# **Im**pact matrix analysis and cost-benefit calculations to improve management **pr**actices regarding health status in **o**rganic dairy farming

Project Number: 311824

## - Deliverable -

# D9.3 - Report exploring the effectiveness of alternative treatment in livestock systems incorporating a variety of different experts' views and perspectives

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## Executive Summary

Increasing antimicrobial resistance worldwide urgently demands reactions to reduce unnecessary use of antibiotics. Alternative treatments, like homeopathy and phytotherapy, are widely used as replacements for antibiotics, particularly in organic livestock production where the use is favoured by European legislation (Council Regulation No 834/2007). However, scientific evidence of efficacy and effectiveness for these treatments is lacking and their potential for reducing the use of antibiotics is therefore uncertain.

This report provides an overview of the results of two experts' workshops arranged in January 2015. The aim of the workshops was to receive feedback on scientific reviews on the efficacy of homeopathy and phytotherapy, elaborated within the IMPRO-project, as well as to identify important factors influencing the effectiveness and use in research and farm practice. Core questions were: What is needed to scientifically validate the efficacy of homeopathy/phytotherapy? Which conditions influence an effective treatment under farm conditions? What has to be altered in future with respect to homeopathy/phytotherapy and in relation to a more effective treatment, improved animal health and welfare and reduced antibiotic use?

The workshops took place in Germany; each workshop (focusing on homeopathy and phytotherapy, respectively) lasted one day. For each workshop twelve participants from 6-8 European countries with different expertise, background in research or veterinary practice, and varying positions towards homeopathy or phytotherapy were invited to share and discuss their views and opinions, guided by a professional moderator.

The review on homeopathy revealed that half of the reviewed studies showed a significantly higher efficacy of the administered homeopathic remedy in comparison to a control group, whereas many other studies showed no medicinal effect. The review on phytotherapy showed that 19% of the studies had a significant positive effect, e.g. reduced clinical symptoms or mortality of the administered phytotherapeutic remedy, while the majority of the studies (60%) showed an uncertain or no effect of the applied remedy. It was concluded that botanical compounds might have potential, but due to the lack of information on the content of the remedies and the absence of a control group or blinding in the trials, the previous results are very vague.

Both reviews displayed that no trial has been repeated under the same or comparable conditions (with respect to species, remedy, context/disease, expertise), therewith lacking reproducibility, while no valid conclusions for the effectiveness in farm practice can be drawn.

The participants in each workshop confirmed that the studies, evaluated in the reviews, showed various weak points in the study design. In studies on homeopathy the individualised homeopathic treatment procedure was usually not appropriately considered. In studies testing phytotherapy, the specification of content or composition of ingredients and dosage of the applied botanical was generally poor.

According to the workshop participants, main obstacles for homeopathic treatment were seen in the lack of expertise when using the corresponding remedies. The use of homeopathy by veterinarians in practice is also influenced by the corresponding national legislation (supporting or declining homeopathy). Homeopathic remedies for humans bought directly over the counter currently fill comparably simple and cheap possible gaps in availability for the use in food producing animals. They are usually applied without advice of an expert or the required veterinarian prescription.

Products of phytogenic origin can be found under various terms and the same botanicals are used as remedies and feed additives. Only few registered veterinary phytotherapeutic products are available, potentially due to high costs for approval combined with small profits and no protection or

patent of the composition or content of the product. Investment in research and development is often not attractive for manufacturers. As a consequence, botanical products are sold and used as feed additives, which leaves decisions on indication for treatment and dosage to the farmer. Without adequate knowledge regarding which level of efficacy can be expected from different botanicals and which dosage is required to achieve it, a results-driven use of these products cannot be expected.

A general estimation was that veterinarians and other users are often lacking sufficient expertise in phytotherapy and homeopathy, respectively. Profound knowledge about the effectiveness of treatments in farm practice does not exist and documentation of treatments and especially of the outcomes is not established on farms.

In order to identify appropriate alternative strategies, studies in farm animals for the reduction of antibiotics should be supported. The efficacy of alternative treatments, as well as dosage and indications for treatments, should be proven by a scientific approach using an appropriate study design, particularly Randomised Controlled Trials (RCT). According to the workshops, this type of study design is applicable to homeopathic and phytotherapeutic products although some adaptations to the specific need of a homeopathic treatment procedure or phytotherapeutic guidelines are required. Guidelines for standardisation of phytotherapeutic remedies on content and ingredients or - for multicomponent herbs - by metabolomic fingerprinting, could support transparent research, reasonable use and appropriate dosage. Currently, homeopathic and phytotherapeutic products are often not registered for veterinary use and therefore not available for treatment by veterinarians. It was proposed to adapt legislation to better describe phytotherapeutic remedies as a class of products and harmonise with human regulations. A registration procedure for veterinary homeopathic and phytotherapeutic remedies on a European level could improve the availability of these remedies for veterinarians.

Effectiveness of any treatment, conventional or alternative, applied in practice depends upon several external factors. Thus, promising results in scientific studies concerning the efficacy of remedies require further evaluation of the effectiveness in practice. To achieve this, it is necessary to monitor the use and effectiveness of treatments by establishing a monitoring programme, documenting the use of treatments, alternative as well as conventional, combined with the monitoring of production diseases on the farm level. Such information is essential for the individual farm as well as for large scale studies to assess the impacts of (new) treatments, interventions or diseases for the benefit of animal health and welfare and food safety.

Current use of homeopathy and phytotherapy is mostly performed by lay people as established and standardised expertise and training is not available. This is critical for an appropriate and effective use and especially with respect to the animal welfare issue, as ineffective treatments will extend suffering of diseased animals. Expertise on therapy and knowledge on the efficacy and effectiveness of treatments should be improved by standard quality training courses. Veterinarians, trained in this way, should supervise the treatment of food-producing animals with homeopathy or phytotherapy, too.

Thus, current European legislation does not lead to the desired and evidence-based results with regard to an improved animal health and welfare and a reduced use of antibiotics. Beside the need of further Randomised Controlled Trials to prove efficacy of remedies, there is simultaneously a need to establish a monitoring system to assess the effectiveness of treatments in farm practice and to shed some light into a farm practice that currently lacks transparency.

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# 1 Part A: Report of the workshop on homeopathy

## 1.1 Abstract

Homeopathy is seen as controversial and is not a generally accepted form of treatment in the veterinary world. Nevertheless, it is widely used in animals for food production and is even supported by European legislation for organic livestock farming. A previously conducted review on the efficacy of homeopathy in livestock as part of the IMPRO project revealed that in 30 out of 60 studies which fulfilled selected criteria, evidence for the efficacy of homeopathic treatment was substantiated. However, notwithstanding the fact that many studies showed numerous weak points in relation to best standards (Randomized-Controlled-Trial (RCT)), due to the high variability in the study designs it is hard to replicate the studies and results widely. Correspondingly, general statements concerning the efficacy of homeopathic treatments are not valid. Homeopathy cannot, at present, claim to have sufficient prognostic validity concerning its therapeutic efficacy. A specialist workshop on the efficacy of homeopathy was conducted in order both to receive feedback on the review previously conducted and to obtain additional information on this issue from different perspectives. A further purpose was to discuss options for the improvement of scientific studies on homeopathy and to identify which criteria should be followed to achieve a successful therapy result. Twelve participants from different European countries with expertise in various disciplines and different opinions on homeopathy were invited to a one-day workshop. The sessions and group discussions were guided by a professional moderator ensuring a comprehensive exchange of expertise.

The workshop emphasized the need for evidence of efficacy of homeopathy provided by research with an appropriate study design which considered the individualized homeopathic treatment procedure and different conditions. The participants recommended the support of research combining internal and external validation.

The biggest influence on the efficacy of homeopathy on farms was seen to be the availability of expertise in homeopathy. Expertise should be practised based on common European quality standard and proven by a final exam and certification process. However, even the best qualification does not provide good results, when the therapeutic effects are not monitored appropriately. Documentation and monitoring of all treatment is a crucial part and indispensable prerequisite of a *lege artis* homeopathic treatment procedure. Besides the feedback information obtained, it provides essential information to prevent extended suffering of insufficiently or untreated farm animals and prognostic information for the further use of homeopathy. Supervision of treatment should be regularly undertaken by a veterinarian trained in homeopathy.

Recommendation to the EU Commission: EU Council Regulation No. 834/2007, Art. 14 (e)ii) on organic livestock farming should be modified as follows: "…chemically synthesised allopathic veterinary medicinal products including antibiotics may be used where necessary and under strict conditions, when the use of phytotherapeutic, homeopathic and other products is inappropriate. Homeopathy and other alternative remedies shall only be used, "provided that their therapeutic effect is effective for the species of animal and the condition for which the treatment is intended" (Commission Implementing Regulation 505/2012, Art. 24 (2)). Farmers have to provide evidence with respect to the efficacy of homeopathy in the farm specific context by implementing a standardised monitoring of single case studies, supervised by a veterinarian".

## 1.2 Glossary

**Homeopathy:** is a system of alternative medicine created in 1796 by Samuel Hahnemann, based on his doctrine of "*similia similibus curentur*" ("like cures like"), according to which a substance that causes the symptoms of a disease in healthy individuals will cure similar symptoms in sick individuals. The remedies are used in a diluted form according to the potentiation procedure described in the homeopathic pharmacopoeia. Ingredients for homeopathy can be of herbal, mineral or animal origin.

a. **Classical homeopathy or individualized homeopathy:**
Every individual and illness is unique and so is the chosen remedy. A holistic approach in respect to body, soul and spirit is employed. It covers inter alia: 1. causa (any influences that caused the disease), 2.modalities (timely, physically, physiological or psychological circumstances under which the symptoms increase or decrease), 3. (extraordinary) behaviour, 4. constitution, 5. general symptoms, 6. organ symptoms, 7. frequency of symptoms, 8. miasma (tendency or disposition for infection).

b. **Clinical homeopathy or Organotrophic homeopathy:**
Remedy will be chosen due to the symptoms of single organs.

c. **Complex homeopathy or Combined-remedies-homeopathy:**
Foregoes the holistic approach – different ingredients for the disease and its symptoms will be combined. Often used for livestock, because of the lack of information about symptoms and the modalities of every single animal.

***Lege artis*:** means according to the law of the medical art or state of the art. It denotes that a certain intervention or procedure is performed in a best known way.

**Nosodes:** The nosodes, which are studied as miasmic conditions, come from diseased matter and are given in a very minimal dose, mainly in ultra-high potency. They are used, in general, for the protective treatment of a group of animals. The nosodes used in homeopathy may be considered a type of isopathy. The difference between nosode and isopathy is that the nosode remedy does not come from the individual to whom it is given. In this way, it conforms to the 'similar' principle. Thus, it is not 'exactly' from the individual's own tissue or cells, but comes from someone who had a similar illness.

**Symptom picture/ Remedy picture:** Each animal shows symptoms of the body, behaviour and mood when it is sick. Some of these symptoms are common to the disease, others are characteristic of that animal in its sickness. The homeopathic practitioner matches the remedy picture (=symptom picture of the homeopathic remedy, meaning all symptoms caused in a healthy animal by the certain remedy) to the symptom picture of the animal, with particular attention paid to those symptoms which are unique to the individual, to choose the appropriate remedy for treatment.

**Syndrome:** A syndrome is a set of medical signs and symptoms that are correlated with each other and, often, with a specific disease. This disease can be caused by different pathogens.

**Randomized Controlled Trials (RCT):** is a specific type of scientific experiment and the gold standard for a clinical trial. RCTs are often used to test the efficacy or effectiveness of various types of medical intervention within a patient population. Randomization means that study subjects (before the studied intervention begins) are randomly allocated to receive one or other alternative treatments. After randomization, the two (or more) groups of subjects are followed in exactly the same way, except using different treatments. The most important purpose of proper randomization is to minimize allocation bias, and to balance known and unknown prognostic factors in the assignment of treatments. Additionally, control groups are included in Randomized-Controlled-Trials to minimize the effects of variables other than the single independent variable. This increases the results' reliability often through a comparison between the control measurements and the other measurements. Control-Groups like a group treated with a placebo, a conventional drug or a group without a treatment are performed parallel to the experimental group (e.g. treated with a homeopathic drug).

**Withdrawal time:** is the time required after administration of a veterinary drug to any food animal to assure that drug residues in the marketable food (e.g. milk, meat, eggs) is below a determined residue limit.

