Quality of Herbal Medicinal Products and Botanical Food Supplements – EU regulation and practical experience

59th International Congress and Annual Meeting of the Society for Medicinal Plant and Natural Product Research
4 – 9 September 2011, Antalya
Workshop III

Hartwig Sievers
Topics

1. Definitions
2. Overview of Quality Regulations
3. Quality and Safety
4. Conclusions
Definitions

**Quality** (ISO 8402-1986)

“the totality of features and characteristics of a product or a service that bears its ability to satisfy stated or implied needs”
Safety and Function: Quality matters

**Safety**
- Adverse effects
- Subtle Tox effects
- Target groups

**Function**
- Taste, Organoleptics
- Therapeutic effects
- Nutr. or physiol. effects
- Bioavailability

**Quality**
**Physical + chemical constitution**
- Botanical identity, Plant part used
- Sourcing, Post-Harvesting,
- Processing (e.g., extr. solvent), DER, Galenic Form
- Purity criteria
- Content, Dose
- Sampling schemes, Test methods
Quality – What for?

Quality

Fitness for Consumption
- Safe
- Not disgusting

Fitness for Purpose
- Nutrition
- Efficacy/Function
Quality – Herbal Medicinal Products

- Common standards
  - Sampling
  - Dosage Forms
  - Dissolution
  - Disintegration
  - …

- Specific standards for HMP
  - Quality criteria (Microbiology, Heavy Metals, Pesticides…)
  - Methods (Heavy Metals, Aflatoxins…)
  - Monographs for Herbal raw materials and extracts
    (inc. Specifications and Methods for Identity, Purity, Assays)
  - General Monographs „Herbal Drugs“ „Extracts“, „Herbal Infusions“…
Quality – Herbal Medicinal Products

- Pesticide residues
- Determination of aflatoxin B₁ in herbal drugs
- Determination of ochratoxin A in herbal drugs
- Heavy metals in herbal Drugs and Fatty Oils
- Microbiological examination of herbal medicinal products for oral use
- Microbiological quality of herbal medicinal products for oral use
- Residual solvents

Chapter

2.8.13
2.8.18
2.8.22
2.4.27
2.6.31
5.1.8
2.4.24
Quality – Herbal Medicinal Products

Directive 2004/24/EC (THMPD)

(5)

„The quality aspect of the medicinal product is independent of its traditional use so that no derogation should be made with regard to the necessary physico-chemical, biological and microbiological tests.“
Quality Guidelines – Herbal Medicinal Products (e.g.)

- Guideline on Quality of Herbal Medicinal Products/Traditional Herbal Medicinal Products CPMP/QWP/2819/00 Rev. 1; EMEA/CVMP/814/00 Rev. 1; 30 March 2006
- Reflection Paper on Stability Testing on Herbal Medicinal Products and Traditional Herbal Medicinal Products; EMA/HMPC/3626/2009, 21 October 2010
- Guideline on Specifications: Test Procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products/Traditional Herbal Medicinal Products CPMP/QWP/2820/00 Rev.1; EMEA/CVMP/815/00 Rev. 1; 30 March 2006
- Note for Guidance on Validation of Analytical Procedures: Text and Methodology ICH Topic Q 2 (R1); CPMP/ICH/381/95; June 1995
- Impurities: Guideline for Residual Solvents ICH Topic Q3C (R5); EMA/CHMP/ICH/82260/2006; March 2011
Quality: Specifications, analytical procedures and analytical validation

<table>
<thead>
<tr>
<th>Topic</th>
<th>Documents</th>
<th>Reference number</th>
<th>Publication date</th>
<th>Effective date</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICH Topic Q8, Q9 and Q10 Quality Implementation Working Group Questions and Answers</td>
<td>Adopted guideline</td>
<td>CHMP/ICH/265145/09</td>
<td>Dec 2009</td>
<td>Dec 2009</td>
<td></td>
</tr>
<tr>
<td>Q 4B Annex 10 Step 3 Polyacrylamide Gel Electrophoresis</td>
<td>Adopted guideline Draft guideline</td>
<td>CHMP/ICH/381133/00 ICH Q4B</td>
<td>Dec 2009 May 2010</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Quality – Herbal Medicinal Products

- HMP quality is highly regulated and defined
- Elaboration of the quality dossier is the main cost driver and the major time factor in establishing marketing authorisations for (T)HMPs
- The elevated levels and narrow margins of quality standards for herbal raw materials impose a strong restraint on the choice of batches and sources
Quality – Botanical Food Supplements

