

## **Evidence-based medicine: Theroretically a good idea, but...**

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The European drug legislation is aimed on consumer protection, which is, in principle, commendable. Specifically the German drug law and the drug registration were created based on the experience of the Contergan catastrophe. Since then, it was continuously expanded. Meanwhile even the old registration is a thing of the past: drugs have to go through a complex registration process requiring the proof of three major topics: quality, efficacy and tolerability.

There is ample documentation what kind of data has to be presented to comply with these requirements. The proof of efficacy has to be oriented at the most recent treatment guidelines.

So far, so good. In practice there are, however, problems with the interpretation of the legislative framework, especially when it comes to preparations of the so-called “special therapies”. Roughly, phytotherapy, homeopathy and anthroposophy count among these special therapies.

As already mentioned drug legislation is a tool for consumer protection. Such instruments can also be applied to simply revert the spirit of the European guidelines aimed on a protection of the status of complementary and alternative medicine to its contrary. In the following the problems shall be demonstrated with typical examples of medicinal plants.

### **The full registration**

Three principal levels of drug registration must be distinguished. The first and most demanding level is the full registration. It is especially aimed on new, chemically defined entities, where efficacy and safety have not yet been demonstrated in mass use. Such drugs have to undergo a whole battery of test models before they can be tested in humans for the first time. Such models are, among others,

- pharmacological examinations of the effects in vitro, ex vivo and in various animal models
- examinations of acute and chronic toxicity, mutagenicity and reproduction toxicity
- pharmacokinetic studies on absorption, distribution, metabolization and elimination
- examinations of the consequences of potential contaminations from synthesis on the safety of use

Only after conclusion of these examinations a drug substance can be cleared for first human trials.

In the examinations in humans the pharmacokinetic properties are again tested, and dose-response curves established. Efficacy has to be demonstrated in clinical trials. The usual standard today is testing against placebo and a reference.

When these requirements are met the drug can be registered. The number of patients in whom the new drug substance was tested in the course of the registration process is of course restricted. Especially rare risks in the range of 1 case in 10,000 patients or more are usually only detected when the drug is broadly used. Examples are rhabdomyolysis with the use of certain lipid lowering agents, or cardiac infarctions or strokes under therapy with antirheumatic agents of the type of selective COX-2 inhibitors.

### **How about plants in the full registration process?**

Principally the way just outlined is also open for herbal drugs – however, given the peculiarities of plant extracts this procedure is mostly rather unlikely. Working on the to-do list of drug registration one encounters a multitude of problems, such as

- The composition of the extracts is to a great degree unknown.
- Pharmacokinetic examinations cannot be made when the active ingredient has not been identified.
- Testing of mutagenicity gives mostly senseless results with herbs, since the stains of Salmonella used in the testing false-positively react to flavonoids, which are more or less ubiquitous in plants.
- The toxicity of herbs can often not be determined. For instance does the dose of kava, which would theoretically lead to the death of 50% of the test animals, by far surpass the feeding capacity of the test animals.
- The requirements for modern proofs of efficacy are adapted to the characteristics of chemical/synthetic drug substances.
- Interactions studies are mandatory for herbal extracts, but not for chemically defined drug substances, when there are hints to suspected interactions from in vitro-studies. Such hints on interactions at metabolizing enzymes have to be expected in almost all cases with herbal extracts.

In practice the question has to be asked how flexible the requirements for registration can be handled. With a purely formalistic view of the requirements no herbal drug will fulfil every single one at reasonable costs. In times of a politically wanted exclusion of herbal drugs from reimbursement by the health insurance systems, and with medicinal societies still apodictically holding up the hypothesis herbal = inefficacious a (later!) refinancing of registration studies through the market is highly difficult – assumed the preparation is in fact registered. They option of a full registration is thus no feasible way for most producers of herbal medicines.

### **European directive: Facilitated registration of herbal drugs**

If the criteria for the full registration were simply applied to herbal medicinal products, there would soon be no more corresponding preparations available. However, this would create problems instead of solving them, since traditional experience cannot be done away with by verbatim observance of directives created with synthetic preparations in view. There is an existing demand for herbal medicinal products in the population. The place of today's well-controlled preparations would simply be substituted by uncontrolled products from internet trading. Nobody can seriously want this type of development, especially since the self-chosen goal of consumer protection would be countered by a deterioration of product quality.