## 1.3 Objectives of the workshop on homeopathy

The previously elaborated “Report on research projects in the field of homeopathy, cooperation between research bodies and initiatives to reduce use of antibiotics by using homeopathic remedies (Review)” captured mainly published research results and revealed a wide variation in the studies and outcome for efficacy. Although half of the studies showed an efficacy of the applied homeopathic remedy, a general conclusion, that homeopathy is effective, could not be drawn. Many studies showed weak points in the study design. The individualized treatment procedure of homeopathy was often not applied and no trial was replicated with the same species, disease and remedy. For a differentiated and comprehensive overview on an appropriate research and use of homeopathy a workshop was arranged to receive feedback and comments on the previously delivered review. Therefore experts with different expertise and varying positions on the use of homeopathy were invited. The intention was to draw a comprehensive picture of the topic by taking into account different perspectives from veterinary science and practice. Recruiting expertise in various disciplines was expected to ensure an intensive exchange and discussion, based on the review.

Moreover, the workshop was organized and structured in order to identify important aspects in the complexity of the area and to raise matters not yet considered in the review but needing to be addressed in the future. The review also formed the basis for a discussion on the weaknesses of the previously identified studies, about factors influencing the efficacy of homeopathy in practice and about how future studies could be optimized.

At the end of the workshop, the experts were also asked to contribute to a list of conclusive suggestions providing a basis for the upcoming final recommendations to the European Commission.

## 1.4 Structure and methodology of the workshop

The participants were selected using a structured search. People were possible participants, if they were educated in veterinary medicine, homeopathy, animal science, animal health and welfare, epidemiology, pharmaceutical legal affairs or research in efficacy of remedies in livestock. At the beginning, a list of 54 possible participants was collected accompanied by information about their education, specific expertise, their publications, contact data and (if accessible) their position on


**Figure 1: Overview on the WP9.3 process.**

homeopathy. Ultimately, a well-balanced and heterogeneous group of 12 people was selected, regarding their specification, expertise and position. The invitations were sent out in restricted numbers and with sufficient time to answer.

The replies which followed determined further new candidates to be invited according to which expertise and position (on homeopathy) was lacking within the group already formed.

A total of 22 invitations were sent out to receive the 12 positive answers required for participation in the workshop. The twelve participants were from different European countries (Great Britain, Germany, Spain, Switzerland, the Netherlands and Denmark), representing different fields of expertise (veterinary medicine, biology, physiology, epidemiology, pharmacology, animal health and welfare, pharmaceutical regulatory affairs, evidence-based medicine, herd health management). The majority of the participants were veterinarians and were previously or currently active in research, teaching or regulatory issues. Half of them presently work or had worked with large animals (mainly cattle) on a practical level. Five experts were specifically educated in homeopathy and three had an interest in homeopathy, but only five of them clearly promoted the use of homeopathy. Nearly all experts expressed their intention to participate in the workshop due to the need for a reduction in antibiotic consumption, the need to find alternative treatments and to improve animal health. Due to a confidentiality policy, none of the experts knew who else was joining the workshop beforehand.

The workshop was developed and guided by a professional moderator, with a scientific background in chemistry and health care and experienced in conflict mediation. It took place in Germany, near Frankfurt and lasted one day from 9 a.m. to 5 p.m.

The research group responsible for the review was present during the workshop, but had a silent, observational role in order not to influence the experts. This meant no interaction with the experts during the workshop, except during a presentation which provided a short summary of the review's results at the beginning (Session 1, see figure 2 below) and for an intervention at the end of the workshop (Session 4) to answer questions which occurred and to support the debate. The moderator introduced the different topics using flipcharts, collected attributes and opinions of each expert with moderation cards and supported the dialogue between the experts. The flipcharts were also used actively during the discussions. After the workshop, photographs of all charts were taken and used as a protocol of the discussions in combination with the researcher's notes. In addition, audio was recorded as a reference and in case clarification was required during the writing up process.

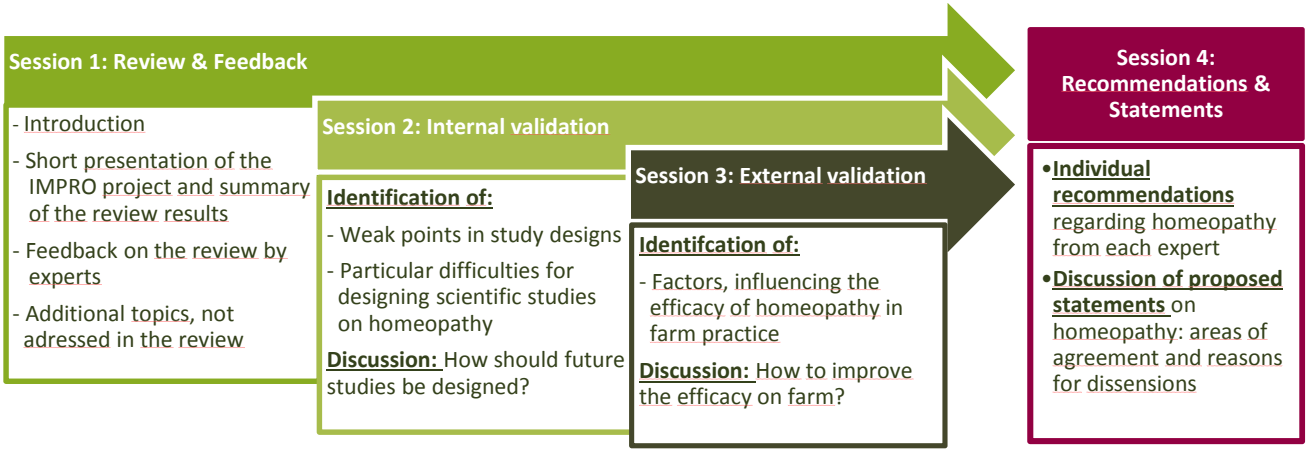


**Figure 2: Agenda for the workshop sessions.**

The first session of the workshop opened with a brief presentation providing an overview of the IMPRO project, followed by a short summary of the main results of the review, which all experts had received in good time via e-mail before the workshop. Afterwards, the experts were able to ask questions on the content as well as the methodology of the review. Subsequently, the moderator asked the experts to rank the results from the review between “in line with their expectations” and “a complete surprise”. One after another, each expert stated his/her thoughts and opinion. The main aspects were written on the board. Feedback and critique regarding the review were gathered and discussed by the group.

The focus of the second session was how studies on homeopathy could be designed and improved to provide a valid assessment of efficacy. This was done by means of a free discussion on the question: “What exactly is the problem in existing studies?” and “What has to be altered in future studies to provide possible evidence for the efficacy of homeopathy?” Gaps in the current studies of the review and requirements and possibilities for future studies were identified and discussed.

In the third session, factors which influence the effectiveness of homeopathy were discussed and explored through an open discussion on the topic “Healing progress and success” employing the questions: “What exactly is the problem with the influencing factors?” and “How to prove the evidence despite this multifaceted situation?” In addition, participants were asked in which fields they saw options and limitations for homeopathy.

In the final session, the experts came up with ideas on their own, based on the discussions from the previous sessions on how the EU-commission should proceed on the topic of research and the use of homeopathy in farm animals. A particular focus was on the need to reduce antibiotic consumption. When adding suggestions to the boards, the experts were asked to explain their arguments and opinions. Ultimately, the contributions were discussed by the whole group. After formulating their views, the experts were confronted with four statements, previously formulated by the IMPRO team, regarding the use of homeopathy. They were asked to individually rank their degree of agreement with the statements on a five point Likert scale from strong agreement to strong disagreement. After this, the group discussed the results and formed opinions on the different statements.

The coordinator of the IMPRO-project then joined the discussion. This was due to a certain amount of confusion and discussion which arose over specific wording and meanings of single statements. On the one hand the coordinator had stepped in to answer questions regarding comprehension, but on the other, he wanted to pose individual experts provocative questions, in order to stimulate the debate and to challenge the validity of arguments previously mentioned.

The workshop ended with a feedback round. Participants were asked whether the workshop and discussions had been a fruitful or worthwhile experience and what should have been added, altered or done differently. This helped the researchers and moderator to validate their methods and improve the workshop on phytotherapy that took place the next day.

### 1.5 Feedback on the report

The feedback provided by the experts regarding the review was generally positive. It was appreciated that the review encompassed a comprehensive overview of the current state of the efficacy of homeopathy for farm animals. The results of the review were in line with nearly all the experts' expectations (10 out of 12, see Annex part A). One expert did not expect the high numbers

of studies which showed that the homeopathic remedy applied under the specific study conditions had had an effect.

Although the results were generally expected, the participants were surprised when they realised the current extent that homeopathy is practised on farms in various European countries. It was concluded that this requires further attention and justifies further research funding.

The few critical remarks referred mainly to the selection process (e.g. time span, study design, type of remedies, type of treatment groups) for the studies evaluated for the review.

Deficiencies in the methodology were seen in the inclusion of studies that monitored remedies with combined active ingredients (complex remedies) together with studies only using single ingredient remedies. Single ingredient remedies are usually applied in classical homeopathic treatment. Additionally, it was mentioned, that the distinction between studies with treatment on herd level and studies that focused on treatment on an individual level was not clear enough.

Looking at the study design, two participants pointed out that only Randomized-Controlled-Trials (RCT) should have been considered in the review or at least separated out for the evaluation, as this would have altered the review outcome. However, no explanations were given as to how this could have modified the outcome. On the other hand, four participants saw weaknesses in an RCT-design and difficulties especially when individualized homeopathy was applied. However, many others thought RCT was the only way; being the “gold standard” for providing evidence of the efficacy of any remedy. Two experts saw the need for a deeper assessment of study quality by considering sample size within the groups.

Concerning the question whether homeopathy might be an aid to the reduction or replacement of antibiotics, one participant felt that only studies comparing allopathic with homeopathic remedies should have been included in the review. According to the participant, such studies should consider organic as well as conventional housing conditions as this might have a high impact on study efficacy. Another participant found that the chosen time span for the considered studies was too long and that older studies should have been excluded as they represented earlier, outdated knowledge of homeopathy; the discipline has developed since then. Some participants felt that there was a lack of crucial conclusions and clear recommendations for the use of homeopathy at the end of the review. Issues were raised about the meaning of the term “preconditions” which was seen as an inappropriate English term. The resulting discussions recommended using the term “conditions”. Furthermore, the term “homeopathic remedies” should have been rephrased as “homeopathy” only, because a homeopathic remedy is always applied in a homeopathic procedure.

***Conclusions on the feedback***

In the experts' view, the results of the review supported previous findings in scientific publications. It showed the need to optimize study designs and its results should be used to improve the currently unsatisfying situation regarding scientific evidence of homeopathic efficacy. The experts confirmed the poor quality of many study designs and ways in which previous experiments were implemented. Experts in the area of homeopathy emphasized particularly that very few studies applied individualized treatments; considered as one of the basic principles of homeopathy. All participants supported the review' conclusion that due to high variability in the study's design, the results of previous studies lacked potential to be replicated. Thus, general statements and conclusions in relation to the efficacy of homeopathy are currently not scientifically valid and should not be drawn.

## 1.6 Internal validation of homeopathy

### *How to optimise the study design*

One of many reasons for the inability to provide a clear answer to the question, 'if and under what conditions is homeopathy effective, was shortcomings in the study design. The review found several weak points within existing studies. The participants pointed out the lack of sufficient description and records of the conditions under which the trials took place in particular. Moreover the concept of individualized homeopathy was not always applied appropriately. Consequently, a general need for an improvement of the study design to assess efficacy of homeopathy was seen by the majority of the group. A wide range of suggestions to improve current study designs were gathered from all experts in a group discussion.

It was generally agreed that, when designing a study on efficacy, a clear definition of in- and exclusion criteria has to be formulated for each study. Referring to this, two experts remarked that homeopathy is inappropriate for therapeutic use when the immune system is not able to respond and react adequately and that this has to be considered. The question of which inclusion and exclusion criteria might be appropriate was point of a longer discussion. Some experts saw a problem in one trial where homeopathic symptom pictures were matched with a conventional diagnosis. Others did not see a problem at all, though after finding a homeopathic symptom picture, the making of a conventional diagnosis or the identification of a syndrome like mastitis was seen as be broad enough to fit both concepts.

It was also discussed that various outcome parameters for determining a therapeutic effect were found in the studies reviewed; something that may have led to different results. Accordingly, outcome parameters for a therapeutic effect should be oriented around scientifically recognized, objective diagnostic methods. As a consequence, a definition of common criteria for efficacy regarding the healing process - initiated or supported by a remedy or treatment - was demanded. One participant pointed out that a “Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances” already exists, provided by the European Medicines Agency (EMA, 2012) and that it could also serve as a base in the case of homeopathy.