Regulation (EC) No 178/2002

Article 8

Protection of consumers’ interests

1. Food law shall aim at the protection of the interests of consumers and shall provide a basis for consumers to make informed choices in relation to the foods they consume. It shall aim at the prevention of:

(a) fraudulent or deceptive practices;
(b) the adulteration of food; and
(c) any other practices which may mislead the consumer.
Quality – Botanical Food Supplements

Regulation (EC) No 178/2002

*Article 14, Food safety requirements*

1. Food shall not be placed on the market if it is unsafe.
2. Food shall be deemed to be unsafe if it is considered to be:

   (a) injurious to health;
   (b) unfit for human consumption.
Quality – Botanical Food Supplements

Regulation (EC) No 178/2002

Article 14, Food safety requirements

3. In determining whether any food is unsafe, regard shall be had:

(a) to the normal conditions of use of the food by the consumer and at each stage of production, processing and distribution, and

(b) to the information provided to the consumer, including information on the label, or other information generally available to the consumer concerning the avoidance of specific adverse health effects from a particular food or category of foods.
Quality – Botanical Food Supplements

- Pesticide residues: Regulation (EC) 396/2005
- Contaminants others: Regulation (EC) 1881/2006
- Irradiation: Directives 1999/2/EC and 1999/3/EC
- Solvents: Directive 2009/32/EC
- Hygiene: Regulation (EC) 852/2004 (HACCP)

* Apart from Heavy Metals the category of (Botanical) Food Supplements is not expressly addressed in these regulations
Quality – Botanical Food Supplements

SCIENTIFIC OPINION

Guidance on Safety assessment of botanicals* and botanical preparations** intended for use as ingredients in food supplements¹

EFSA Scientific Committee²

European Food Safety Authority (EFSA), Parma, Italy

This guidance document published on 9 September 2009, replaces the earlier version published on 20 June 2008 with the Question Number: EFSA-Q-2005-233.

¹ EFSA Journal 2009; 7(9):1249

2 European Food Safety Authority (EFSA)
Quality – Botanical Food Supplements

Data requirements for the safety assessment of botanicals

Technical data

- Identity and nature of the source material
- Manufacturing process
- Chemical composition
- Specifications
- Stability
Quality – Botanical Food Supplements

- Like for all food the producer is mainly responsible for defining a quality level that provides compliance with 178/2002/EC Art. 14
- Specific quality regulation applicable to BFS is in place for main purity criteria, e.g., contaminants or residual solvents
- No common harmonised basis for identity or adulteration of botanical raw materials or products, no common standard for „fitness-for-purpose“ criteria
Quality - Botanical Food Supplements

Industry Self-Regulation (examples)

- EHIA - European Herbal Infusion Association
  Compendium of Guidelines for Herbal and Fruit Infusions and Products thereof
  http://www.ehia-online.org/publications.html
- EBF - European Botanical Forum
- EHPM - European Health Products Manufacturers
- SYNADIET (France)
  http://www.synadiet.fr/synadiet/les-groupes-de-travail/gt-charte-de-qualite---details.html
- ESA - The European Spice Association
  http://www.esa-spices.org/index-esa.html/publications-esa
Quality - Botanical Food Supplements

other Quality Guidance Documents or Initiatives, e.g.,

- AOAC
  http://www.aoac.org/News/FDA_IDIQ.htm
- Health Canada
  Evidence for Quality of finished Natural Health Products
Quality and Safety

**Identification**
- macroscopic examination
- microscopic examination
- TLC

**Purity**
- foreign species
- foreign matter
- spiking, adulteration
- contaminants
- microbiology

**Tests and Assay**
- Loss on drying
- Total ash
- Assay (where applicable)
  - markers
  - active compounds
  - limited compounds
- Bulk density
- Particle-size distribution
Quality and safety

- Quality-related causes for unsafe botanicals
  - Adulteration or mix-up with toxic species/plant parts
  - Wilful admixture of chemical drugs, counterfeit extracts
  - Processing technology/galenic preparation
    - (with influence on level of toxicologically relevant compounds)
  - Contaminants (pesticides, mycotoxins, heavy metals, other)
Suspected hepatotoxicity by *Cimicifugae racemosae rhizoma* (black cohosh, root): Critical analysis and structured causality assessment

Rolf Teschke*, Alexander Schwarzenboeck

*Medical Department II, Klinikum Hanau, Teaching Hospital of the Johann Wolfgang Goethe University of Frankfurt/Main, Leimenstraße 20, D-63450 Hanau, Germany*

38 out of 42 patients: no causal relationship established
4 patients: causal relationship possible
  • 1 case: no valid evaluation possible due to lack of basic information
  • 1 patient had an autoimmune hepatitis unrelated to BC
  • 2 other ones obviously had a hepatic liver disease
In some cases not *C. racemosa* but *C. foetida* was used
Adulteration or mix-up of safe herbs with toxic species

*Cimicifuga racemosa*: liver-toxic?

