



Evidence-based medicine: Theoretically a good idea, but...

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European Drug Legislation

Primary aim: Consumer protection!

- German National drug legislation created based on the experience with Contergan
- Uniform requirement:
 - Safety
 - Efficacy
 - Tolerability
- Oriented at the most recent treatment guidelines
- What about herbs a long tradition of use?



Full registration

- Essentially for new entities
- Proofs of efficacy and safety
- Pharmacological studies
- Toxicological data on acute/chronic toxicity, mutagenicity, reproduction toxicity
- For herbs also: Interaction potential



Risk-benefit ratio

In contrast to long-known herbs the risks of new entities only become known on broad application after registration!

Examples:

Cardiovascular effects of COX-2-inhibitors („Vioxx“)

Rhabdomyolysis with CSE-inhibitors („Lipobay“)

But:

Efficacy of new chemical entities mostly demonstrated in state of the art clinical trials

Efficacy of herbs often demonstrated through experience and lower-level evidence

- Differences in acceptable threshold of risk level between chemical and herbal drugs



Herbal drugs in full registration

- Same requirements as for chemical entities
 - Questions regarding pharmacokinetics and bioavailability can often not be addressed with herbs
 - Testing of mutagenicity often yields meaningless results (AMES-test)
 - Interactions studies (mandatory for herbs, but not for chemical entities) must be expected to yield positive results
- Full registration is nearly impossible with herbs
→ Alternative approach: Well-established/traditional use



Why facilitated registration for herbal products?

Undeniable demand in the population

Well-controlled quality of drugs preferable over uncontrolled and barely legal material from internet trading

Question of consumer safety!

- Quality of raw material and processing?
- Adulterations?
- Traceability/GACP?



Today's situation

- D: Mostly registered herbal products, relatively few food supplements, strict controls
- F: Similar legislation, but few controls. Many products marketed as food supplements
- B, NL, UK: Almost exclusively „food supplements“
- Harmonization process involving the EMEA



EMEA-monographs: An impossible task?

- Time is running: Deadline defined for 2011
- What will happen after 2011?
- EMEA is working on monographs for the best-known herbs.
- Hundreds of herbs on the market, in various combinations. What about TCM, Tibetan herbs, Campo, Ayurveda...?
- EMEA suffers from a lack of financial support
- Potential impact on speed and output of monographs?



EMEA-monographs: Automatically acceptable for national authorities?

- Questions of similarity of traditional and modern preparations
- Some national authorities claim 100% similarity in practise!
- Full toxicological details and quality dossier required!

Affordable for small to middle-size companies?



The EMEA-guideline HMPC/32116/2005

- No need for new data on acute and repeat-dose toxicity, when there is ample bibliographic data on safety of use
- But: This guideline is immediately invalidated by national authorities when potential risks are discussed!
- When (even hypothetical) risks are discussed, the registration process practically turns into a full registration!



A fictitious example: Peppermint

- Long tradition of use in stomach disorders, but not proof of efficacy
- Candidate for traditional registration?
- 30 years of use within the EU, so no problem to be expected
- Use in the intended form? 100% similarity?
- Safety of use granted?
- Peppermint counts among the top ten herbs with reports in the WHO database on adverse events!



The Sword of Damokles

- Even with a traditional registration granted for peppermint, any discussion on safety of use can lead to an immediate ban of peppermint products!

“If there is the slightest risk without proven efficacy, the drug has to taken off the market”

Citation from a presentation of the German authorities on the London Pharmacovigilance conference on April 26-28, 2006



Peppermint was only a fictitious example, but...

- More than 90% of the herbs currently traded as medicinal plants would fall under traditional use and are thus directly threatened by this simple mechanism allegedly aimed on an improvement of consumer safety!
- The same herb, traded via uncontrollable internet channels, will remain available!



What about well-established herbs?

- Bibliographic data is disregarded for formal reasons when risks are discussed.
- The standards then applied correspond to full registrations of new entities!

Examples:

- Kava (*Piper methysticum*)
- Greater Celandine (*Chelidonium majus*)



Call for more common sense

- Bibliographic data can never correspond to latest treatment standards. This also applies to chemical entities after some years!
- In risk discussions the alternative treatments and the incidence rates should be taken into consideration!
- Therapeutic experience must not be disregarded on the background of heavily hypothetical discussions of potential risks!



Ceterum censeo...

We claim yesterday's medicinal experience to be outdated and not applicable for formal reasons.

But: Today's scientific standard will be as outdated tomorrow!

Evidence-based medicine cannot be reduced to tiny details, but must be assessed as a whole picture!



Thank you for your attention

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