The experts considered an effect as valid, when the tested remedy was superior to a placebo or no worse than a standard antibiotic treatment. One expert disagreed about this statement, as for some diseases antibiotics are no longer a successful therapeutic option, due to increased bacterial resistance and the lack of sensibility tests within the trials. Only a well-chosen antibiotic (after susceptibility testing) and an untreated group as a control would provide a scientific base for delivering unbiased results.

Similar to the RCT-standard, a random assignment of test subjects to different groups and a comparison with one or more control groups e.g. placebo, antibiotic and an untreated group were demanded by the majority of experts. An opposing argument was that RCT is not applicable in real-life cases and for real patients not suffering from one disease exclusively – a pragmatic trial should be performed under farm conditions. The use of standardised protocols would allow a repetition and comparison of analogue trials under different conditions, and would provide a base for assessing replicability and more valid conclusions about the efficacy of a remedy or procedure in farm practice. Future studies should also include documentation of the specific context and conditions in which the remedies were used (e.g. housing conditions, production form, geographic location etc.). Side effects, which arise, whether positive (e.g. improved hygiene, increased sensitivity to changes in animal behaviour) or negative (e.g. prolonged disease or treatment duration due to animal welfare

aspects) should be recorded and published as well. Animal welfare aspects were only marginally touched upon, but it was agreed that a change in treatment or exit criteria would prevent prolonged suffering of animals.

Finally, it was concluded that an improved RCT design adapted to homeopathy can be applied to test the efficacy of homeopathy. An added benefit in the implementation of an RCT design might be that it is more likely to be published by peer-reviewing scientific journals than any other type of study design; as experienced/reported by one expert. The question of blinding - and how this could be performed - was raised briefly and was concluded to be possible when animals were randomly assigned to different treatment groups by a trial instructor after a homeopathic expert had chosen the appropriate homeopathic remedy.

The fact that not a single homeopathic remedy was tested more than once on the same species or the same indication makes a comparison within a meta-analysis impossible. Accordingly, it was proposed to replicate analogue trials with “candidate remedies”, which showed homeopathic efficacy, with a different research group under different conditions. The question was, whether the results of previous trials could be repeated and confirmed.

Another very specific problem, addressed by the participants with a homeopathic background was that homeopathic remedies were applied to conventionally diagnosed animals in most of the studies. However, when aiming to test the efficacy of a homeopathic remedy, it should be applied within an individualized homeopathic procedure. This involves a comprehensive anamnesis and clinical examination to define an individual symptom picture for each animal. In the end, this usually leads to a different single remedy for each individual, although all of them might suffer from the same disease by conventional definition. When dealing with individualized homeopathy, it has to be taken into account that an experimental design including randomization and grouping is difficult to apply. Considerations were given to test the efficacy of the homeopathic treatment itself rather than only testing a certain homeopathic remedy or a specific dilution.

One expert pointed out, that there might be a risk of transmission of homeopathic information between animals and between the remedies stored at the same place. This was supported by personal experience of two other participants using homeopathy. As this cannot be completely ruled out at the moment with a still unconfirmed homeopathic mode of action, a complete and reliable separation of the animal groups and also of the remedies might minimize undesired effects and improve the scientific quality of the trial.

An additional aspect raised in the discussion was of a possible study design for nosodes that were usually applied on herd or group level for prevention or metaphylaxis of a disease. It was proposed that criteria from conventional vaccine studies might be appropriate and used for prevention studies with homeopathic nosodes. One prerequisite for a repetition of trials and successful preventive treatment is that the source of the nosode has to be known. It can be herd specific, local or generic. According to the experts, nosodes prepared from an own farm sample (herd specific) or at least from a local farm sample were definitely preferred, leaving the last choice to generics of a sample from animals showing similar symptoms. Availability can be an obstacle for commercial marketing if no company or pharmacy is able to prepare a farm specific nosode in an appropriate period of time. The fact that the production of herd-specific nosodes cannot be easily marketed commercially is expected to lead to low interest from manufacturing companies.

***Conclusions for internal validation***

It became clear that there is ample room for improvements regarding the previous study designs in order to achieve a valid assessment of the efficacy of a homeopathic remedy. In the future, an appropriate study design should include clearly defined in- and exclusion criteria, criteria for efficacy, a standardized protocol and the indispensable individualized homeopathic treatment procedure. The study design should be based on a Randomized-Controlled-Trial design adapted to the needs of a homeopathic treatment procedure. This is a prerequisite for avoiding possible bias and also for receiving recognition in the scientific world.

But how widely applicable will those future results be? To draw any possible conclusion about the efficacy of a homeopathic remedy in farm practice, it has also to be tested under various conditions (external validation). Only this will enable the user to make a prudent prognosis of the healing effect when using homeopathy within a specific farm situation.

## 1.7 External validation of homeopathy

### 1.7.1 Factors influencing the efficacy of a homeopathic treatment in farming practice

In the workshop participants' view, a relevant factor affecting the efficacy of homeopathy negatively is the lack of expertise in homeopathy under farm conditions. Currently, many livestock are treated with homeopathic remedies by lay people (farmers, animal healers, and veterinarians without a homeopathic education). This arises from an insufficient availability and quality of homeopathy courses. Even if courses are available, the uptake (especially by veterinarians) was seen as very low. The situation might be the result of poor quality standards in the courses, but it is thought to be even more due to the low public acceptance of homeopathy and the dark corner homeopathy still stands in.

The presence of different national legislation rules in European countries regarding homeopathy in livestock farming was experienced as confusing and contradictory by the participants. It leads to different availabilities and use of homeopathy on farms in the different member states. Although a simplified registration procedure exists for homeopathic veterinary products (Directive 2004/28/EC) companies do not make use of it to register their homeopathic remedies for livestock/animals on a national or a European level or only for certain countries. Whether the investment of money (e.g. registration fees) is avoided by companies due to the small market or whether this is due to restrictive national regulations for the use of homeopathy remains speculative. Additionally, the cascade regulation (that allows veterinarians to prescribe medicine authorized for another species or condition or authorized in another European country when no suitable product is available) enables the use of human homeopathic products in animals. Often they are bought directly over the counter and fill comparably simple and cheap possible gaps in availability.

All participants agreed, that the primary or contributing causes of diseases e.g. poor hygiene, inappropriate feeding, bad management and ill-fitting housing conditions are often not shut down on farms and have the biggest impact on the animal health status of the herds and of every single animal. Homeopathy is not able in any way to compensate for these inappropriate conditions. On the other hand, the efficacy of a remedy can be substantially suppressed by it.

The participants also discussed the possible influence of the remedies itself. One expert saw a need for retesting homeopathic symptom pictures (symptoms the remedy could cure) and remedy pictures (symptoms evolving, when the remedy or its active ingredient is given to a healthy animal) to fit the treated species. This opinion was not shared by other participants, who saw the main need

for a further improvement in the prescription procedure and the expertise of the prescriber. Others saw the remedy pictures as not being fixed. To them it was not important whether they were tested on humans or on animals. Also the quality of the remedy was of concern as it can be reduced by inappropriate transport or storage.

Many participants saw a lot of options for the use of homeopathic remedies, especially the opportunity to treat diseases causing financial losses (that were usually not treated at all) with relatively cheap remedies without residues in the environment or in food. The remedies were easy to apply when given orally via drinking water or applied to the (oral, nasal, vaginal) mucosa. The restriction of antibiotic use and the prolonged withdrawal time according to the organic livestock production legislation, as well as the prohibition of a preventive use of antibiotics in Europe, may promote the use of homeopathy.

The discussion on possible limitations concerning the appropriate use of homeopathy consumed a longer period of time. Depending on previous exposure to pathogens and development of the immune competence, every individual should be examined thoroughly on its ability to react and respond to a certain homeopathic treatment. High yielding cows, young calves, and animals under stress in general, were seen as disadvantaged in this context. Another obstacle to the use of homeopathy was seen by one expert as the additional amount of time and effort the use of homeopathy may require, e.g. when used at big commercial farms. The majority shared the opinion that homeopathy should not be used in contagious outbreaks of (compulsorily notifiable) diseases. Those two limitations were not shared by one expert in homeopathy.

### 1.7.2 Future steps to improve the efficacy of homeopathy in practice

1. ***Improve knowledge:*** The participants shared the opinion that to ensure the effectiveness of homeopathy on farms, homeopathic remedies should only be employed under the responsibility of a person with expertise in homeopathic remedy pictures for the species being treated. The development of a consistent European standard diploma course on homeopathy in livestock - including animal health, farm management and all species specific topics - might improve the quality of education. Supervision of treatment by veterinarians with a homeopathic education and use of homeopathy by trained farmers would support “good homeopathic practice”-standards on the farms.
2. ***Support research considering homeopathic individualization:*** Acceptance of homeopathy by veterinarians and by public can only be improved when research shows that homeopathy is effective. To deal with animal welfare concerns regarding unsuccessful treatments and subsequent extended suffering of diseased animals, options for a successful treatment with homeopathic remedies have to be proven by evidence. Therefore, the suggestion most frequently given by the participants was to establish monitoring concepts for the success of treatments. Furthermore, research in homeopathy in promising fields should be supported by funding. Future trials have to be designed by researchers and homeopaths and should be able to be adapted to real-life on farm patients. The repetition of studies with a positive outcome on the efficacy of homeopathy was suggested. Research networks should be implemented respecting knowledge transfer between science and practice.
3. ***Provide a centralized registration:*** A transparent legislation for all European countries on the use of homeopathy, and one centralized registration valid for all member states, could improve the availability of high quality homeopathic remedies. In member states where

veterinarians are only permitted to prescribe remedies that are registered for veterinary use and which encompass an indication, the use of homeopathy is left to the farmer. A centralized registration of homeopathic remedies could broaden the market for manufacturing companies and offer new options for prescription and use of homeopathic remedies by veterinarians.

4. ***Ensure correct handling of the remedies:*** Homeopathic remedies should be of controlled quality and correctly transported and stored. Every homeopathic remedy should give advice on correct transport and storage of the remedy on the label and on the package leaflet.
5. ***Establish monitoring of treatments and animal health:*** Accompanying measures for homeopathic treatment should include regular checks of housing, hygiene, management and feeding conditions. Animal health and the success of any treatment should be monitored and controlled regularly by the farmer and the local veterinarian. Valid criteria for defining and measuring animal health and for monitoring prevalence and incidence of diseases should be specified.

### 1.7.3 Statements for future use of homeopathy in farm practice

In order to receive feedback from the participants on preliminary conclusions drawn by the IMPRO team regarding the future use of homeopathy in farm practice, the following statements were presented by individual sheets. The answers provided were gathered and presented on a flipchart for further discussion. Possible reasons for disagreement were further discussed where such cases occurred.

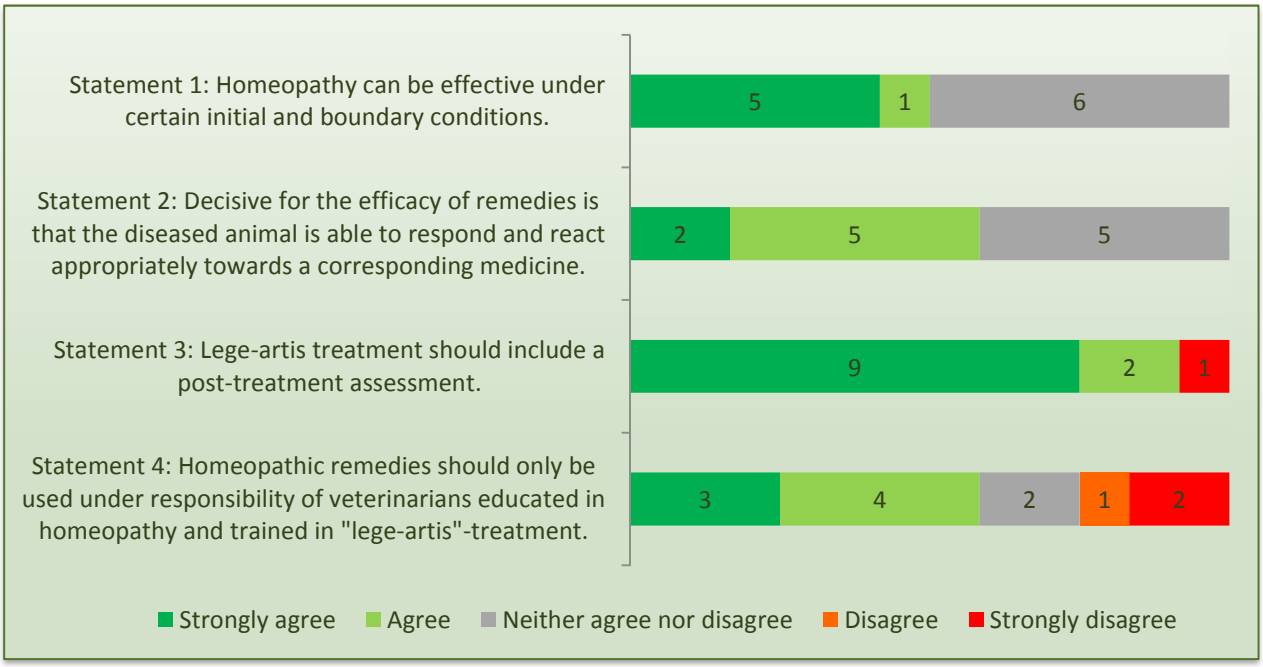


**Figure 3: Level of agreement by the 12 experts with the presented statements.**

***Statement 1: "Homeopathy can be effective under certain initial and boundary conditions (regarding the interaction between animal, remedy and the environment)".***

Half of the participants agreed with the statement while the others neither agreed nor disagreed. The inconclusive answers were on the one hand due to the uncertainty, if homeopathy is effective at all and on the other hand due to the wording. A misunderstanding emerged from the term "initial and boundary conditions". Also the term "interaction between animal, remedy and the environment"

caused some uncertainties. The statement was experienced as too complex and the participants proposed to reformulate it as “Homeopathy can be effective under certain conditions.”

