Harmonizing the evaluation of botanicals

The regulatory system in Belgium and the “BELFRIT” project
The cutting edge?

cutting knots

Axe or Scalpel

Joris GEELEN
Regulatory Expert Botanicals
Secretary of Advisory Commission on botanicals

9 September 2014 - Berlin

Harmonization for Botanicals
1. **Belgian legislation**
   - 1.1 Lists of plants
   - 1.2 Notification - FoodSup
   - 1.3 Advisory Commission
   - 1.4 Maximum levels + Mandatory warnings

2. **Harmonization: the ‘BELFRIT’ project**
   - 2.1 Concept
   - 2.2 Approach
   - 2.3 Future

3. **Conclusions**

Joris GEELEN
Regulatory Expert Botanicals
Secretary of Advisory Commission on botanicals
1. Royal decree on Plants: facts

- 1st publication in Belgian Official Journal 21/11/’97
- 9 decrees with adaptations ’99 - ’08
  - Conditions of use, specific warnings + maximum levels for ~27 plants March 2005
- Amending decree notified - EU COM - TRIS April 2010
  - Justification warnings @ COM → + advice July 2011
1.1 Royal decree on Plants: scope

- Applies to foods and supplements that contain plants.

- In annex 3 lists:

  **List 1:** Plants that may not be used in or as food.  
  ➞ Derogation possibility

  **List 2:** Edible mushrooms

  **List 3:** Plants - predosed form. To be notified.  
  Only applies to Food supplements

  (*) Maximum levels
1.1 Royal decree on Plants: List 1

Aconitum spp., Brugmansia spp., Ipomoea spp.

Mandragora officinarum L. Zigadenus spp.

Exemptions to the prohibition

toxicological + analytical proof
free of toxic properties or substances

Borago spp.: max. 1 µg/kg toxic pyrrolizidine alkaloids

# 390 genera + species
1.1 Royal decree on Plants : List 2

Edible (wild and cultivated) mushrooms

*Cordyceps sinensis*, *Agaricus blazei*, shiitake, reishi, maitake

+ also supplement use

# 90 species
1.1 Royal decree on Plants: List 3

Aesculus hippocastanum L.  
Ginkgo biloba L.

Hypericum perforatum L.  
Passiflora incarnata L.

Camellia sinensis (L.) Kuntze  
Valeriana repens Host

Panax ginseng C.A.Mey.  
Zingiber officinale Roscoe

# 645 species  
http://plantaardigheden.nl/  
http://www.theplantlist.org/
1.2 Royal decree on Plants: Notification

- Extensive notification dossier submitted at market intro
- Thorough technical and scientific evaluation of all the characteristics of the product
- Check conformity vertical & horizontal legislation
- Expert advice if necessary
- Within month letter of receipt + possibly with remarks

- Online notification system: FOODSUP
1.2 Digital notification system: FoodSup
Clear overview of workflow

Bill & Pay - automated

Fast search & filter in dossiers

3 languages
**Active Ingredients**

<table>
<thead>
<tr>
<th>Latin name</th>
<th>French name</th>
<th>Dutch name</th>
<th>Used plant part</th>
<th>Used preparation</th>
<th>Qu. dry recommended portion</th>
<th>Unit</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinium Corymbosum</td>
<td>myrcéne</td>
<td>bloemkaneel</td>
<td>ribes</td>
<td>10:1 drogeextract</td>
<td>0.5</td>
<td>mg</td>
<td>View, Edit</td>
</tr>
<tr>
<td>Vitis vinifera L.</td>
<td>Vigne cultivée, Vigne vinifère</td>
<td>druif, wijnstok, wijnboompot</td>
<td>fructus</td>
<td>10:1 drogeextract</td>
<td>108</td>
<td>mg, View, Edit</td>
<td></td>
</tr>
<tr>
<td>Rubus fruticosus L.</td>
<td>Ronce commune, Ronce des buissons, ...</td>
<td>greisgebraam</td>
<td>fructus</td>
<td>10:1 drogeextract</td>
<td>106</td>
<td>mg, View, Edit</td>
<td></td>
</tr>
<tr>
<td>Citrus sinensis (L.) Osbeck</td>
<td></td>
<td>sinasappel</td>
<td>fructus</td>
<td>10:1 drogeextract</td>
<td>25</td>
<td>mg, View, Edit</td>
<td></td>
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</tbody>
</table>

**Type & quantity of preparation**

- Use the tab "Ingredients" to view and update the types and quantities of plant parts used.

