

Legal Requirements for the Control of Contaminants in Herbal Medicinal Products

**Workshop III: Quality/Agriculture
GA International Congress, Antalya 2011
Dr. Barbara Steinhoff**

Bundesverband
der Arzneimittel-
Hersteller e.V. **B.A.H**

Contents

- ❖ Plant protection products
 - Approval and authorisation of active substances and products, respectively
 - Minor use
 - Integrated pest management
 - Maximum residue limits
- ❖ Heavy metals
- ❖ Microorganisms
- ❖ Mycotoxins

Plant Protection Products

- **Regulation (EC) No 1107/2009** concerning the placing of plant protection products on the market (in force since 14 June 2011)
- High level of protection of both human and animal health and the environment and to safeguard the competitiveness of agriculture
- Harmonised rules for the approval of active substances and placing on the market of plant protection products including mutual recognition (climatic zones with comparable conditions)

3

Bundesverband der Arzneimittel-Hersteller

Bundesverband
der Arzneimittel-
Hersteller e.V. **B.A.H**

Plant Protection Products: Authorisation

- Rules for active substances plus e.g. safeners* and synergists** AND final products
 - Preconditions:
 - effective
 - no harmful effects (human, animal health, water)
 - no unacceptable effects on plants
 - no unacceptable effects on environment
- *) eliminate or reduce phytotoxic effects
**) can give enhanced activity to active substances

4

Bundesverband der Arzneimittel-Hersteller

Bundesverband
der Arzneimittel-
Hersteller e.V. **B.A.H**

Plant Protection Products: Authorisation

Active substances

- Data requirements for **approval**: Annexes II and III of Directive 91/414/EC
- Application submitted by the producer to the Rapporteur Member State
- Specific derogations for low-risk active substances and basic substances*
- First approval 10 years, renewal 15 years possible

*) not predominantly used für plant protection purposes

5

Bundesverband der Arzneimittel-Hersteller

Bundesverband
der Arzneimittel-
Hersteller e.V. **B.A.H**

Plant Protection Products: Authorisation

Plant protection products

- Application for authorisation after approval of the active substance
- Pre-conditions such as
 - Safe technical formulation
 - Active substances and impurities etc can be determined
 - Residues can be determined
 - MRL included in Regulation No 396/2005
- Provisional authorisations possible

6

Bundesverband der Arzneimittel-Hersteller

Bundesverband
der Arzneimittel-
Hersteller e.V. **B.A.H**

Plant Protection Products: Minor Use

- Defined as use on plants or plant products which are not widely grown in a Member State or widely grown and meets an exceptional plant protection need
- Specific rules for minor uses (Article 51):

"The authorisation holder, official or scientific bodies involved in agricultural activities, professional agricultural organisations or professional users may ask for the authorisation of a plant protection product already authorised in the Member State concerned **to be extended to minor uses not yet covered** by that authorisation."

7

Bundesverband der Arzneimittel-Hersteller

Bundesverband
der Arzneimittel-
Hersteller e.V. **B.A.H**

Plant Protection Products: Minor Use

- Preconditions for extension e.g.
 - Use is minor
 - Public interest
 - Data on residues
 - Amendment or separate authorisation
- "Member States may take measures to facilitate or encourage the submission of applications to extend the authorisation of already authorised plant protection products to minor uses."
- Option of Article 51 implemented in German Draft Plant Protection Law of 4 July 2011

8

Bundesverband der Arzneimittel-Hersteller

Bundesverband
der Arzneimittel-
Hersteller e.V. **B.A.H**

Plant Protection Products: Minor Use

- "Member States shall establish and regularly update a list of minor uses." (implemented in German Draft Plant Protection Law of 4 July 2011)
- "By 14 December 2011, the Commission shall present a report to the European Parliament and the Council on the establishment of a **European fund for minor uses**, accompanied, if appropriate, by a legislative proposal."

Integrated Pest Management

- **Directive 2009/128/EC** establishing a framework for Community action to achieve the sustainable use of pesticides defines 'integrated pest management':
- "Careful consideration of all available plant protection methods and subsequent integration of appropriate measures that discourage the development of populations of harmful organisms and keep the use of plant protection products and other forms of intervention to **levels that are economically and ecologically justified** and **reduce or minimise risks to human health and the environment**. 'Integrated pest management' emphasises the growth of a healthy crop with the least possible disruption to agro-ecosystems and encourages natural pest control mechanisms."