***Statement 2: “Decisive for efficacy of remedies is that the diseased animal is able to respond and react appropriately towards a corresponding medicine.”***

Seven experts agreed that it is decisive for the efficacy of a remedy whether the animal is able to respond and react to it – five neither agreed nor disagreed. No further discussion followed, due extended discussions about other statements and the limited amount of time.

***Statement 3: “Evidence of efficacy can only be proven after a post- treatment assessment of the animal's health status as part of a “lege artis” treatment.”***

The meaning of the third statement caused a lot of discussion. After an explanation of the statement by one of the project researchers, the statement was changed to “*Lege artis* treatment includes a post-treatment assessment”. With the exception of one participant, it was agreed, that *lege artis* treatment should always include a post-treatment assessment. This should not be restricted to homeopathy, but was seen as necessary for all treatments. The remaining expert disagreed, because the wording “proven” was interpreted as if the treatment success could be proven by single case documentation and that the effect measured after a treatment might be caused by a variable other than the homeopathic remedy. The participant also explained that evidence for efficacy has to be proven first and then documentation and monitoring of treatment can be done. The reply by another participant was that documentation of post-treatment assessment is always needed for the learning it provides; even if a treatment fails, the farmer and veterinarian can still learn from it. Current European regulation recommends the use of alternative treatment on organic farms if their therapeutic effect is effective for the species of animal, and the condition for which the treatment is intended. However, an assessment and a documentation of results are not regularly implemented in farm practice. Therefore, the on-farm monitoring of the therapeutic effects was regarded as essential by the majority of the participants.

***Statement 4: “Homeopathic remedies should only be used under the responsibility of veterinarians educated in homeopathy and trained in “lege artis” treatment.”***

The fourth statement caused the most extensive discussion. Seven experts agreed that homeopathic remedies should only be employed under the responsibility of a veterinarian educated in homeopathy and trained in *lege artis* treatment. Two experts were inconclusive on this statement and three disagreed (two strongly). The disagreement mainly concerned the concept of leaving the final responsibility exclusively in the hands of a veterinarian. The opponents argued that non-veterinarians, especially farmers, were also able to recognize symptoms in their animals and to select and apply homeopathic remedies to them after homeopathic training. Another positive aspect seen by three experts was that farmers can act immediately, when symptoms first arise in their animals and start the homeopathic therapy without the risk of prolonged suffering. Treatment by the farmer alone should only be undertaken in “easy, acute cases”. In contrast, it was admitted, that there is no external control of use and appropriateness of the treatment, if the farmer takes the full responsibility alone. It was severely doubted that the farmer would be educated enough in diseases diagnosis to be able to decide what the best treatment for his animal and consumer’s protection might be. Who is most qualified to decide whether the animal has received the best treatment option for the healing process - and to reduce suffering if not the veterinarian?

The IMPRO researcher stressed the fact that with constant high (and even increasing) prevalence of production diseases on the farms, the current system is apparently not working sufficiently, and satisfactorily. No quality assurance and documentation is currently established at farms regarding

the treatment outcome. The responsibility, when dealing with food-producing animals and animal welfare, should not only rest on the farmer. This was supported by one expert especially, who saw a conflict in giving the responsibility to a person (the farmer) who is economically forced to keep the costs low by spending less money on each case. There is a need for external supervision for all treatments in view of food safety, antimicrobial resistance and animal welfare.

Another expert saw a maximum benefit, when the farmers were trained in homeopathy for a limited range of cases and first aid therapy and knew when to seek the advice of a veterinarian. The involvement of the veterinarian would depend on how well the farmer is trained. It was feared that adhering to the statement would shut down a future avenue for homeopathy in farm animals. It was proposed to change the statement to “Homeopathic remedies should be used under the supervision of a veterinarian and well-educated farmers” and “Farmers are only allowed to treat, what they are trained upon”.

For some member states (e.g. Denmark), it would not be possible to use homeopathy in livestock, if the prescription were to be restricted to veterinarians, because they are only allowed to prescribe remedies that are registered for veterinary use and imply an indication. This kind of registration, especially combined with an indication, is actually not given for the majority of homeopathic remedies. Nevertheless, if the vets are not allowed to use homeopathy, they still would be able to assess the potential success of the treatment and monitor the outcome. The use of homeopathy on the farm could be supervised by regular checks and could also include the provision of some homeopathic or other remedies that the farmer can use under previously agreed conditions.

Finally, no common agreement could be reached on this statement, but a monitoring of treatments by a veterinarian was supported by all participants. Furthermore, it was added that the animal's health status should be monitored at the same time.

***Conclusions for external validation***

It can be concluded, that expertise in homeopathy was seen as crucial by all participants. The use of homeopathy in food-producing animals should only be carried out under the supervision of a person with expertise in homeopathy. Simultaneously, the recovery process of the treated animals has to be assessed and monitored. Expertise should be promoted using education courses with a defined quality standard for veterinarians and farmers. Farmers (and their veterinarians) should regularly document the post-treatment assessment (both with conventional and alternative medicine) to monitor the course of treatments and the herd health status. The veterinarian should provide an external supervision for the success of treatments and herd health. Additionally, a control of good husbandry practice in housing, feeding, hygiene and management has to be established in the form of regular checks. Every increase in the incidence of diseases should lead to an investigation on the farm regarding the possible causes.

The participants of the workshop also recommended the support of research combining internal and external validation: Stakeholder e.g. farmers and their veterinarians should be able to identify and ask important (research) questions, the researcher would acquire the required knowledge using trials with an appropriate study design and would evaluate scientific results, while the stakeholder e.g. practitioner would apply and assess the results on the farms by monitoring and reporting them back. This would correspond with the 5 steps according to the cycle of evidence-based veterinary medicine: Ask, Acquire, Appraise, Apply and Assess (Dean, 2014).

## 1.8 Discussion

***Feedback on the review***

The feedback and review discussions raised several questions regarding an appropriate selection of studies and the selection of variables to be evaluated in detail. A longer debate about the study design took place with further queries on whether Randomized Controlled Trial (RCT) is an appropriate design for homeopathic remedies and their treatment approach. It was hypothesised, that the review results regarding efficacy would have been different if only RCT-studies had been considered. The review found and evaluated 46 studies with RCT design and 14 studies designed as observational studies. This means 77% of all evaluated studies in the review were performed as RCT. A renewed examination with exclusion of all observational studies verified that the result hardly would have differed from the original review outcome. A comparison of the outcome regarding the efficacy – on the one hand including all studies and on the other only including studies with RCT design, only differed by one percent.

Although RCTs are currently considered as the gold standard for evaluating the efficacy of a remedy, they cannot replace the need for an external validation. This is due to the fact that results from RCTs cannot be applied in a variable context or real-life situations in farm practice. In turn, well-designed observational studies can fill the gap between experimental and farm conditions, but may be influenced (e.g.) by the observer and/or by an uneven distribution of group members. In the absence of a “perfect study design” for evidence of the efficacy of a homeopathic remedy and the required individualized treatment procedure, all studies which met the applied criteria were chosen for the review. This therefore provided the opportunity to compare different study designs.

The timespan of the considered studies was deemed to be too wide by one expert. It is true that this time-frame was arbitrarily selected, to fit with the results from a free search through publications, their publication year and the time period for changed production conditions. A reduction to a shorter timespan would not have resulted in a different outcome. The period of time selected provided an opportunity to supply a comprehensive overview of studies available, which met the selection criteria. Furthermore, we would not have been able to make the important conclusion that, at this stage, not one homeopathic trial has been repeated in a similar way.

The review focused on studies which applied homeopathic remedies with a therapeutic, metaphylactic or preventive purpose. A separate evaluation of the studies was done regarding this purpose of application. The majority of preventative studies in the review applied the remedy on herd level e.g. using drinking water as is also usually done with metaphylactic antimicrobial treatments on herd level. This was the reason that treatment on both individual level and herd level were considered for the review.

The proposal to only consider studies that compared conventionally treated groups with homeopathically treated groups would have let to a 63% reduction in studies available. However, the aim was to answer the question whether homeopathy can be effective and if it could be used to replace or reduce antibiotics in any way. Without considering placebo or untreated groups (and apart from a conventionally treated group), the influence of a so-called self-healing effect or wishful thinking by the observer regarding the outcome could not have been discarded.

It was not possible to compare studies with animals housed under conventional conditions to studies with organic conditions (as one expert suggested) due to the absence of this information in most of the studies. Such a comparison also ignores the fact that, in the case of dairy cows, housing

conditions even vary within one production method; not just because one farm is organic and the other is not.

Homeopathic remedies containing single active ingredients and multiple ingredients were included in the study due to the availability of both types of remedies on the market and the opportunity to detect possible differences in the study outcome when evaluating them.

The sample size of test subjects was not captured within the data extraction in the review and might have made the information in the single studies more detailed. Nevertheless, the general results of the review would have been the same.

Some experts felt that crucial conclusions on the efficacy and recommendations regarding the use of homeopathy were missing in the review. This is understandable as there was a common wish to conclude with a clear and general statement on the evidence of homeopathic efficacy and under which conditions it should be applied. However, conclusions could only be based on the results obtained from an evaluation of existing studies and the information provided by them. Due to the high variability of the studies, resulting in lack of replicability and prognostic validity, formulating general conclusions risk to become too speculative. On the other hand, we restricted ourselves to some degree in view of the following workshop to come in order to leave more room for the experts to develop their own conclusions.

## 1.9 Reflection on the workshop approach by the IMPRO researcher

In general, the workshop approach was felt to be very valuable by the IMPRO team. At the very beginning, it was clear that the development and results of the workshop would always very much depend on the selection of participants present. Therefore, participants were very carefully chosen with a wide distribution of expertise and position upon homeopathy in order to receive a broad range of perspectives in the workshop.

In the discussions, it seemed the participants, with their specific knowledge and opinions, were be (consciously or unconsciously) directed by their own interests and favouring a particular position. In addition, when mixing a group of strangers, different personality types behave in different ways and may clash; influencing or determining the discussion to a greater or lesser extent. Taking all this into account, it was reasonable that not much common interest in the group was assessed.

The moderator lacked a background in the topic, which ensured neutrality when thoughts and feelings of all participants on the material were being induced from them. At the same time, however, she had the scientific background required to understand the language used by the experts and in order to interpret their statements. The IMPRO-team met and discussed with the moderator before the workshop in order to prepare it and clarify the aim.

The project team and the moderator sometimes experienced resistance from the participants. From time to time, the discussion got stuck without developing further, when some participants adhered to a single aspect or were reluctant to answer questions or statements directly. It has to be taken into account that results from the review or the discussions might have intervened with their own perspectives.

Although the moderator emphasized that there was no need for agreement, some participants struggled to accept other opinions within the discussions and the moderator had to intervene several times. The IMPRO-team was able to process different positions, but the above

disagreements reduced the chance of ending up with common conclusions from the targeted discussions.

