



“Traditional Herbal Drugs – From a Tradition to new Perspectives”

Report by the german Federal Institute for Drugs and Medical Devices (BfArM)

(The german BfArM is a member of the HMA (–Heads of Medical Agencies) an a partner of the EMEA/ HMPC)

by Monika Gerhardus, ANME

On 18 October 2007, an event with this title took place in Bonn. Around 160 people from the area of politics, associations, and pharmaceutical companies attended this meeting which was chaired by Dr. Werner Knoess from BfArM.

The BfArM has created a new internal structure:

Licensing Division 5	Responsible for the marketing authorisations of “Special Therapies and Traditional Medicinal Products”
Subdivision 51	Procedure management
Subdivision 52	Traditional herbal medicinal products
Subdivision 53	Homeopathic drugs and anthroposophic medicine

1. Marketing Authorisation

The event’s objective was to show ways how products can be preserved in the future and how new products can be marketed in Europe. Dr. Knoess stressed the fact that BfArM wants to improve the German position in Europe, that it should be made possible to expand the market, and that the future of phytotherapeutic drugs should be shaped actively.

Ms Stolte asked in her presentation whether or not it was true that requirements for traditional documentary evidence were exaggerated. She then explained the transference of § 109a with § 141 (paragraph 14) into §§ 39a ff AMG (German Medicines Act) and talked about the implementation of the EC directive 2004/24 and their particular transposition into national law (§§ 39a ff., AMG).

In accordance with §§ 39a ff. AMG, those proprietary medicinal products which are herbal in nature and pharmaceuticals defined in §2, paragraph 1 AMG, can only be marketed if they are registered. There is scope for interpretation, however, because this also applies to herbal drugs containing vitamins or mineral supplements provided that they complement the effect of traditional herbal drugs in the area of application or the areas of application.

! The national transitional regulation from §109a to §39a AMG is important:

The marketing authorisation of a traditional herbal drug which was renewed according to § 105 in connection with § 109a will expire on 30 April 2011, unless:

An application for authorising the registration has been filed in accordance with § 39a AMG before 1 January 2009.

Thus, a new application for the registration of the identical pharmaceutical has to be filed by 31 December 2008. Without a new application the drug will disappear from the market as of 2011.

The authorisations can be put into 2 categories:

category 1:	authorisation procedure:	proof of efficacy + clinical trials
category 2:	simplified procedure:	plausibility of efficacy : long tradition (Efficacy is plausible because the pharmaceutical has been used for many years) = traditional documentary evidence

The traditional documentary evidence proves that the same preparation has been used for at least 30 years.

15 years in the EU + 15 years worldwide = 30 years

! Problem:

What happens to those drugs that have faced changes in the last 15 – 30 years in their composition and their administration form under the renewal of the marketing authorisation or because of other reasons?

- What does the traditional documentary evidence now look like?
- BfArM decides on that after the whole package of applications has been presented.
- Beforehand, BfArM offers intensive consultations.

2. Ideas concerning the Requirements for Innocuousness according to BfArM

The presentation “**Ideas Concerning the Requirements for Innocuousness**“ by Dr. Jaqueline Koch, BfArM, can be highly important for the future of the diversity of our phytotherapeutic drugs.

In accordance with the EC directive 2004/24 from 31 March 2004, the following applies:

- The information about the traditional use of a product is sufficient.
- If used properly the product is not harmful.
- The pharmacological effect or efficacy is plausible and is based on many years of use and experience

But:

HMPC can decide on deviations at the request of a member state!

When looking at EMEA / HMPC / 32116 / 2005 (1), one can assume that since bibliographical information on preclinical trials is widely used, a lot of information will be available.

There it is described that

- Minimum requirements for preclinical safety packages have to be stated when registering a product.

- If minimum requirements are not met by published literature, additional preclinical tests may be necessary (mixed application).

According to EMEA / HMPC / 32116 / 2005 (2) the following is **not necessary**:

- **Testing acute and chronic toxicity, immunotoxicity testings, local tolerance testings if there is sufficient and well documented experience available in humans**
- **Pharmacological testings (including safety pharmacology and pharmacokinetics if there is no reason to expect a specific risk from pharmaceuticals)**

According to EMEA / HMPC / 32116 / 2005 (2) the following must **be discussed**:

- **How to assess the potential for pharmacokinetic interactions between the drug and/or preparation and other medicinal products**
- **Special attention should be paid to:**
 - 1.) **Reproductive toxicology**
 - 2.) **Genotoxicity**
 - 3.) **Carcinogenicity**

1.) Reproductive toxicology

BfArM considers the testing regarding **fertility** an **important task**:

- Is this testing necessary if there is cause for concern or if the product is used explicitly during pregnancy?

