that the **HMPC / EMA considers the substance of *Pelargonium sidoides* as an active pharmaceutical ingredient** especially if those dosages are reached. In addition, the **substance should only be used under the conditions set out by the HMPC / EMA.**

A second example of a herbal monograph ignored by Italy is the substance *Actaea racemosa* L., synonym *Cimicifuga racemosa* (L.) Nutt. radix, rhizoma[8]. Special warnings and precautions are completely missing in the Italian list for food supplements which only refers the "consumer" to the physician but **does not repeat significant warnings set out by EMA such as**:

> *"Skin reactions (urticaria, itching, exanthema), facial oedema, peripheral oedema and gastrointestinal symptoms (i.e. dyspeptic disorders, diarrhoea) have been reported. The frequency is not known."*

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[6] European Medicines Agency, Community herbal monograph on *Pelargonium sidoides* DC and/or *Pelargonium reniforme* Curt., radix, Committee on Herbal Medicinal Products (HMPC), EMA/HMPC/560961/2010; 20.11.2012: http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_Community_herbal_monograph/2013/02/WC500138439.pdf.

[7] See for details the EMA website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001132.jsp&mid=WC0b01ac0580033809.

[8] European Medicines Agency, Community herbal monograph on *Cimicifuga racemosa (L.) Nutt. radix, rhizome*, Committee on Herbal Medicinal Products (HMPC), EMA/HMPC/600717/2007 Corr., 25.11.2010: http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_Community_herbal_monograph/2011/01/WC500100981.pdf.

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"Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended."

"Patients who have been treated or who are undergoing treatment for breast cancer or other hormone-dependent tumours should not use Cimicifuga preparations without medical advice. Please see section 5.3. 'Preclinical safety data'."

In addition to that, *Cimicifuga racemosa* is also listed in the EURD list of the EMA which clearly identifies it as active pharmaceutical ingredient[9].

It would be contrary to the objective of harmonisation and consumer protection if Italy would be allowed to simply ignore these special warnings and precautions set out in a scientific review process by EMA by way of the herbal monograph and the EURD list.

3. The Italian list ignores the EFSA opinion

The Italian decree is also in conflict with the position of EFSA which has included plants such as *Althaea officinalis L., Ginkgo biloba L., Hypericum perforatum L. and Pelargonium sidoides* in a list of botanicals substances that contain a possible concern for human health when used in food and food supplements[10]. Although the document and assessment of EFSA might not be considered as binding upon national authorities, it has to be considered by the Italian Republic in the evaluation process. **Specific reasons have to be given why Italy intends to divert from those decisions taken by EFSA and EMA**.

Given the objectives of the Italian decree, namely harmonisation and consumer protection, it seems disproportionate to simply refer to the BELFRIT assessments and the mutual recognition principle while at the same time ignoring the special warnings and precautions set out by EFSA and EMA.

4. Substances are switched from negative lists to positive lists without any justification

[9] See line 973 of the list of European Union (EU) reference dates and frequency of submission of periodic safety update reports (PSURs); http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500133159.
[10] SCIENTIFIC REPORT OF EFSA, Compendium of botanicals reported to contain naturally occurring substances of possible concern for human health when used in food and food supplements, EFSA Journal 2012;10(5):2663; http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2012.2663/epdf.

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Until recently, the Italian Republic had included the substance ***Pelargonium sidoides*** **in a negative list of herbal substances not allowed in food supplements**[11]. This is in conformity with its decision to qualify the substance as Novel Food.
However, no justification has been given why the substance has been moved from a negative to a positive list. Such **justification is especially needed if a substance is switched from a negative to a positive list** because some precautions and warnings must have existed in the past which justified the inclusion in the negative list which must be completely resolved to justify such a drastic shift. To our knowledge no additional label warnings similar to those used in other EU Member States have been issued in Italy for *Pelargonium sidoides*.