The face-to face discussions allowed a direct interaction and every individual opinion could be heard. However, participants tended to present potentially controversial statements in a more round-about way to the group in order to avoid confrontation with known people or a person that they might meet again.

To help draw a more precise picture of every individual opinion and consider the personality of each participant, influencing the later workshop discussions, individual interviews with each participant could have been performed. However, his additional step was not part of the workshop's scope.

As one day is not enough time to create a team, building a consensus was not the workshop's purpose. This lack of time was also perceived by the participants at the end of the workshop. The given time-frame was experienced as being too short, especially due to the complexity of the topic. More time would have helped participants come up with common solutions and to develop recommendations further.

The project researcher's passivity was criticized by some participants. Interacting with the research team would have influenced the discussion, but could have helped answer some important questions.

During the workshop, there were some linguistic misunderstandings. Words like “preconditions” or “initial and boundary conditions” caused comprehension issues for native speakers. A clear definition of these terms might have improved shared understanding between the participants. On the other hand, discussions about the meaning of relevant terms were supportive for the clarification process. Certain misunderstandings cannot be prevented when people from different countries meet.

### *Internal validation*

In the discussion on study design, the participants touched on plenty of aspects and nearly got lost in details, so that the moderator had trouble refocussing the group back to direct answers. However, these various aspects, addressed from different perspectives, were helpful as the IMPRO team could gain an even more comprehensive understanding of the issue.

### *External validation*

Asking “What exactly is the problem with the influencing factors?” and “How to proof evidence despite the multifactorial and heterogeneous situation in farm practice?” may not have been the best way to address influencing factors. Those questions opened a wide field for possible answers and discussion. A more targeted question might have led to a different outcome.

Asking for “options and limitations” cannot be regarded as successful/expedient at the workshop. In the discussion on it, the participants experienced problems and concluded that the topic didn’t fit well into those categories. It was emphasized that homeopathy follows a different approach in strengthening the immune system (indirect effect) whilst conventional medicine addresses the pathogen (direct effect). They felt that they had only theorized about options and limitations in the absence of proven research evidence for the efficacy of homeopathy. Nevertheless, the experts were able to identify several important points that could limit or promote the use of homeopathy in livestock.

After presenting all individual suggestions regarding homeopathy on a flipchart, a grouping of the recommendations had been planned. This was skipped due to the small amount of time left at this point. It would have given the participants the opportunity to vote for what they felt the most important recommendations were and could have highlighted them for the project researcher.

The abrupt change from formulating their own recommendations to the task of voting for different statements provided by the IMPRO-team using a Likert scale confused the experts to some degree at the end of the workshop. The statements should have been introduced and discussed earlier to build an understanding and opinion of them. Asking for individuals' opinion on each statement using extra sheets and presenting them later on the board using dots received positive feedback. This was regarded as very valuable by the participants as it sharpened the discussion.

Many statements were not clear or were contentious for the experts, mainly due to specific wordings. The wordings were changed by the moderator whenever possible according to participants' suggestions. Nevertheless, an unplanned intervention by one project researcher was needed to revive the discussion at a point of deadlock and to avoid going round in circles. This was criticized and perceived to some degree as an interruption.

## 1.10 General conclusions

A common drive amongst all workshop participants was the aim of improving animal health by reducing the prevalence of production diseases, and at the same time finding alternatives to reduce the use of antibiotics in food-producing animals. The workshop was perceived as a fruitful chance of exchanging different scientific perspectives on this controversial topic.

In organic livestock production, homeopathy and other alternative remedies should be used in preference to chemically-synthesized allopathic veterinary treatment or antibiotics, provided that their therapeutic effect is effective for the species of animal, and the condition for which the treatment is intended (European Council Regulation 834/2007; Commission Implementing Regulation 889/2008). Due to the fact that the quality of internal validation is low and external validation is generally missing, it is currently not possible to predict the therapeutic effect of a homeopathic remedy in a certain diseased animal case.

It became clear that the efficacy of homeopathy in practice depends on multiple factors e.g. the individualized treatment procedure, expertise of prescriber and user, the remedy, the treated animal, the conditions and the environment it is living in. Not all experts saw the evaluation of these multiple factors as crucial to assess the efficacy of homeopathy and stuck to single aspects e.g. the remedy, tested under *ceteris paribus* assumptions. Even if single randomized controlled trials may provide evidence of efficacy under very specific experimental conditions, they fail to provide a valid prognosis concerning the possible effects of interventions in real-life on farm situations. In farm practice, results gained under specific conditions cannot be extrapolated and directly transferred to quite heterogeneous situations. Thus, general statements that homeopathy is effective for treating animal health conditions is not scientifically sound.

To provide empiric and evidence-based information about the efficacy of a homeopathic treatment and the context in which it is used, documentation and monitoring of single cases (prerequisites, diagnosis, treatment and therapeutic success) by veterinarians and farmers - by making use of a standardised procedure - is required. Only an encompassing retrospective evaluation of monitoring processes can be expected in order to provide reliable results that can be used for prognostic estimations.

# 2 Part B: Report of the workshop on phytotherapy

## 2.1 Abstract

Botanical remedies have been used across the world long before modern pharmaceuticals entered the stage and are still used in many areas with the aim to improve animal health. In the prior review of studies, where phytotherapy was used to treat or prevent disease in food-producing animals', weaknesses of the study designs as well as external factors affecting efficient and evidence-based use of this type of products were identified. The majority of the studies were non-reproducible, often due to poor standardization and information regarding the remedy. The external factors were associated with low availability of approved products. An expert workshop on phytotherapy was conducted to obtain additional information and reveal new perspectives. The purpose was to receive feedback to the previously elaborated review, to find options to improve scientific studies on phytotherapy and to identify influencing factors that have to be addressed in future. Twelve participants from different European countries with expertise in various disciplines were invited to a one-day workshop. The sessions and group discussions were guided by a professional moderator ensuring a comprehensive exchange of expertise.

In general, the workshop discussions supported the results and conclusions of the review and also gave new insights on underlying reasons affecting both the research and the use of phytotherapy. In the discussion on study design, the new possibilities of modern methodologies for establishing adequate levels of standardization were recognized. There was also agreement that studies on phytotherapy can fulfil requirements of scientific studies on pharmaceuticals. However, some adaptations to the nature of phytotherapy need to be performed and the studies should be adapted to the expected efficacy and use of the particular remedy. Knowing what can be expected of the product would enable an effective use without risking suffering in animals due to ineffective treatments. It should be kept in mind that even if some products prevent disease only to a small extent the effect of fewer diseased animals that need antibiotic treatment also leads to an overall lower use of antimicrobials in the end. Development of specific guidelines for standardization of phytotherapeutic products as well as guidelines for studies on prevention of diseases is needed to conduct high quality studies in the future. The discussion also revealed that external factors greatly affect the quality of the studies on phytotherapy as well the number and type of phytotherapeutic products available on the market. Currently the approvals of medicinal phytotherapeutic products are associated with high costs but combined with small profits from sale, possibly discouraging companies from developing these types of products. The necessary requirements of documenting content and standardization also make it difficult to protect and patent the product. Instead there is a drive for selling promising products as feed additives/single feeds with no indication for treatment or prevention of diseases. Thus, there is a need for an alternative way to increase protection of content with remaining control of quality and potentially a new classification that enable easier categorization of "border-line" products including phytotherapeutic remedies used for prevention of disease. Finally experts agreed that efficacy of all treatments, phytotherapeutic to conventional, are affected by many external factors on the farm level. In addition to controlled clinical studies for e.g. dose-finding, there is a need to monitor the use and effects of use in practice. A monitoring system is also necessary to enable epidemiological studies where smaller effects and trends due to increased use of particular substances may be identified.

It can be concluded that the current use as well as the knowledge about the efficacy of phytotherapy is far from satisfactory and acceptable from an animal welfare point of view and that the situation is greatly affected by external factors. Currently, there are no veterinary herbal medicinal products,

leaving farmers and veterinarians to use feed additives and non-registered products mainly based on own experience and associations, to a large extent without scientific and unbiased assessment of efficacy. Improving the knowledge, availability of high quality products with specified content/doses combined with a European monitoring system for production diseases and treatments would significantly improve the prospects of using botanical products in the most effective way as well as for the sake of animal health, welfare and food safety.

## 2.2 Glossary

***Active ingredient:*** Any ingredient/s present in the product, that is/are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body

***Antimicrobial substance:*** A naturally occurring, semi-synthetic or synthetic substance that exhibits antimicrobial activity (kill or inhibit the growth of micro-organisms) at concentrations attainable in vivo. Antiparasitics and substances classed as disinfectants or antiseptics are excluded from this definition (OIE, 2011)

***Metabolomic fingerprint:*** The Organisation for Economic Co-operation and Development refers to metabolomics as a discipline, which "deals with endogenous metabolite profiles of tissues or organs derived from mass spectrometry or nuclear magnetic resonance spectrometry analyses of plasma or homogenates. Metabolic profiling can give an immediate picture of the physiological state of the tissue (EFSA, 2014).

***Metaphylaxis: refers to a use in*** still clinically healthy but likely to be infected due to close contact with diseased animals (EMA, 2012).

***Standardisation***: means adjusting the herbal substance/preparation to a defined content of a constituent or a group of constituents with known therapeutic activity respectively either by adding excipients or by blending batches of the herbal substance and/or herbal preparation (e.g. standardised extracts)(EMA, 2005).

## 2.3 Objectives of the workshop on phytotherapy

The workshop was arranged to receive feedback from different perspectives on the "Report on research projects in the field of phytotherapy, cooperation between research bodies and initiatives to reduce the use of antibiotics by using phytotherapeutic remedies (review)". The intention was to gather different areas of expertise in the context of phytotherapy, practicing veterinarians as well as experts in other areas of veterinary medicine, in order to achieve a comprehensive exchange and discussion based on the review. In addition, the aim was to identify important aspects regarding the complexity of the area as well as future research not considered in the review but in need to be addressed in the future. The review also formed a basis for a discussion about the effects of the weak points in the reviewed studies and how future studies can be optimized. In the end of the workshop, the experts were also asked to contribute to a list of conclusive suggestions to provide a base for the coming final recommendations to the European Commission.

## 2.4 Structure and methodology of the workshop

The structure and debate of the workshop was developed and guided by a professional moderator, also experienced in conflict mediation. It took place in Germany, near Frankfurt and lasted one day from 9 a.m. to 5 p.m. The twelve participants were from different European countries (Great Britain, Germany, Spain, Switzerland, Austria, Sweden, Netherlands and Denmark), representing different fields of expertise (veterinary medicine, veterinary epidemiology, biology, epidemiology, pharmacology, animal health and welfare, pharmaceutical regulatory, evidence-based medicine, herd health management in practice). Approximately half of the participants were active in the field of phytotherapy, the majority representing researchers but also veterinarians practicing

phytotherapy as well as representatives of the industry. The previous experience and contact with phytotherapy varied among the remaining experts. Some had a special interest in the topic while others had little experience prior to reading the review. The experts were selected with the aim to achieve an atmosphere of debate. Representatives of the IMPRO-group discussed which areas of expertise should be included to provide a wide-ranging picture of the topic from different perspectives from the practical and the research world. After this, the group searched for experts in the chosen areas. The evaluation of the expertise of the persons was based on previous publications and experience. When approximately thirty experts had been identified, the IMPRO team discussed the composed list of experts and sent out invitations to twelve experts. If no reply was received a reminder was sent approximately two weeks after the first invitation. If the invited expert declined participation or no answer was received after the reminder had been sent, a new expert covering the missing areas was identified from the list. Invitations were sent until twelve experts had been recruited.

In order not to influence the experts, the research group responsible for the review restricted itself, apart from the introduction and the final session, to an observing role. This meant no interaction with the experts during the workshop except during a presentation of the IMPRO-project, a presentation of the main results of the review in the beginning and the finals session (described below). The moderator introduced the different topics by flipcharts, collected single aspects and opinions of each expert by moderation cards and supported the dialogue between the experts. The flipcharts were used actively during the workshop and filled in during the discussion together with the experts. After the workshop the charts, in combination with the researcher's notes, were used as a protocol. In addition audio recording was collected as a reference and for clarification during the writing process.

The outline of the workshop is illustrated in figure 4. In the first session of the workshop an overview of the IMPRO-project was presented to the experts followed by a short summary of the main results of the review, which all experts received by e-mail before the workshop. Afterwards the experts had the possibility to ask the authors questions on the content as well as methodology of the review. After this presentation the moderator asked them to rank their impression of the results of the review between "in line with their expectations" and "a complete surprise". Each expert was asked to evolve the reason for his/her reaction and the main points were written on the board. Specific feedback and critique on the review was gathered during this discussion as well as extracted from the questions and discussion after the presentation of the review.