Reality shows, however, that this is happening already today! Herbal medicinal products facing tremendous problems through requirements from drug registration authorities can already now be obtained via the internet in similar presentation without any control of composition and quality. This may cause toxicological consequences which shall be more closely discussed in the following.

Europe's legislators understood that the current requirements for drug registration would put herbal medicinal products at a disadvantage. In order to meet the peculiarities of the so-called alternative therapies and especially of medicinal plants the European authorities created a guideline for the simplified registration of herbal medicinal products. Principally there are two ways open for plants: the registration under "well-established use" and as a traditional remedy. The difference between the two depends on the size of the available documentation.

### **The registration under “well-established use”**

The simplified registration allows the use of bibliographic data for many aspects of drug registration, i.e. studies taken from the literature. The indication is correspondingly restricted – only indications can be claimed for which there is bibliographic evidence.

Producers cannot choose by themselves what they might see as an acceptable indication area. A commission of the European registration authority (EMA) is tasked to create monographs where the scientifically proven and traditional uses are compiled. This possibility was defined in the framework of the European legislation. However, the same legislation defines a time window: herbal products for which there is no EMA-monograph in the year 2011 can from then on not be commercialized any longer.

Thus far this is theory – now to reality. The capacities of the EMA are limited, even more so the financial means. Already now the EMA draws on external expertise from academic experts, who, however, already now complain about the additional work-load bearing no fruits for their institutions. There is a lack of funding for the organisation of literature or the translation of relevant papers into English. Currently approximately 40 monographs are under development – with hundreds of herbs and combinations existing. Already now it becomes clear that many producers will potentially face the situation of losing the possibility to sell their products in 2011, based on the lack of a corresponding monograph.

However, even an existing monograph on a given herb is no guarantee a producer may lean on in drug registration. The question had to be asked how similar today’s extracts have to be compared to those from the bibliographic works. There is leeway for goodwill as well as for rigidity. In view of the usual German attitude towards an extremely restrictive interpretation of guidelines from Brussels without obvious need to do so it is not surprising that already a deviation of 5% ethanol content in the extraction solvent is sufficient to deny the comparability of the product with literature data.

### **The quality module**

The EMA-monograph is only one of the requirements for drug registration. All herbal medicinal products for which this path is to be taken need a complete quality module with a full documentation of origin and quality of the herbal raw material, the analytical methods, the exclusion of contaminants etc. For German producers this might pose a lesser problem than for producers from the Netherlands, the United Kingdom, Belgium, Denmark or France, countries where to date herbal preparations are usually sold as food supplements without preparation-specific documentation. Larger changes of the market situation are to be expected in these countries from 2011 on.

### **The registration as a traditional remedy**

For the majority of medicinal plants there is no bibliographic data to support the use in a given indication through studies. For these cases the European regulation foresees the simplified registration with the restriction “traditionally used for...”. Again the EMA is tasked to compile the corresponding lists of herbs and indications.

Regarding statements of indications there is no leeway for producers who will refer to EMA-monographs in the future. Most producers will probably be able to live with this situation. However, what will pose problems is the claim for a full quality module. In this part of the registration dossier the producer has to demonstrate the quality of his product by validated analytical methods, including stability testing. The financial efforts needed to achieve this will in many cases exceed the expected turnovers from trading the then-registered product.

The registration authorities also call for toxicological data, e.g. reproduction toxicity. A most recently published new guideline (EMA/HMPC/32116/2005) foresees simplifications in

cases where there is no hint on toxic effects from existing literature data. It will have to be seen whether this will be transferred to practice in national authorities, or – as experience teaches – whether older studies will simply be rejected for formal reasons and based on theoretical risks.

### **The risk-benefit evaluation as the largest obstacle**

The efficacy even of well-examined medicinal plants is often doubted. One of the reasons for this is the constant evolution of requirements for the conduct of clinical trials. New drug substances are at an advantage here, since due to their novelty they are able to present clinical data according to latest standards. In contrast, they lack the broad experience of application which is almost always present with medicinal plants.