- Cimifugin is present in *C. foedita* and other *C.* species but not in *C. racemosa*
- Adulteration with *C. foedita* can be found by detecting the chromone cimifugin

2.5% *C. foedita* in *C. racemosa*
Adulteration of Star Anise with Shikimi Fruit

Illicium verum Hooker
Star anise

Illicium anisatum L. (religiosum Sieb.)

I. Lederer, K. Reif, J.-P. Steffen: ISOLATION OF ANISATIN AS REFERENCE SUBSTANCE FOR THE DETERMINATION OF TOXIC ADULTERATIONS IN ILLICIUM VERUM BY HPLC-MS/MS; ICNPR, Phoenix, 30 July-4 August 2004
Quality and safety

➤ Quality-related causes for unsafe botanicals

➤ Adulteration or mix-up with toxic species/plant parts

➤ wilful admixture of chemical drugs, counterfeit extracts

➤ processing technology/galenic preparation
  (with influence on level of toxicologically relevant compounds)

➤ Contaminants (pesticides, mycotoxins, heavy metals, other)
Quality – adulteration of extracts

Ginkgo Flavone Glycosides

R = H: Kaempferol
R = OH: Quercetin  MW: 302.2
R = OCH₃: Isorhamnetin

Flavonol

Diglycoside

Coumaroyl Ester
adulteration of extracts

e.g., Ginkgo biloba extracts

4 surveys in last 10 years with results indicating a progression of sophisticated adulteration

- Addition of rutin/quercetin from, e.g., buckwheat approx. $10/kg
- *Fructus sophorae* additions to enhance Quercetin/Kaempferol ratio
- GBE cost $35-90/kg

Literature:
Obermeyer, W.: *FDA Public Meeting on Economically Motivated Adulteration*, May 1, 2009
Quality - adulteration of extracts

Ginkgo

Roth-Ehrang, R.: 8th Annual Oxford International Conference on the Science of Botanicals; Oxford, Mississippi, April 4-6, 2009
Quality - adulteration of extracts

Ginseng Comparison
Quality - adulteration of extracts

Overlay

Coffee Extract, aqueous

Artichoke Leaf Extract, aqueous
Quality and safety

- Quality-related causes for unsafe botanicals
  - Adulteration or mix-up with toxic species/plant parts
  - wilful admixture of chemical drugs, counterfeit extracts
  - processing technology/galenic preparation
    (with influence on level of toxicologically relevant compounds)
  - Contaminants (pesticides, mycotoxins, heavy metals, other)
Processing technology/galenic preparation

The extent of induction of CYP3A by St. John's wort is linked to hyperforin dose
Quality and safety

- Quality-related causes for unsafe botanicals
  - Adulteration or mix-up with toxic species/plant parts
  - wilful admixture of chemical drugs, counterfeit extracts
  - processing technology/galenic preparation
    (with influence on level of toxicologically relevant compounds)
  - Contaminants (pesticides, mycotoxins, heavy metals, other)
Contaminants

- Pesticides
- Toxic Compounds
- Colorants
- Irradiation
- PAH
- Mycotoxins
- Residual Solvents
- Heavy Metals
- Microbiol. Purity
## Quality of botanicals

<table>
<thead>
<tr>
<th>Contaminant</th>
<th>Regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pesticides, Fumigants</td>
<td>Commission Directive 396/2005/EC as amended*</td>
</tr>
<tr>
<td>Mycotoxins</td>
<td>1881/2006/EC as amended*</td>
</tr>
<tr>
<td>Heavy Metals</td>
<td>1881/2006/EC as amended</td>
</tr>
<tr>
<td>PAH</td>
<td>1881/2006/EC as amended*</td>
</tr>
<tr>
<td>other (Dioxins, Nitrate, Furan …)</td>
<td>1881/2006/EC as amended*</td>
</tr>
<tr>
<td>Microbial contamination</td>
<td>no limits regulated</td>
</tr>
</tbody>
</table>