**Scientific name**

- The scientific name of each plant is listed under the "Latin name" column.

**Plant part used**

- The plant part used is listed under the "Used plant part" column.

**Active Ingredients**

- The active ingredients are specified under the "Active Substance per recommended portion" column.

**# AI / daily dose**

- The daily dose is indicated in milligrams (mg).

**Detailed info on ingredients**

- The detailed info on ingredients includes scientific names, plant parts used, and active ingredients.

**Possibility to add comments**

- Comments can be added under the "Comments" section.

**Possibility to add attachments**

- Attachments can be added for data on stability, toxicity, datasheets, and certificate of analyses.

**Federal Public Service - Health, Food Chain Safety and Environment**

- Date: 9 September 2014

- Berlin Harmonization for Botanicals
1.2 Notification - content dossier

- **Labeling**
- **Nature of the product**
  (presentation, packaging, recommended daily portion)
- **List of ingredients**:
  (plant name, part used, galenic form, amount, function)
- **Nutritional analysis**
- **Qualitative and Quantitative data of**
  Nutrients, Plants (% active substances), Other subst.
- **Data on Non-toxicity, Stability**
- **Commitment to carry out frequent analyses**
- **Production method, % solvent, Drug-Extract-Ratio, ...**
1.3 Advisory Commissions

- FPS (DG4...)
- FASFC
- FAMHP
- ACB
- SHC
- HMPC (BEL)

Mixed Commission

Harmonization for Botanicals
1.3. Advisory Commission for botanicals

= Em. Prof. Dr. A. Vlietinck + 14 experts

Scientific safety evaluation of plant preparations

• Evaluate plants not listed - conditions not fulfilled
• Advice on exemptions for plants on list 1
• Determine maximum levels / warnings
• Evaluate products with encapsulated essential oils
• Follow-up literature, side effects, incidents
• Progressive revision of the lists

Advice is published online
1.3 Advisory Commission for botanicals

DATA
- Notification dossier
- Datasheet Essential oils, Guideline New plants
- Analyses

EVALUATION
- Correct characterization
- Extensive search literature & traditional use
- Risks identification
- Proposition appropriate measures

DECISION
- Control the risks identified
- Communication decision
- Integration into legislation
1.4 Maximal levels - Substances of concern

Dangerous substances known to be present in plant → Assure not present in botanical preparation

1. Characterization of the botanical
   Scientific name, plant part, nature of preparation, CoU

2. Collection of bibliographic data
   - National or Int. regulatory bodies or advisory org.: EFSA...
   - Recognized standard reference text books
   - Monographs, Pharmacopoeia
   - Extensive literature search in various scientific databases

3. Collection of information from traditional use
1.4 Maximal levels - Active ingredients

Distinction between food & medicine → ECJ cases

- Garlic case: Case-by-case approach, all characteristics
- Red rice case: Dose is key factor
- COM >< ESP: MEDs proven significant pharm. properties

- If necessary + possible for “ambivalent” plants (list 3 *)
- Max. level = % of Minimal Daily Therapeutic Dose (MDTD) obtained after evaluation of clinical trials

- Taking into account all info: TU, EMA monographs...
1.4 Maximal levels: MDTD

Maximal level = % of Minimal Daily Therapeutic Dose

Higher levels may lead to therapeutic or prophylactic properties

% depending on physiological activity of preparation
1.4 Maximum levels: %

- **Literature studies**

  Maximum level = % of Minimal Daily Therapeutic Dose
  - **20 % or more** depending on physiological activity of preparation

  - **-10 % conformity demands - analytical fluctuations**
  - **-10 % bio-equivalence** = 80 % e.g. Echinacea, Valerian
    - **-15 %** = 75 % e.g. Hypericum, Ginkgo
    - **Aesculus, Glycine max**
  - **-20 % safety profile** = 70 % e.g. Senna

- **No literature studies** → Limiting substances with possible negative effect after long-term use
1.4 Mandatory warnings

- to ensure a high but proportional level of consumer protection + information
- inform specific target group
- based on case-by-case risk assessment
- available scientific data, EFSA Compendium, monographs
- potentially adverse effects identified
- the extent of scientific uncertainty evaluated
- measures take into account precautionary principle
1.4 Maximal level + Mandatory warnings: example

Rheum officinale Baill.