The question of acceptability of older studies is a typical example of rigidity versus flexibility regarding the requirements for drug registration: Older studies can either be accepted as supporting material, or can be disregarded. Experiences with drug registrations of the past years and contacts to representatives of drug registration authorities show that currently rigidity is prevailing. The key word is – once more – consumer safety. Already single hints on adverse effects supposedly force to only accept data material conforming the latest directives as a basis for establishing a risk-benefit profile. In this place the question has to be asked whether the same rigidity is also applied to older chemical drugs – preparations for which on closer inspection and application of the most recent standards the demonstration of efficacy is likewise less than convincing. In chemically defined drugs an incidence rate of adverse effects of 1:10,000 seems to be totally acceptable, whereas much lower incidences can conjure a catastrophe in the case of herbs. Recent examples of well-examined plants having this kind of problem are kava, Cimicifuga or greater celandine.

In addition in the case of medicinal plants a single negative study can achieve more importance than a multitude of positive results. There are many recent examples to demonstrate this mechanism: E.g., St. John's Wort was accused of lacking antidepressant efficacy in the media after a comparative trial with Fluoxetine and placebo. It was, however, not added that St. John's wort was tested outside of its normal indication. Even worse: It was also not pointed to the fact that Fluoxetine was likewise lacking efficacy in this trial. Thanks to a rather skilled "anti-marketing" the buck was exclusively passed to St. John's Wort.

In the case of St. John's wort the authorities seem to have trouble with the acceptance of the indication "mild to moderate depression". Although tolerability has been shown to be better than with conventional antidepressants, and although efficacy was demonstrated in dozens of studies, the regulatory authorities over-proportionally point to safety issues such as a supposed phototoxicity and potential interactions. The former has long since been shown to be irrelevant, whereas the latter are clearly a consequence of an artificial enrichment of hyperforin in certain special extracts, whereas no relevant adverse effects are to be expected from the use of normal Hypericum extracts. All corresponding proofs do, however, not count much: in the assessment of a risk-benefit profile the principle of suspicion overrules everything – in herbs, but not necessarily in chemically defined preparations.

### **A fictitious example: Peppermint**

Peppermint has a long history of use. The effects are general knowledge. This, however, causes the first problem: Registrations have to be granted based on facts. Outside observers would suppose that there is no problem with a registration of peppermint for the treatment of digestive disorders.

However, the fact that everybody knows that peppermint is good in cases of stomach complaints, and the therapeutic experience covering decades, if not Centuries, is insufficient for drug registration. An undisputable proof of efficacy is warranted. Clinical studies for the

application of peppermint in gastrointestinal disorders? Zero. Why do such a study, when the effects are generally known?

As a result the way of a regular registration or a registration under “well-established use” is closed for peppermint. Fortunately there is still the possibility to register as a traditional remedy. This path was created to accommodate plants long known but without clinical trials. It has to be demonstrated that the herb has been used in the applied indication for at least 30 years, 15 of which within the EU. This should not pose too large a problem for peppermint – except that there is leeway for interpretation.

This would not be Germany if guidelines from the EU were simply adopted as such. In Germany requirements regarding the proof of use were added to the definition of the time frame. The word “use” was thus changed into “substantial use”, together with the claim that this substantial use has to be demonstrated for every single year of the 30-year period. An intelligent claim, since company documentation has usually only to be stored for 10 years. Experience shows that mostly statements regarding the use of a given preparation 30 years ago can be obtained, but the trade figures can only be reconstructed in very rare cases. Thus, the good intention is simply turned to its opposite.

Let us assume that our fictitious peppermint preparation managed to obtain the registration under “traditional use”. There will still be the constant threat of risk-benefit evaluation hanging over the herb like a sword of Damokles. Peppermint counts among the plants for which the largest figure of signals pointing to potential adverse effects can be derived from databases such as the one of the WHO. This does not necessarily mean that peppermint really causes such adverse effects. It simply says that the herb was associated to the occurrence of adverse events. According to the rules of the pharmacovigilance department of the BfArM, as presented on the London Pharmacovigilance conference in April of 2006, even the suspicion of a severe adverse effect would be sufficient to ban a herb for which there is no proof of efficacy.

Like any other product registered as traditional remedies for which there is by definition no modern proof of efficacy, peppermint will have to live with the threat of an immediate ban, based on the argument of a negative risk-benefit profile. In view of the fact that the overwhelming majority of medicinal plants are to be considered traditional remedies this is not exactly a reassuring situation; and it surely was not intended by the creators of the European guidelines.