*Apart from Heavy Metals the category of (Botanical) Food Supplements is not expressly adressed in these regulations*
Contaminants

Cadmium in herbal drugs

Angelica root
Arnica flower
Birch leaf
Daisy flower
Dandelion herb
Eyebright herb
Golden Rod herb
Kelp
Lovage root
Marshmallow root
Mistletoe herb
Seaweed
Spinach leaf
St. John’s wort herb
Strawberry leaf
Thyme herb
Watercress herb
Willow bark
Wormwood herb
Yarrow herb

90th percentile Cd [mg/kg]

## Irradiation

<table>
<thead>
<tr>
<th>Product</th>
<th>n</th>
<th>negative</th>
<th>positive</th>
<th>not assessable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garlic</td>
<td>5</td>
<td>5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ginger</td>
<td>12</td>
<td>5</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Santalum</td>
<td>2</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Plantago husk</td>
<td>3</td>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ginseng</td>
<td>12</td>
<td>9</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Herb- and Fruit Tea</td>
<td>3</td>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rhodiola Extract</td>
<td>3</td>
<td>-</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Red Clover Extract</td>
<td>25</td>
<td>14</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Soy Extract</td>
<td>13</td>
<td>5</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

Salmonella in processed herbs (n = 17,833)

EHIA limit:
not detectable in 25g
Quality – What for?

Quality

Fitness for Consumption
- Safe
- Not disgusting

Fitness for Purpose
- Enjoyment
- Nutrition
- Efficacy/Function
Conclusions

- Defined and controlled quality is an indispensable basis for safety and efficacy/function of both HMP and BFS
- Violation of existing regulatory quality standards is no prominent cause of safety concerns for BFS
- HMP standards are not 1 by 1 transferable to BFS but reference to certain Pharmacopoeial standards (identity, purity) would be an easy and efficient improvement
- For BFS with approved claims an adequate quality to ensure fitness for purpose needs to be defined
A safe situation is one where risks of injury are low and manageable.

http://www.google.de/search?hl=de&q=wiki+safety&meta=
Thank You!

Dr. Hartwig Sievers
PhytoLab GmbH & Co. KG
Dutendorfer Straße 5-7
91487 Vestenbergsgreuth
Germany
Tel.: +49 9163 88-154
Fax.: +49 9163 88-349
Hartwig.Sievers@phytolab.de
Copyright and liability

We emphasise that the contents of this presentation constitute works subject to protection under the laws of copyright. Any reproduction, dissemination, further processing or other use of the presentation, of the information and contents thereof, or of corresponding excerpts thereof, shall be subject to our express consent.

The presentation was drawn up to the best of its authors’ knowledge and belief and is offered for information purposes. Absent further agreement, any information or contents found therein shall serve as non-binding indications only and shall represent no promise or pledge. The authors of the presentation cannot accept liability for damage that may arise as a result of utilisation of the information and contents of which the presentation consists, unless information and contents of which the presentation consists have been made part of a concrete agreement as between our customer and us.
Where do signals of potential risks come from?

<table>
<thead>
<tr>
<th>Herb</th>
<th>suspected risk</th>
<th>source</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Piper methysticum</em></td>
<td>liver toxicity</td>
<td>case reports</td>
</tr>
<tr>
<td><em>Tussilago farfara</em> (+ other)</td>
<td>liver toxicity</td>
<td>case reports</td>
</tr>
<tr>
<td><em>Cimicifuga racemosa</em></td>
<td>liver toxicity</td>
<td>case reports</td>
</tr>
<tr>
<td><em>Chelidonium majus</em></td>
<td>liver toxicity</td>
<td>case reports</td>
</tr>
<tr>
<td><em>Aristolochia spec.</em></td>
<td>nephrotoxicity</td>
<td>case reports</td>
</tr>
<tr>
<td><em>Ginkgo biloba</em></td>
<td>bleeding</td>
<td>case reports</td>
</tr>
<tr>
<td><em>Hypericum perforatum</em></td>
<td>interactions</td>
<td>case reports</td>
</tr>
<tr>
<td><em>Vaccinium macrocarpon</em></td>
<td>interactions</td>
<td>case reports</td>
</tr>
<tr>
<td><em>Cinnamomum cassia</em></td>
<td>liver toxicity</td>
<td>animal studies</td>
</tr>
</tbody>
</table>