- Plant parts allowed: rhizome, root.
- Maximal level: 25 mg anthrachinones (calculated as rhein)
- Analytical results for each batch of products.
- Mandatory warning of labeling:
  - “Do not use below 12 years”
  - “No prolonged use without professional advice”
  - “When pregnant or breastfeeding consult your doctor”
### 2. Harmonization: current situation

<table>
<thead>
<tr>
<th><strong>General Food Law</strong></th>
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<tbody>
<tr>
<td>Reg EC 178/2002</td>
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<tr>
<td>General food safety requirements</td>
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<td>Manufacturer responsibilities</td>
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<tr>
<td>Notification duty</td>
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<td>Recall</td>
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<th><strong>Food Supplements Law</strong></th>
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<tr>
<td>Dir 2002/46/EC</td>
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<tr>
<td>Definition</td>
</tr>
<tr>
<td>Permitted forms (vitamins/minerals)</td>
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<tr>
<td>Maximum levels (vitamins/minerals)</td>
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<tr>
<td>Specific labeling provisions</td>
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<td>Reg EC 852/2004</td>
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<td>Rules for hygienic production based on the principles of HACCP</td>
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<td>Microbiological criteria</td>
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<td>Reg EC 258/97</td>
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<td>Pre-marketing approval procedure for novel ingredients</td>
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<tr>
<th><strong>General labelling rules</strong></th>
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<tr>
<td>Dir 2000/13/EC</td>
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<tr>
<td>How to label content, composition, etc</td>
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<td>Quantitative ingredient declaration (QUID)</td>
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<td>Allergen labelling</td>
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<td>Reg EC 1924/2006</td>
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<td>Pre-marketing approval procedures for nutrition and health claims</td>
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<tr>
<td>Reg EC 1925/2006</td>
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<tr>
<td>Risk assessment and risk management procedure in case the use of a substance would result in harmful effects</td>
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<tr>
<td>Reg EC 1333/2008</td>
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<tr>
<td>Pre-marketing approval procedures</td>
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<tr>
<td>Allowed additives, including sweeteners and colourings</td>
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<tr>
<td>Conditions of use</td>
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<tr>
<td>Reg EC 1881/2006</td>
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<tr>
<td>Maximum levels of selected contaminants in ingredients that can be used in foods</td>
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<th><strong>Pesticides residues</strong></th>
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<tr>
<td>Reg EC 396/2005</td>
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<tr>
<td>Maximum residue levels</td>
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<th><strong>Extraction solvents</strong></th>
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<tr>
<td>Dir 2009/32/EC</td>
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<tr>
<td>Permitted extraction solvents</td>
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<th><strong>Irradiation</strong></th>
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<tr>
<td>Dir 1999/2/EC</td>
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<tr>
<td>Permitted ingredients to be irradiated</td>
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2. Harmonization

No harmonisation for botanicals at this point

- Variety of risk management measures
  - Notification: Label → Extensive dossier
  - Lists subst./plants (Negative / Positive lists)
  - Conditions of use (Restrictions, Max. levels)
  - Labelling requirements
  - Scientific advisory bodies
  - Guidance / ...

- Different attitudes
  - Established markets based on FS or Meds
  - Botanicals considered ‘medicinal by function’

NFR?  Mutual Recognition?
Discrepancies  Uncertainty Safety & Quality
2. Harmonization : current situation

- Free movements of goods : Art 34/36 of EU Treaty
- Regulation 764/2008 mutual recognition

MS has to accept on its territory any product lawfully marketed in another Member State. Unless it can show that there is a danger for health

- Proof of lawfull marketing by competent authorities?
- Not sufficient to govern borderline issues
- Degression to lower level of consumer information & protection
2.1 Harmonization: the BELFRIT project

- Initiative of BELgium, FRance and ITaly
- Harmonize evaluation of botanicals in food supplements
- Started 2 years ago
- Accelerated mutual recognition on a scientific basis