As a rationale for the decree the Italian Republic refers mainly to a cooperation project between Belgium, France and Italy known as 'BELFRIT', which has drawn up a list of plants eligible for use in food supplements. According to the "Statement of Grounds" for the decree the Italian Republic refers to an alleged need to harmonise national list of food supplements in compliance with the BELFRIT countries:

> *"… common aim of the BELFRIT project was to bring to the EU's attention the* ***need to harmonise*** *the issue at hand,* ***demonstrating the feasibility of its implementation****. In order to facilitate the application of the* ***principle of mutual recognition****, the Ministerial Decree of 9 July 2012 laid down a streamlined procedure for amending Annex 1… "*

While it might be the political interest of Italy, Belgium and France to obtain "harmonisation" in their food supplement market, it is not justified to disregard EU law. **The fact that Belgium might have allowed certain substances on its positive lists by no means requires Italy to do the same especially if this substance has been qualified as Novel Food**. The principle of mutual recognition does not require Italy to follow the Belgian or French example. In addition, according to our information France itself has prohibited the use of *Pelargonium sidoides* in food supplements. It is not included in the French positive list of substances allowed to be used in food[12].

[11] Ministero della Salute, ESTRATTI VEGETALI NON AMMESSI NEGLI INTEGRATORI ALIMENTARI; https://www.salute.gov.it/imgs/C_17_pagineAree_1268_listaFile_itemName_3_file.pdf.
[12] Arrêté du 24 juin 2014 établissant la liste des plantes, autres que les champignons, autorisées dans les compléments alimentaires et les conditions de leur employ, JORF n°0163 du 17.7.14, p. 11922, n° 26: https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000029254516&categorieLien=id.

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5. Products with Novel Food status should not be included in national food supplement lists

The Italian Republic might have the competency to regulate its food supplement market. This competency, however, is limited by way of EU law. Article 14 (9) Regulation (EC) 178/2002 stipulates that,

> *"…food shall be deemed to be safe when it conforms to the specific provisions of national food law of the Member State in whose territory the food is marketed … where there are no specific Community provisions"*

Substances which are considered Novel Food according to Regulation (EU) 2015/2283 or Regulation (EC) 258/97 are subject to a specific authorisation procedure set out in these Regulations. It is obvious, that individual **Member States are not supposed to circumvent the Novel Food authorisation procedure set out by EU law by including Novel Food substances in national positive lists for food supplements which have not undergone the authorisation procedure foreseen for Novel Food**.

Pursuant to Article 4(3) Treaty of the Functioning of the European Union (TFEU) the EU Member States shall take any appropriate measure, general or particular, to ensure fulfilment of the obligations arising out of EU law or resulting from the acts of the institutions of the EU and facilitate the achievement of the EU's tasks and refrain from any measure which could jeopardise the attainment of the EU's objectives.

An authorisation according to Regulation (EC) 258/97 for certain substances included in the Italian list - such as *Pelargonium sidoides* - to be used as Novel Food does not exist. Any inclusion of *Pelargonium sidoides* in an Italian positive list for food supplements would be contrary to the Novel Food authorisation procedure foreseen in Articles 4 – 7 Regulation (EC) 258/97 as it would de facto authorise the use of a substance which has not undergone the procedure foreseen by EU law.

Article 4 (2) of the notified decree on mutual recognition shows that the Italian Republic has recognised the fact that Novel Food should not be contained in national positive lists but it seems Italy has not recognised that some substances included in its own positive list have been qualified as Novel Food in the past:

> *"For the purposes of applying subparagraph 1, documentation should be provided certifying that the product is legally marketed as a food supplement in the Member*

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State of origin where the vegetable substances and preparations contained ***are not considered as 'novel foods' within the meaning of Regulation (EC) No 258/97****."*

We therefore kindly ask the European Commission to either object to the implementation of the Italian decree or to require certain amendments to be made to the decree according to Article 12 (3) Regulation (EU) 1925/2006 by requesting Italy to remove those substances from the positive list which have been qualified as Novel Food by Italy such as *Pelargonium sidoides*.