In part two the focus was to discuss how studies on phytotherapy should be designed to enable assessment of efficacy. This was done through a free discussion on the topic "What is necessary to provide evidence for efficacy". Gaps in the compiled studies on the report as well as requirements and possibilities for future studies were identified and discussed. This was followed by a third session where external factors that influence the effective use of phytotherapy were discussed and explored through open discussion on the topic "What is necessary to ensure that efficacy is still visible under varying practical conditions".

The fourth session of the workshop was based on the discussions in previous parts. The experts individually composed suggestions on how the European Commission should proceed on the topic of research and use of phytotherapeutic products in farm animals, especially in order to reduce the use of antibiotics. After this the suggestions were put on display boards and experts were asked to reflect on their thoughts. Suggestions were further discussed by the whole group and at the end of the discussion the experts were asked to vote for three suggestions they thought to be the most important ones.

In the final session, four statements, elaborated by the IMPRO team regarding the use of phytotherapy were presented. The participants were asked to individually rank if they strongly agreed, agreed, neither agreed nor disagreed, disagreed or strongly disagreed according to a Likert scale. The compiled results were displayed and discussed so that the participants had the possibility to reflect on dissensions as well as develop their opinions on the different statements. During this stage, the coordinator of the IMPRO-project joined the discussion due to the evolving discussion on specific wordings and meaning of single statements. During the session he addressed questions regarding the understanding but also addressed single experts with provoking questions in order to spark the debate and to challenge the validity of the arguments during the following discussion.

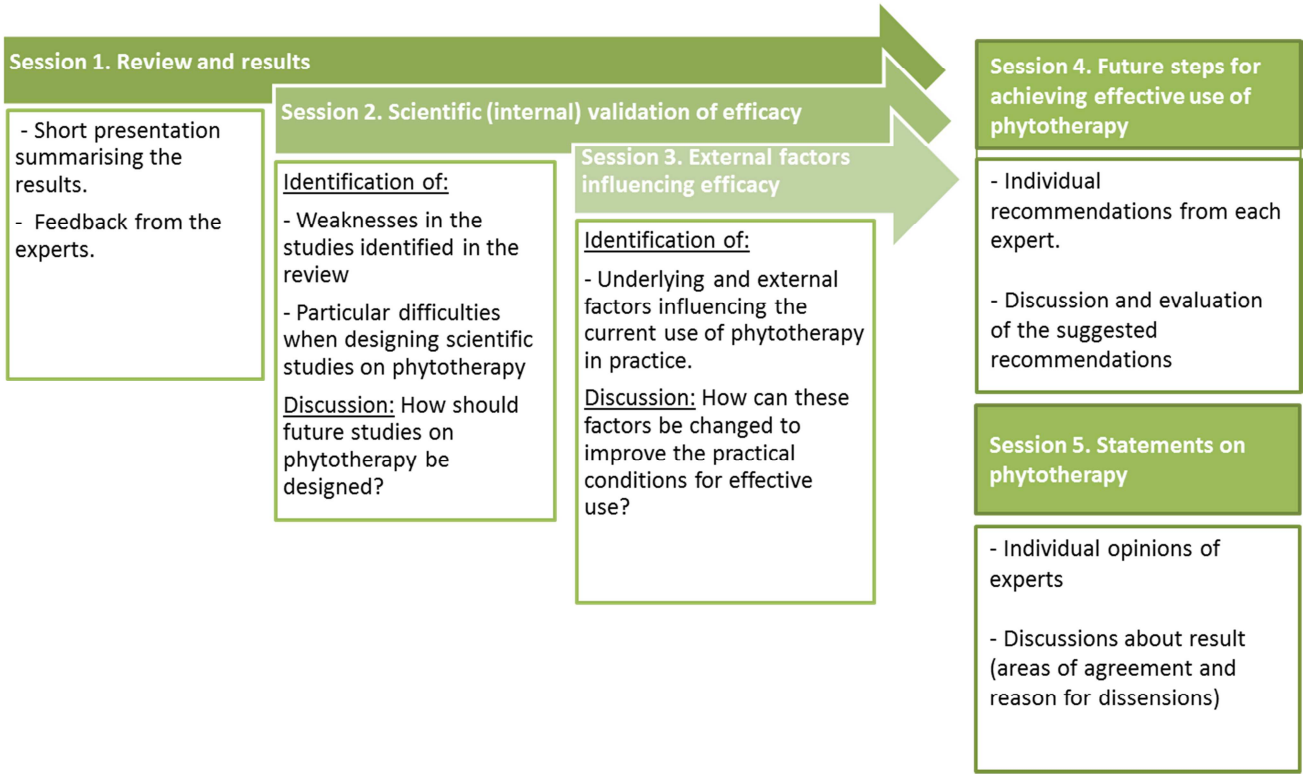


**Figure 4: Agenda for the workshop and the major topic of each section**

## 2.5 Feedback on the report

The results of the review were in line with the expectations of the majority of the workshop participants (75%) (See Annex part B). Two of the remaining participants considered that they did not have enough specific knowledge about phytotherapy in livestock and thus did not have any expectations before reading the review. However, some experts expressed surprise over number of studies that had chosen “vague”, not easily diagnosed diseases to study, thus making it more difficult to carry out a study.

The reactions to the quality and number of studies included in the review also varied. Some were surprised about the low number of studies that fulfilled the selection criteria and about the general low quality of the studies. Some argued that the inclusion and exclusion criteria and the approach might not have been adequate (discussed below). Others expressed that the variation in quality reflected the general variance seen in many areas of veterinary medicine and saw similarities with studies on allopathic treatments (like antibiotics).

When discussing the review, several points regarding the methodology were raised and discussed. The majority of the remarks of the experts were focused on the inclusion and exclusion criteria that were considered very tough, leading to the small number of studies in the end. There was also critique that the focus should have been more on the reduction of antibiotics, and not primarily on replacement of antibiotics. Another suggestion was inclusion criteria should have focused on quality rather that type of study, thereby including studies on preventive effects against diseases in general.

Some participants of the workshop confirmed the general confusion regarding terminology in the area of phytotherapy that was pointed out in the review and expressed that this might have affected the selection of the final studies included in the review. One of the experts was concerned that the existing lack of consistent terminology might have lowered the specificity of the search method, meaning that there may have been more studies on botanical substances, such as pectins and other substances, which were not covered by the review.

There were also some concerns that studies may have been overlooked due to specific aspects regarding the inclusion criteria. The experts discussed if a wider time-span (studies before 2000) and if studies from other regions should have been included. A significant amount of research on phytotherapy is done in India and China where for some animals, like poultry and pigs, the conditions may be similar to European conditions. Another suggestion from participants was to include horses among the domestic species in the review, bearing in mind the progress in phytotherapy for horses. There was also an opinion that the studies should only have been focused on infectious diseases as the aim was to reduce the use antibiotics. Another opinion voiced was that general prophylactic studies (not focused on treating/preventing a specific disease, but improving health in general) should have been included. One expert also suggested that studies on human products should have been considered for argumentation.

#### *Conclusion on review result*

In general, the participants supported the conclusion that for a large proportion of the studies the observed effect or lack of effect cannot be evaluated due to the poor study design. In addition, they agreed that only a small selection of the studies can be used as a basis for further scientific developments against specific diseases, especially due to lacking information regarding specific ingredients of the remedies. Nevertheless, it was of particular concern for some participants to stress that this conclusion should not to be interpreted as a statement that phytotherapeutic remedies do not have effects. The majority of the participants expressed that they saw substantial potential of phytotherapeutic substances in the results and for reducing the use of antibiotics in the future. The review and workshop also identified important gaps between the inclusion criteria and the current situation and level of knowledge about phytotherapeutic products where there is a need for research.

### 2.6 Internal validation of phytotherapeutic remedies

#### *How to optimize the study design*

One of the main constraints for the research on phytotherapy identified in the review was a low reproducibility of the studies. There was general agreement among the participants regarding the importance of defining and standardising the ingredients of remedies to reproduce results from research studies, and to perform dose-finding as well as dose-optimisation studies. The participants also agreed that phytotherapeutic products as multicomponent products are difficult to define and standardise. However, according to researchers in the area, the methods needed to resolve this are available although they are not fully implemented in the previous studies. According to one of the

participants, metabolomic fingerprinting might solve the difficulties with standardisation. There are also comprehensive monographs, providing detailed descriptions of methodologies for an acceptable standardisation and safety for a large number of botanical products, available through the European Scientific Cooperation on Phytotherapy (ESCOP) and European Medicinal Agency's Committee on Herbal Medicinal Products (HMCP).

One of the main reasons for the lack of use of available methods in clinical studies was seen in legislative aspects, e.g. in the difficulties to protect the composition of commercial products towards free-riders and product pirates. The demands for a scientific description of a phytotherapeutic preparation are very extensive, covering very detailed information about content and production. In addition, the original product is often a non-patentable botanical. Thus, commercial reasons restrain companies from publishing the information. It also makes companies less inclined to fund studies that intend to publish this type of detailed information. Some participants see the need for public funding for this area of research.

According to some participants, several of the studies selected by the review were not optimally designed for the particular botanical product. Some botanicals were used to replace treatments, for example coccidiostatics, when perhaps it would have been more suitable to focus more on the general preventive effect of some products which requires a different design of the study. In addition, the majority of the studies identified in the review did not include information why the particular botanical and the particular dose were chosen or which effect was expected. The experts discussed the importance of choosing products, diseases and doses based on previous knowledge of practitioners and other experience bases when designing trials. It was also considered that it would be possible to be inspired by products where studies exist for human use and adapt these and find doses suitable for other species. Relying on experience might also give an indication of which effect could be expected of the botanical and support with adapting the study design to investigate this.

The participants also discussed the need for field trials where the farm conditions are also taken into account. Different farms have different conditions that add complexity when designing studies to measure efficacy of remedies. Studies taking practical conditions into account are difficult to design and it would therefore be helpful if there were guidelines and templates for studies on phytotherapeutic remedies as well as other potential alternative products available. These could partly be based on the review-results but also with contributions from experienced, well renowned scientists in the area. They could also include guidelines on standardisation/safety analysis for future studies to ensure harmonisation.

#### *Conclusion regarding study design*

The experts generally agreed that the traditional scientific approach of proving efficacy of remedies through randomized, double-blinded, controlled trials is appropriate also for phytotherapeutic products. According to experts in the area there are methods for identifying the ingredients, and ensuring standardization and safety of the remedies. However, as these products are more complex and the exact effect mechanisms are not always known, the study design may require some adaptations based on the particular substance, use and expected efficacy. Improved understanding and characterization of the expected effects of the phytotherapeutic products is an important objective for future studies.

## 2.7 External validation of phytotherapeutic remedies

### 2.7.1 Main factors affecting use and efficacy of botanical products in farm practice

***Current use***

A main problem affecting the use of phytotherapy that emerged during several discussions was the lack of an appropriate classification of botanical products. This was considered in reference to regulatory classifications but also in the wide variety of practical applications and types of botanical products available. The participants expressed a need for clarification of how some botanical products, like single feeds and feed additives, should be considered. The consequence of current legislation is that the same botanical given to an animal can be categorized as a feed, a feed additive or as a veterinary medicinal product, depending on the purpose for which it is given. It was pondered whether the difficulty to classify botanical products could be a reason for the existing multitude of “borderline” products available on the market. There was also a discussion about the disparity in the regulations for human botanical products compared to veterinary medicinal products. For botanical products intended for human use it is possible to apply for approval as a “traditional herbal medicinal product” through a simplified procedure where mainly the safety of the product is assessed. Some participants missed this possibility for veterinary herbal products.

The low number of botanical products approved as veterinary medicinal products was seen mainly as the result of little interest from commercial companies in getting them approved. This lack of interest was considered to be due to the expensive process and trials required for approval in combination with difficulties in patenting the final product (as discussed above). Participants further discussed that similar financial aspects surround the development of all new remedies. It is very expensive to develop new botanical drugs, while antimicrobials on the market are cheap. Companies may therefore not see the benefit of investing in development of new remedies as long as the cheaper alternatives are available. According to the discussion, this may lead to a more ineffective search for alternatives to the existing antibiotics. Considering the serious threat of antimicrobial resistance, concern was expressed that little effort is put into finding appropriate alternatives. Especially since phytotherapeutic remedies require costly identification and standardization of ingredients and offer only low potentials for return of investment as the manufacturing process and the product are not patentable. Therefore, alternative funding apart from the pharmaceutical companies was recommended.