### **Long term experience is often disregarded**

In comparison with chemical drugs medicinal plants mostly have the advantage of a long experience of use in traditional medicine. This experience might allow the deduction of a risk profile. E.g., cinnamon has been known as a medicinal plant for 5,000 years, and was consumed in incredible quantities in the Middle Ages. Today consumers are seriously warned against the consumption of star-shaped cinnamon cookies, since the baked goods may contain coumarins which are theoretically toxic (in pure form and in certain models). It does not seem to matter that such toxicity has never been observed with cinnamon, and is likewise not reflected in toxicological examinations. Most importantly, the consumer is protected – not only from star-shaped cinnamon cookies, but also from new dietary supplements for diabetics. One has to admit that the toxicological studies do not correspond to the latest guidelines...

Long-term experience usually correlates with a high degree of safety of application. To avoid misunderstandings: herbal preparations can have adverse effects, and occasionally even severe ones. On making a decision regarding the treatment of individual patients a physician will, however, not so much ask if such adverse effects can occur, but rather how often. He will also have to consider the probability of such adverse effects in comparison with other drugs used in the same indication. This question is, however, never answered in the single-

sided discussion of the risks of herbal preparations. It may even be declared as irrelevant. A typical example is kava. In this context there is data demonstrating a potential liver toxicity of benzodiazepines – a medication frequently used in practice. The incidence rate seems to be by far higher than what has to be expected from the use of kava. However, this argument does not count in favour of kava, since the latest treatment directives of social anxiety do not propose benzodiazepines, but rather antidepressants as the treatment of choice. These preparations do not have an acute effect, and – under the conditions of daily practice – are no solution for the imminent problems of the patient. Still, the situation in the physician's practice does not need to make an impression on public servants in the pharmacovigilance departments of regulatory bodies, who do not know the situation in the real world. The fact that even the antidepressants are not free from risks does likewise not impress...

For many medicinal plants there are clinical case reports and pharmacological/toxicological examination from the founding times of rational phytotherapy. Often there is even evidence of higher degrees, such as randomized double-blind studies. However, in national drug registration authorities today the attitude seems to prevail to exclude older – and often also younger – data for formal reasons, since this kind of research data does often not correspond to today's standards or terminology. From the scientific point of view, such an attitude is at best deplorable. Even we have not reached the summit of scientific knowledge in 2006. Quite the contrary – we have to assume that within a few decades our work will be regarded as naïve and unusable under the same attitude. Some more modesty and respect for the scientific achievements of our foreborders is warranted. Firstly, we build up our current knowledge on these former works, and secondly highly valuable hints on effects and safety of application can also be derived from old studies – with a little bit of goodwill.

### Conclusions

The field of tension between exaggerated requirements for safety of application of herbal drugs and the application of rules for simplified registration does not instil much confidence for the future. Evidence-based medicine was created to give phytotherapy and complementary and alternative medicine the chance to acknowledge therapeutic experience assembled during decades. The EMEA is currently doing a highly praiseworthy job with great efforts. However, these efforts are thwarted by a rigid and formal application of rules regarding safety of application.

This calls for the following demands:

- **The assessment of bibliographic evidence must not fall victim to formalistic evaluations.** As an example, on the last annual meeting of the Society for Medicinal Plant Research in August 2006 in Helsinki representatives of the EMEA explained that studies on acute and chronic toxicity will not be claimed for herbs with a long tradition of use – in accordance with the new guideline EMEA/HMPC/32116/2005. Correspondingly, it is absolutely not understandable that currently in the case of kava the performance of a clinical trial requested by the BfArM itself is now rejected by the pharmacovigilance department, based on the argument of a lack of toxicity studies. However, such studies do exist!
- **The safety of application of a given therapy must be assessed in the context of therapeutic alternatives.** It is well possible that an isolated risk of a medicinal plant may suddenly become irrelevant when assessed in its context.
- **Well-controlled herbal medicinal products must not be displaced from the market by exaggerated requirements, especially not such using consumer safety as an argument.** The alternative is badly controlled preparations from internet trading, and thus a deterioration of consumer safety.