- Authorities besides myself:
  Guillaume Cousyn (DGCCRF)
  Bruno Scarpa & Stefania Dalfrà (Ministero della Salute)

- Experts pharmacognosy:
  Robert Anton: University of Strasbourg, France
  Mauro Serafini: Sapienza University, Italy
  Luc Delmulle: IFAO Proform education, Luxembourg
2.2 BELFRIT: 1st phase

Harmonization of the lists of authorized plants

- Combined 3 lists → BEL: 645, FR: 548, IT: 1182 = +2000 species
- Verify accepted botanical names & synonyms
  → theplantlist.org, ars.grin.gov, experts botanicals garden (Meise)
    algaebase.org, indexfungorum.org and lichens.ie
- Mention: Synonyms
  Families (chemo-taxonomical relation)
  Traditional used plant parts
  Plant parts of concern
  Chemicals (substances, markers)
  Further info (subst., preparations, essential oils, effects...)
  References

- Advice (to analyse certain substances, safety warnings)
2.2 Harmonization: 1st phase, literature

For each plant literature research was done:
used plant parts, chemistry, preparations, traditional knowledge
side-effects, contra-indications, case-reports...

with
• Standard reference books: Counsil of Europe, EFSA, AFSSA...
• Monographs: Pharmacopoeia, WHO monographs & guidelines
  ESCOP, EMA
• Other references: AFNOR, ISO, ICH....
• Many bibliographic data available
• Data bases: COSING...
• Official advice
• Publications till 2013
2.2 Harmonization: 1st phase, result

Harmonized list (section A): +1000 plants
  396 in 3 countries
  180 in 2 countries
  449 in 1 country

Some plants taken out because:
  ○ No accepted name
  ○ Subspecies, variety or hybrid fall under general species
    (if chemical profile is similar)

Section B: ~ 150 plants for which more info is needed about:
  ○ Traditional use, ...
  ○ Safety, substances, toxicity
3.2 Harmonization: 1st phase

- Provides a precise identification of the plants = 1st step
- Indicates some key points to control in the production and regulation of PFS
- Takes the traditional knowledge into account
- Based on expert advice

- Can be a pragmatic tool for risk managers and operators, to assure quality and safety of botanical preparations

- It’s a ‘living’ list
- List of other MS could be evaluated
- Plants can be added or taken of depending available info
2.2 Harmonization: publications

4 accompanying articles of experts
→ European Food and Feed Law Review

1. Traditional Knowledge for the Assessment of Health Effects for Botanicals - A Framework for Data Collection” - Issue 2/2012, pp. 74-80

2. The role of Traditional Knowledge in the Safety Assessment of Botanical Food Supplements - Requirements for Manufacturers - Issue: 5/2012, pp. 241-250

3. The Substantiation of Claims for Botanical Food Supplements in Relation to Traditional Use - Issue: 5/2013, pp. 321-328

4. The BELFRIT project - Harmonizing the Use of Plants in Food Supplements in the European Union: Belgium, France and Italy - A first Step - Issue 3/2013, pp. 27-40
2.3 Harmonization : the way forward

• 2012 - 2013 : BELFRIT consultations
  o Drafting of the harmonized list by experts
  o Finalization of harmonized list
  o Meetings with EC, member states, stakeholders

• 2014 - 2015 : Integration into national legislation
  o Further consultation to harmonize conditions
    (Maximal levels & mandatory warning)
  o Consultation sector
  o Update the lists
  o Improve exchange of scientific advice
  o Evaluation of other MS lists
3. Conclusions

- **Belgian system = proof of concept**
  Notification / Lists / Advisory Commission

- Applicable framework for botanicals is not adapted

- **Harmonization is possible and necessary**
  - Coherent policies based on scientific advice
  - Pragmatic approach
  - Appropriate and proportionate measures
  - Taking traditional use into account
  - Assure safety and consumer information
  - Legal security for SMEs
For questions regarding legislation on botanicals:

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+322/524.73.82 or 0478 94 55 01

www.health.belgium.be

> Food safety > Foodstuffs > Food supplements
I’m a broccoli and I look like a tree

I’m a walnut and I look like a brain

I’m a mushroom and I don’t like this game