The participants also discussed that a consequence of the costs associated with approving botanical products as medicinal remedies was that selling the botanicals as feed additives to farmers could be more profitable. This procedure also requires less extensive testing before the product can be put on the market. However, while selling botanical products as feed additives, it is forbidden to claim specific health effects (meaning as treatment or prevention for specific diseases or symptoms of disease). Consequently, farmers might use these products for treatment or prevention based on their own associations and experiences or other information regardless of the way they are being marketed. Also the decision about the dosage is left to the farmer by own accord. An ineffective dosage can also be due to varying contents in different initial products of the same botanical. Some participants saw the possibility of selling botanicals as zootechnical feed additives with general claims on health improvements, like improved resistance to diseases or general stimulation of the immune system, once these effects had been proven through high quality studies based on templates and guidelines discussed above.

One of the practicing veterinarians raised the subject that selling botanical products mainly as feed additives instead of veterinary medicinal product affects the possibilities of practicing veterinarians to recommend and prescribe these products. The cascade-principle (Directive 2004/28/EC) clearly states that veterinarians should in the first hand use a product approved for the particular condition and the particular species. If botanicals are not approved this means that veterinarians are not allowed to prescribe them for treatment and prophylaxis of diseases. As the cascade principle applies to all treatments of animals, including preventive and metaphylactic treatments, it is not possible for veterinarians to recommend non-approved products in these circumstances either.

An additional, nevertheless essential factor affecting the appropriate use of phytotherapeutic products in general is lack of knowledge about how and when they should be used. As also discussed in the review, experts in the area agreed that the possibility for interested farmers and veterinarians to gain more knowledge is limited and also varies between countries in the European Union. Reintroducing phytotherapy into the curriculum of the European veterinary education was discussed as an option although associated with concerns like adaptation to international accreditation schemes. Currently, the botanical products mainly have a place in the subject of toxicology.

***Efficacy***

Although the general opinion of experts in the area was that botanical products are being used frequently in practice, the variability in use makes it very difficult to assess the efficacy on farm-level. The farmer, being the main person in-control of the use of botanical products, can only base the success or failure of products subjectively on personal judgement and discussions with colleagues or a veterinarian. Due to a lack of registration of botanical products, lack of monitoring the use and lack of assessment of therapeutic success, it is not possible to conduct overall large-scale scientific studies on the effectiveness of phytotherapy in farm practice.

Contemplating on treatments in general, there are numerous on-farm factors that influence the success of a treatment on a particular farm. Even the effects of antimicrobial treatments are highly dependent on factors not associated with the quality or efficacy of the particular remedy proven in RCT studies. For example, the diagnosis of the disease has to be correct, the particular strain of bacteria may have developed resistance to the substance used, or the pathogen is sensitive to the substance but the substance does not reach the infected tissue due to the method of application. Thus, even an approved product for a particular disease may have very low or no effectiveness in farm practice. The monitoring and control of effectiveness of all treatments in veterinary practice in Europe was considered as insufficient by all participants. Under these circumstances, it is very difficult to prove effectiveness of phytotherapy, as well as conventional treatments, in practice. All participants agreed that a monitoring system where animal health traits, treatments and pathological carcass traits across Europe would provide essential preconditions to improve therapeutic success in areas where health improvements are most important. It would also enable large scale studies to assess the effects of both allopathy and phytotherapy in farm practice, as well as to identify good husbandry practices and prevention programs that encourage strong resistance to disease. One of the participants gave an example of a large scale study on humans where a change in the prevalence of a disease was observed after an alternative botanical product was marketed, indicating a preventive effect of this particular substance. An appropriate monitoring system would make it possible to perform similar studies with food producing animals to assess preventive effects and impacts on prevalence and incidence of production diseases. It would also make it possible to follow the impacts of health improving measures (like herbal treatments as well as other measures

like increased biosecurity) on specific farms over time, taking into account different farm characteristics, management routines, feeding regimes, etc.

### 2.7.2 Future steps for achieving effective use of phytotherapy

The participants of the workshop identified and discussed several steps needed to ensure an effective use of phytotherapy in practice. The order is based on the importance of the experts according to voting and length of discussion (see Reflection on the structure of the workshop).

1. **Establish a monitoring system** for efficacy of both antibiotics and herbal medicines by monitoring animal health traits, treatments and pathological carcass traits across Europe. This would provide essential preconditions to improve therapeutic success in areas where improvements of animal health and welfare and food safety are most important.
2. **Improve knowledge:** Phytotherapy is applied on many levels (as feed material/additive by farmers or nutritionists; as remedy or metaphylaxis/prevention-prescription by the veterinarian). Each application requires adequate knowledge and if products are used there should be high quality courses available for interested farmers and veterinarians. New specialization for veterinarians in Switzerland and Austria in veterinary phytotherapy might be used as a model to follow regarding education on phytotherapeutic substances and treatments for veterinary students.
3. **Adapt legislation** to better describe phytotherapeutic remedies as a class of products and harmonise with human regulations. Potentially make it possible to register traditional veterinary herbal medicinal products through a simplified registration procedure or support the registration as health improving feed supplements (zootechnical feed additives). Especially requirements for safety assessment need to be adapted to special circumstances surrounding botanicals that have been used for a long time and are included in European monographs for human use. One suggestion was to follow Switzerland and exclude phytotherapy from the cascade principle in order to simplify the use.
4. **Develop guidelines** and templates for field studies in phytotherapy as an alternative to antibiotics. This will help designing controlled experiments that address the complexity on farm and capture variability of these products with established recommendations for dosage and effective use for the target species.
5. **Support research and development of alternatives to antibiotics:** Existing antibiotics are cheap compared to costs of developing and selling alternative treatments, like phytotherapy. In order to support alternatives, a new funding program was suggested, e.g. in Horizon 2020, to support clinical studies in farm animals for the reduction of antibiotics. The participants emphasized the need of practitioners and researchers working together to identify new potential botanical treatments as well as implementing the results from conclusive scientific studies in practice. Effective dose finding studies for the intended uses should also be supported.
6. **Increase the cost-benefit of producing phytotherapeutic remedies:** It is important to establish research conditions for not patentable common goods (e.g. pure drugs and easily available herbs), based on identified and standardised ingredients. Incentives for companies to perform clinical trials with herbal medicines could be established through a period of data protection or protection of composition of treatments. The experts suggested a period of five years. Once proven effective according to scientific standards, environmentally friendly

alternatives to antibiotics should be cheaper to support its use and decrease the development of antimicrobial resistance.

### 2.7.3 Statements for future use of phytotherapy in farm practice

Four statements were presented by the IMPRO team to the participants to receive a feedback if they agreed/disagreed individually (Fig 5). After the individual results, a discussion regarding each statement took place and is described below.

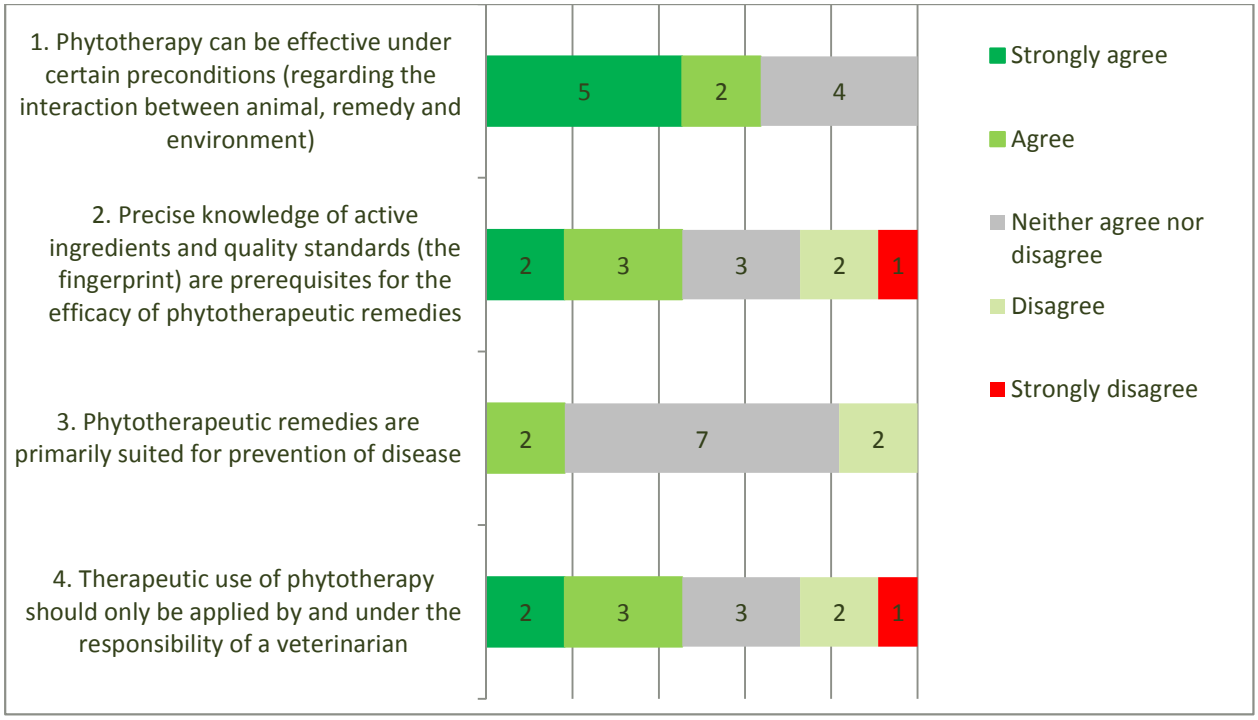


**Figure 5: Level of agreement by the 12 experts with the presented statements.**

***Statement 1: Phytotherapy can be effective under certain preconditions (regarding the interaction between animal, remedy and environment)***

The meaning of this statement was discussed. Participants were not sure if they were agreeing to if phytotherapy is effective, if it can be effective in some cases or if it can only be effective under certain preconditions. In general, the attitudes to the potential of phytotherapy were positive which is represented by seven participants agreeing to the statement and that none disagreed. Four participants neither agreed nor disagreed, possibly due to the multifaceted meaning of the statement or misunderstanding of the meaning of preconditions.

***Statement 2: Precise knowledge of active ingredients and quality standards (the fingerprint) are prerequisites for the efficacy of phytotherapeutic remedies***

Discussion about the wording of this statement also arouse when many of the experts in phytotherapy objected to the word “active” ingredients stating that it was not applicable. The discussion also revealed that this word had affected answers on agreement differently. Two participants argued that they disagreed because they did not believe information about all active components was necessary for determining effect. However, they agreed that a level of standardization is needed for reproducibility. After the discussion the group agreed that knowing the exact content as well as the active ingredients may be beyond our power for complex botanical products but using standardization methods already available (fingerprints, composition) will give sufficient information for quality of products as well as reproducibility in scientific studies.

***Statement 3: Phytotherapeutic remedies are primarily suited for prevention of disease***

The majority of the participants neither agreed nor disagreed. The discussion revealed that many of the participants did not want to restrict the use exclusively to prevention although this is the most common way botanicals are being used currently. There were also comments that review mainly included products used for prevention making it difficult to draw conclusions on treatment. However, one participant argued that there are many phytotherapeutic remedies that are used for treatment of mild symptoms in humans and that this knowledge could possibly also used for animals.

***Statement 4: Therapeutic use of phytotherapy should only be applied by and under the responsibility of a veterinarian***

There was little consensus on this statement. Participants discussed if therapeutic use also includes prevention and the role of the veterinarian in different cases. For treatment, there is a need to diagnose, administrate and follow–up the treatment which is not necessarily needed when preventing diseases in general. This adds complexity to the use of phytotherapy as treatment. Some participants argued that in some cases phytotherapy could be used similarly to the human side where people use phytotherapy to self-medicate against mild conditions. Thus, farmers were seen as being able to treat some symptoms themselves. Other participants disagreed and stressed that a veterinarian should at least be supervising and overseeing the use although maybe not administering the treatments. There was disagreement on to which extent farmers and lay-persons are able to diagnose as well as follow-up all treatments. However, all participants saw that the herd veterinarian plays an important role in supervising, advising and educating the farmer as well as taking responsibility for the treatment, animal welfare and food safety. One participant pointed out that as long as there are no or few approved products in a member state, veterinarians in the country cannot recommend or apply botanical products if there are other approved products for the particular disease/symptom. Thus, when no products are approved, the use is left to be under the responsibility of the farmer without control of a veterinarian.