Integrated Pest Management

- "Member States shall adopt National Action Plans to set up their quantitative objectives, targets, measures and timetables to reduce risks and impacts of pesticide use on human health and the environment and to encourage the development and introduction of integrated pest management and of alternative approaches or techniques in order to reduce dependency on the use of pesticides."
- "By 14 December 2012, Member States shall communicate their National Action Plans to the Commission and to other Member States."

Integrated Pest Management

- "Member States shall establish appropriate incentives to encourage professional users to implement **crop or sector-specific guidelines** for integrated pest management on a voluntary basis. Public authorities and/or organisations representing particular professional users may draw up such guidelines. Member States shall refer to those guidelines that they consider relevant and appropriate in their National Action Plans."
- General principles for such guidelines: Annex III to Directive 2009/128/EC
- Implemented in German Draft Plant Protection Law

Integrated Pest Management

Annex III:

General principles of integrated pest management

- Prevention/suppression of harmful organisms, e.g. crop rotation, cultivation, seed and planting material, fertilisation, irrigation, hygiene, beneficial organisms
- Monitoring by adequate methods
- Decision on whether to apply plant protection measures
- Preference of sustainable non-chemical measures
- Application of pesticides
- Level/extent of use
- Risk of resistance
- Recording and checking of the success

13

Bundesverband der Arzneimittel-Hersteller

Bundesverband
der Arzneimittel-
Hersteller e.V. **B.A.H**

Integrated Pest Management

- Joint project of the German Committee on Medicinal and Spice Plant Cultivation (DFA) and the German Medicines Manufacturers' Research Association (FAH):
- Development of **sector-specific guidelines for medicinal and spice plants** in accordance with Article 14 and Annex III of CD 2009/128/EC
- Detailed guidance on how to implement the general criteria for this sector
- Crop-specific guidance might follow later on

14

Bundesverband der Arzneimittel-Hersteller

Bundesverband
der Arzneimittel-
Hersteller e.V. **B.A.H**

Plant Protection Products: Limits

- European Pharmacopoeia Chapter 2.8.13
- Regulation No 396/2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin
- Amendments:
http://ec.europa.eu/food/plant/protection/pesticides/community_legislation_en.htm
- Database (by products and by substances):
http://ec.europa.eu/sanco_pesticides/public/index.cfm

15

Bundesverband der Arzneimittel-Hersteller

Bundesverband
der Arzneimittel-
Hersteller e.V. **B.A.H**

Heavy Metals: European Pharmacopoeia

- Monograph "Herbal drugs" (draft "Extracts")
 - Lead 5 mg/kg
 - Cadmium 1 mg/kg
 - Mercury 0.1 mg/kg
- Database of the BAH WG on Contaminants
- 7100 samples tested on Cd and Pb, 2002-2007
- Published* with proposals for limits of 5 mg/kg for Pb and 0.5 mg/kg for Cd with certain exemptions

*) Gasser U, Klier B, Kühn AV, Steinhoff B. Pharmeuropa Scientific Notes 2009-1

16

Bundesverband der Arzneimittel-Hersteller

Bundesverband
der Arzneimittel-
Hersteller e.V. **B.A.H**

Heavy Metals: European Pharmacopoeia

Exemptions in individual monographs, e.g.

Cd	Pb
Fumitory 1.5 mg/kg	Nettle root (draft) 7.0 mg/kg
Tormentil 2.0 mg/kg	Iceland moss 10.0 mg/kg
Willow bark 2.0 mg/kg	

17

Bundesverband der Arzneimittel-Hersteller

Bundesverband
der Arzneimittel-
Hersteller e.V. **B.A.H**

Heavy Metals: Food and Food Supplements

Regulation (EC) No 1881/2006 setting maximum levels for certain contaminants in foodstuffs (in force since 1 March 2007, several amendments), e.g.

- Pb in vegetables excl. fresh herbs: 0.10 mg/kg
Pb in berries and small fruit: 0.20 mg/kg
- Cd in vegetables excl. fresh herbs: 0.050 mg/kg
Cd in fresh herbs: 0.20 mg/kg
- Pb in food supplements: 3.0 mg/kg
- Cd in food supplements: 1.0 mg/kg (except seaweed 3.0 mg/kg)