Concerning **embryo-foetal and peri-postnatal development** the following questions arise:

- Should the toxicological potential be considered (i.e. duration of application)?
- Tests are required in cases in which the significance of the results is not clear and if there are reasons for suspicion.

BfArM does not consider trials necessary if:

- Results from post-marketing studies or epidemiological data are available.
- The assessment of the results of a comprehensive scientific literature search and post-marketing experience does not identify a positive signal of reproductive toxicity and the product is not intended to be used during pregnancy and lactation.
- Results from trials in pregnant women and neonates are present.
- The medicinal product is not intended to be used by women of childbearing potential.

2.) Genotoxicity

BfArM considers the testing of a possible mutagenic effect **indispensable**:

The pharmaceutical industry has to cope with the following problems:

- **Data:** Are new data needed (e.g. comprehensive studies)?
- **Result:** What happens if the data are insufficient or show a positive result?
- **Gene mutation:** Is the AMES-test sufficient?
- **Chromosome mutation:** Are more tests necessary to also record chromosome aberrations?

- Procedure: Which testing procedures are considered necessary and/or do mutations take place?

More: What do standard tests for genotoxicity look like?

a. in-vitro-tests

- in bacteria (AMES) Gene mutation
- in cells of mammals Chromosome mutation in permanent cell lines and human lymphocytes

b. in-vivo-tests

- in rodents
- in the microcore Bone marrow

3.) Carcinogenicity

Carcinogenicity studies are **not needed** if carcinogenic potential is **not suspected**.

If there is a suspicion the drug will be assessed as follows:

- Is the suspicion based on results of genotoxicity studies and can it be clarified in further genotoxicity studies (in vivo)?
- Is the suspicion based on a possible epi-genetic mechanism?
- Are the extent and the quality of the available scientific data sufficient to refute the suspicion?
- Are the extent and the quality of the available scientific data sufficient to come to a positive benefit-risk assessment?

BfArM splits the **realisation of testings** for reproductive toxicology, genotoxicity, and carcinogenicity into three groups of drugs:

1st group = Known to be genotoxic (e.g. Colchicum)

BfArM demands strict guidelines with respect to corresponding tests (AMES-Test, Chromosome aberration tests, micronucleus in vivo-test, carcinogenicity study (2 years), and reproductive toxicology tests in rodents/ non-rodents)

2nd group = There is a possible connection with the hormonal efficacy (literature or own indications, e.g. Sabal, Cimicifuga)

BfArM demands AMES - test, Chromosome aberration tests, reproductive toxicology testings in rodents / non-rodents

3rd group = all other drugs (no risks known)

BfArM demands

- AMES-test,
- Chromosome aberration tests,
- Reproductive toxicology testings in rodents/non-rodents

BfArM requires warning notes for pregnant women and nursing mothers. If necessary, BfArM requires a reproductive toxicology after 5 years.

BfArM does not consider further tests necessary for

- Drugs that are also comestible goods and that have a negative AMES -test result.
- Drugs that have been widely used for many years as a herbal drug and that have a negative AMES-test result.
- Drugs that are less commonly used but which are nevertheless used traditionally (as individual pharmaceuticals) and that have negative AMES-test results.

These questions continue to be open:

- What happens if an AMES-test turns out to be positive?*
- What happens with mixtures of drugs/preparations?

*If an AMES-test turns out to be positive, then comprehensive justifications are necessary, e.g. by proving that this pharmaceutical is just applied temporarily, that it should only be applied externally on small areas, and that dosages should be taken with a safety gap.

Conclusion:

The requirements by BfArM pose a new threat to natural remedies that have just gone through many years of the renewal procedure. The requirements listed above mean high costs for pharmaceutical companies and involve a heavy administrative burden. At the request of BfArM, manufacturers and those who treat patients are supposed to prove something which is merely based on a suspicion. All herbs (drugs) are accused of being toxic to reproduction, mutagenic and carcinogenic!

Great efforts are needed to weaken this argument. And at the end of the day it is the patients who will have to pay the price: Either the remedies disappear from the market or they increase greatly in price.

Even though these herbal drugs have been used for decades (this should really prove their innocuousness), they are pushed to the sidelines in the area of comestible goods. That is detrimental to the quality of these remedies. Will soon a vast number of natural remedies be taken from the market once more?