## 2.8 Discussion

***Feedback on the review***

The discussion about the results and methodology of the review revealed several aspects and potential approaches that could have been used when developing the methodology. During the development of the review and the inclusion criteria the aim was to relate to the regulation in organic agriculture, requiring that alternatives to chemically synthesized, conventional veterinary drugs should be used preferentially when they are safe and efficacious (EG 889/2008 Art. 24 (2)). Thus, the ambition was to assemble and identify studies where specific treatments used against specific conditions to identify effective treatments that practicing veterinarians can use while fulfilling all aspects of the regulations. On this basis, studies using botanical supplements as general prophylactic remedies/feed additives to improve general disease resistance and/or solely focusing on studying the growth promotion effect were not included in the review. During the process it became obvious that there is a large amount of such studies as well as recent comprehensive reviews on the subject. In addition, the workshop discussions revealed that phytotherapeutic substances are often used in a prophylactic way. The workshop participants highlighted that the exclusion of studies investigating general prophylactic effects was unfortunate. The authors agree with the participants that there is a need to look further into the prophylactic use. The studies identified during the search will be summarized in an additional following publication. However, it should be kept in mind that these general prophylactic studies often relate to unspecific outcome measures, and as such escape a sound scientific evaluation, apart from the fact that the ingredients

are often not specified. When reviewing such studies inclusion criteria should be designed to include studies where the outcome measure is clearly associated with a validated measure of a positive health effect. Yet, such studies may be important as a basis for future studies.

An additional opinion expressed during the discussion regarding the diseases included was that only studies on infectious diseases should have been included, in order to focus the review on reduction of antibiotics. In the current review all specific diseases, regardless if they were caused by parasitic, viral or bacterial agents or production factors were included. The authors' reason behind including all these aspects was that in many cases viral infections and production diseases, although not directly treatable by antibiotics, weakens the animal and increases the risk for secondary infections leading to antibiotic treatments. In field practice it is also possible that viral diseases are not diagnosed by diagnostic tests but only by symptoms and therefore treated with antibiotics in the absence of other treatments. Similarly parasitic diseases may open up for secondary infections and reduced resistance to disease and there is also a developing problem in the form of increased resistance to antiparasitic treatments.

It was argued that the quality of studies should have been part of the exclusion criteria. Given the high amount of studies, and the time and resources available to carry out the review, a detailed assessment of quality of each study was not possible to perform. Furthermore, assessments of quality require an agreement on the criteria. The inclusion and exclusion criteria for the selection studies were thoroughly discussed and agreed upon within the IMPRO team. The timespan (studies published after 2000) was chosen to limit the very large amount of publications available as the confusion in terminology made it difficult to design a specific search methodology. In the process of scanning the references of the included publications, publications fitting the inclusion criteria but excluded due to the time-span was noted. In this process only one publication from 1997 was identified. Thus, it is the authors' opinion that the time-span did not have effects on the results.

As the aim was to identify treatments to diseases occurring in Europe, the review was restricted to studies conducted under conditions characteristic for European farms while studies from other regions were excluded. However, some experts questioned if this was an appropriate approach when an international market enables producers of botanical products outside of Europe to register and sell their products. It was also argued that some production conditions (e.g. laying hens and broilers chickens) are relatively similar across the world, especially regarding breeds and production systems used. These are relevant aspects that could have been used to widen the inclusion criteria and thus would have resulted in identification of a higher number of studies. However, it is the opinion of the authors of the review that it would have been complicated to draw the line and clearly define which studies were similar enough and which were not, especially when many publications provide little information on the context in which the studies took place. There is a considerable variation between disease-panoramas, breeds as well as production systems within Europe and adding further regions would have caused even more variability.

Finally, some participants missed studies on some promising phytotherapeutic substances. In order to perform a comprehensive literature study in this area, it is necessary to develop a more harmonised terminology in order to ensure effective identification of published studies. At current point the different terminology used and the tendencies for only including keywords specific to the disease, species and specific botanical substance makes straightforward identification of relevant literature very difficult and probably narrowed the search.

## 2.9 Reflection on the structure of the workshop

Screening of opinions from different perspectives: Experts may be directed by their personal or commercial interests. This refers to the tendency of the participants of the session to favour a particular position that may affect the validity of the information obtained. All participants were informed that they should keep in mind that they were not representing any organization.

Selective perception: The moderator lacked a background in phytotherapy which ensured neutrality in drawing out the thoughts and feelings of all participants while at the same time she had enough scientific background to understand the language used by experts and interpret their statements. Meeting and discussing with the moderator was carried out before the workshop in order to clarify its aim.

Linguistic misunderstandings: A clear definition of prophylaxis/treatment and health /disease concepts might have improved understanding among the participants. Prophylaxis/treatment and health/disease need a more clearly defined line to avoid “grey areas”. On the other, as the participants had different backgrounds and came from different countries, a clarification process about the use of core terms is unavoidable and can even be quite fruitful for a deeper understanding of the issue. Also the concept of “preconditions” needed a further clarification at the time of presenting the statements. For the sake of clarification this term and was explained to the experts as the specific context where the remedy is used. The experts suggested the term “preconditions” to be changed to “influencing factors” in the course of the workshop. Interpretation of the statements by the participants was in some cases different from what the research group intended. In addition the statements were complex with different levels which led to difficulties for participants that disagreed to some parts of the statement but not others. On the other hand, the discussion revealed that the perception and understanding of the statements was particularly influenced by the respective perspective of the participants.

Voting on recommendations, similarities between suggestions for the EU Commission provided by the participants suggests that a grouping of these might have been performed prior to the voting stage. A result of the current set-up was that that votes on several similar, but not identical, suggestions were split up making it difficult to get a clear picture of the participants’ opinions. A better way would have been to gather the suggestions and extract those that could have been used for a final vote.

Instructions from moderator were not always successful: before writing suggestions down, a better explanation about the context and aim that these suggestions should follow (common good and not particular interests) would have increased the probability of obtaining more conclusive and convincing suggestions from some participants.

During the workshop the option of not voting, e.g. no opinion, wasn’t available for the experts. This limitation was raised by one participant during the voting of the statements where participants with no opinion had to choose the “neither agree nor disagree” option. This makes it more difficult to interpret the answers to the statements but would also have been good to include in all voting sessions.

## 2.10 General conclusions

All participants agreed that finding alternatives to antibiotics is of high priority and emphasized that prevention of disease also is an important factor when it comes to reducing the overall use of

antibiotics for food producing animals. In addition, it is not only an issue of organic agriculture but also a conventional issue. Future research on the efficacy of phytotherapeutic remedies on specific indications where antibiotics are widely used, both as prophylactic and as treatment to critical diseases (in terms of antimicrobial resistance) in pig and poultry, should be encouraged. The core of the debate regarding evidence of efficacy revealed a need for species-specific, dose-finding studies with well-defined, standardized substances. These studies would require higher investments and companies might be reluctant to provide details on the substances used. This might explain the current focus on general health claims present in phytogenic feed additives. In addition, the level of complexity and heterogeneity of phytotherapeutic products compared to conventional treatments makes them impossible to incorporate into present regulations. Furthermore, a potential result of the difficulties in categorization and that the products are sold under very different regulations and premises, is a lack of a cohesive overall control of the content and safety of botanical products in general. The fact that phytotherapeutic remedies are surrounded by a grey area puts further requirements on the profile and design of randomized clinical control studies.

Furthermore, there is a need to establish in which way particular phytotherapeutic remedies should be used (treatment/prevention) and which effects can be expected in practice. To achieve this, field trials following the Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances, where naturally infected animals are given treatment/prophylactic for specific indication and housing conditions, production forms and geographical location are also taken into consideration should be conducted. For all treatments, including conventional synthetic pharmaceuticals, farm specific contexts affect the result, restricting generalisation of effects and effectiveness. This issue is not unique for phytotherapy and has to be dealt with in the area of conventional remedies as well. In order to monitor the efficacy of all treatments as well as the effects of new alternative treatments, a European monitoring program encompassing production diseases in food producing animals, their treatments and the success of treatment is needed in order to ensure the most efficient use of the most appropriate treatment for the sake of animal health and welfare and food safety.

# 3 Acknowledgements

We wish to thank various people for their contribution to this project: First and foremost all participants invited for their interest and the fact that they travelled from various countries to participate at the workshop, giving their feedback and sharing their opinions openly in the discussion.

Dr. Karina Gregory for the excellent moderation, guiding the sometimes difficult discussions with confident and charming demeanour. We especially enjoyed the very good cooperation we experienced.

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# 5 Annex

## 5.1 Annex Part A


**Figure 6: Participants´ opinion and comments on the results of the review on homeopathy as shown by the moderator in the blackboard.**

## 5.2 Annex part B

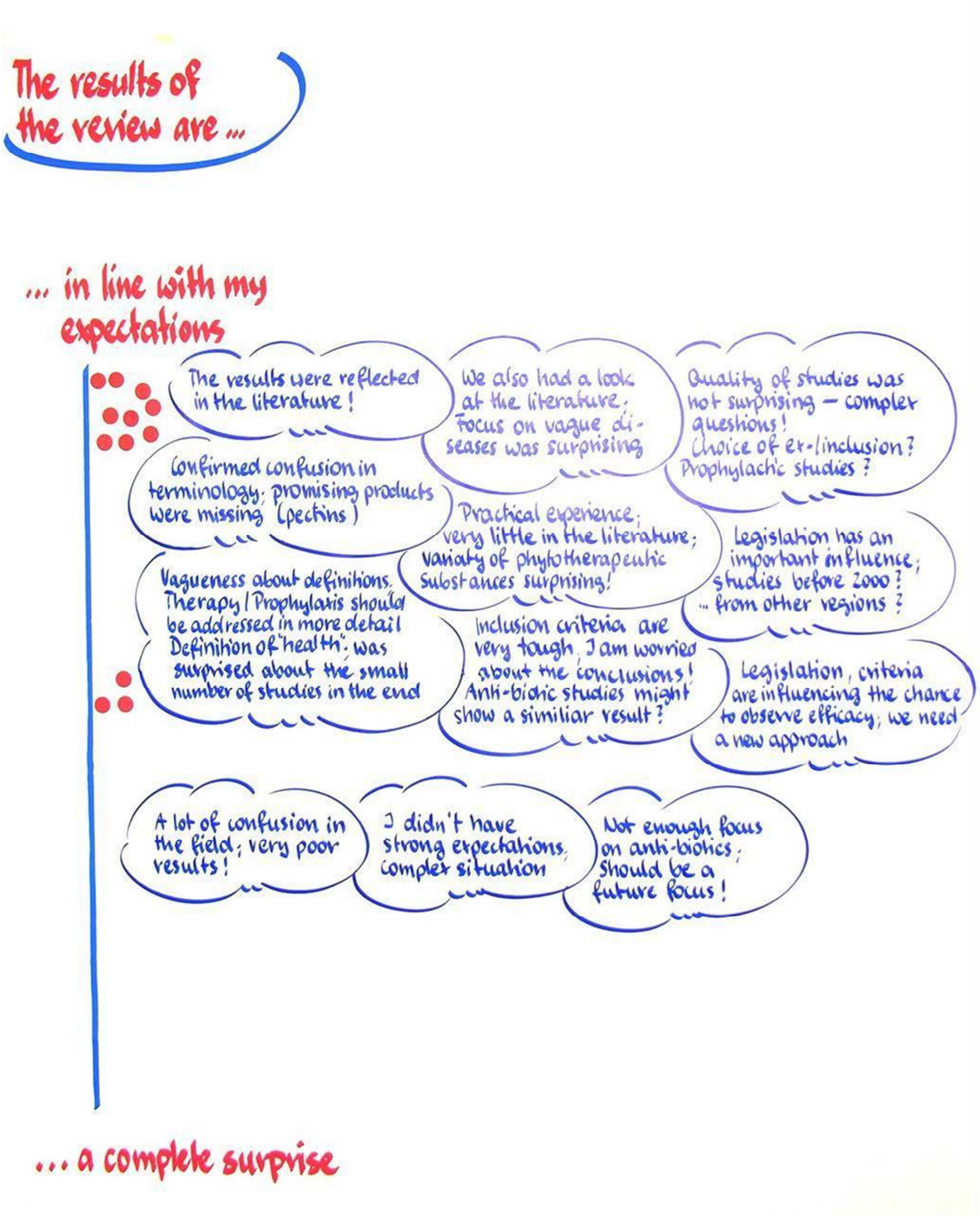


**Figure 7: Participants´ opinion and comments on the results of the review on phytotherapy as shown by the moderator in the blackboard.**