18

Bundesverband der Arzneimittel-Hersteller

Bundesverband
der Arzneimittel-
Hersteller e.V. **B.A.H**

Heavy Metals: USP

Draft monograph no. 2232: Elemental contaminants in dietary supplements

- Individual component limits for arsenic 1.5 µg/g, cadmium 0.5 µg/g, lead 1.0 µg/g, mercury (total) 1.5 µg/g, methylmercury 0.2 µg/g
- 10 fold permitted daily exposure (PDE)
- Three options for compliance: (1) analysis of the serving size compared to PDE, (2) individual component option with daily intake of ≤ 10 g, (3) summation option for > 10 g daily intake or individual component limit exceeded

19

Bundesverband der Arzneimittel-Hersteller

Bundesverband
der Arzneimittel-
Hersteller e.V. **B.A.H**

Heavy Metals: ICH

Development of a Guideline Q3D on Metal Impurities

- Proposal for class 1 metals ("big four"): arsenic 1.5 ppm, cadmium 0.5 ppm, lead 1 ppm, mercury 1.5 ppm
- Class 2 metals (moderate safety concerns) and class 3 metals (low safety concern)
- "Herbals are excluded from the scope"

20

Bundesverband der Arzneimittel-Hersteller

Bundesverband
der Arzneimittel-
Hersteller e.V. **B.A.H**

Microorganisms

Acceptance Criteria Ph.Eur.

- Chapter 5.1.4. Microbiological quality of non-sterile pharmaceutical preparations
- Chapter 5.1.8. Microbiological quality of herbal medicinal products for oral use: 3 different categories
- A. ... containing herbal drugs ... using boiling water
- B. ... containing e.g. extracts (or pre-treatment)
- C. ... not complying with category B

21

Bundesverband der Arzneimittel-Hersteller

Bundesverband
der Arzneimittel-
Hersteller e.V. **B.A.H**

Microorganisms

Method of Determination Ph.Eur.

- 2.6.12 and 2.6.13: Microbiological examination of non-sterile products
- 2.6.31: Microbiological examination of **herbal medicinal products** for oral use: TAMC and TYMC according to 2.6.12 plus tests on specified microorganisms

22

Bundesverband der Arzneimittel-Hersteller

Bundesverband
der Arzneimittel-
Hersteller e.V. **B.A.H**

Mycotoxins (Medicinal Products)

German "Aflatoxin-Verbotsverordnung"

- Not more than 5 µg aflatoxin B₁ per kg and not more than 20 µg aflatoxins B₁, B₂, G₁ and G₂ per kg

European Pharmacopoeia

- **"Herbal Drugs" and "Herbal Drugs for Homoeopathic Preparations":** "where necessary/appropriate, limits ... may be required"
- Liquorice dry extract and Liquorice dry extract for flavouring purposes: 80 µg/kg ochratoxin A

23

Bundesverband der Arzneimittel-Hersteller

Bundesverband
der Arzneimittel-
Hersteller e.V. **B.A.H**

Mycotoxins (Food)

- **Regulation (EC) No 1881/2006** setting maximum levels for certain contaminants in foodstuffs (in force since 1 March 2007, several amendments)
- Aflatoxins in nuts: B₁ 2.0-8.0, sum 4.0-15.0 µg/kg
- Aflatoxins in spices*: B₁ 5.0, sum 10.0 µg/kg

*) Capsicum spp., Piper spp., nutmeg, ginger, turmeric

24

Bundesverband der Arzneimittel-Hersteller

Bundesverband
der Arzneimittel-
Hersteller e.V. **B.A.H**

Mycotoxins (Food)

Regulation (EC) No 1881/2006

- Ochratoxin A in dietary foods for special medical purposes intended for children: 0.50 µg/kg
- Ochratoxin A in spices*: 30 µg/kg from 1 July 2010 and 15 µg/kg from 1 July 2012
- Ochratoxin A in liquorice root: 20 µg/kg
- Ochratoxin A in liquorice extract: 80 µg/kg

*) Capsicum spp., Piper spp., nutmeg, ginger, turmeric

Mycotoxins (USP)

USP Chapter 561: Articles of Botanical Origin

- Not more than 5 µg aflatoxin B₁ per kg and not more than 20 µg aflatoxins B₁, B₂, G₁ and G₂ per kg
- The extend of testing may be determined using a risk-based approach that considers the likelihood of contamination, and the presence of unexpected contamination is to be considered in determining compliance

Summary and Conclusion

- High quality requirements, in particular on contaminants, for herbal medicinal products and related areas guarantee optimum consumer protection.
- Realistic criteria as well as practical experiences should be taken into consideration when new rules are established.
- The development of a sector-specific guideline on integrated pest management might serve as a useful example for the benefit of cultivators, herbal industry, authorities and consumers.

