

THE EFFICACY OF HERBAL MEDICINAL PRODUCTS

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1) THE RULES OF EVIDENCE

A review of the requirements for establishing efficacy and safety for suppliers of herbal medicinal products in the European Community.

Introduction

Herbal medicinal products, or phytomedicines, are subject to the same legislative controls as other medicines. There are particular features of phytomedicines however that distinguish them and affect how these controls apply.

Phytomedicines consist of many chemical constituents with complex pharmacological effects on the body.

Phytomedicines have been used continuously for many decades or centuries, often in ways that differ from those of conventional medical prescribing.

Research and development in phytotherapy has suffered through lack of patent protection, and the diversity and relatively small-scale of the industries involved compared to the rest of the pharmaceutical industry. Established guidelines for assessing the efficacy and safety of phytomedicines [1], although scientifically consistent, could impose impracticable financial demands on phytomedicine licence-holders.

The differing regional uses of traditional herbal remedies present extra difficulties for the already complex harmonisation of licencing procedures across Europe [2].

Legislators concerned to assure the public that drugs in general are safe and effective enough to be licensed can therefore present difficulties for the suppliers of herbal medicinal products.

Efficacy and Clinical Trials

Although preliminary assessments of efficacy can be obtained through the results of *in vitro* testing and experiments on animals, authorities licensing **new** medicines for public use require evidence of their effect on human beings. Only carefully planned clinical trials that clearly minimise experimental bias are able to satisfy these requirements.

Established licensed herbal medicinal products are subject to Phase IV or post-marketing level of scrutiny [3], which is by definition less demanding than that for new synthetic medicines but potentially also includes a requirement for clinical trials.

Most herbal remedies can call on a tradition of popular use which has in practice allowed licence holders to submit relevant bibliographic evidence in reviewing their earlier licences of right. Nevertheless this has been a reluctant concession by licensing authorities and in reviews of licences there is the prospect that additional evidence may be required.

The requirements for the conduct of clinical trials have been clearly defined.

*A clinical trial is **any systematic study** of medicinal products in human subjects whether in patients or non-patient volunteers in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or study their absorption, distribution, metabolism and excretion in order to ascertain the efficacy and safety of the products. [Reviewer's emphasis] [4]*

Evaluation of the application for marketing authorization shall be based on clinical trials ... designed to

determine the efficacy and safety of the product under normal conditions of use... Therapeutic advantages must outweigh potential risks.[5]

All test procedures shall correspond to the state of scientific progress at the time and shall be validated procedures; results of the validation studies shall be provided [6].

The clinical particulars to be provided pursuant to point 8 of Article 4 (2) of Directive 65/65/EEC must enable a sufficiently well-founded and scientifically valid opinion to be formed as to whether the medicinal product satisfies the criteria governing the granting of marketing authorization. Consequently, an essential requirement is that the results of all clinical trials should be communicated, both favourable and unfavourable [7].

The particulars of each clinical trial must contain sufficient detail to allow an objective judgement to be made...[8]

*In general, clinical trials shall be done as 'controlled clinical trials' and if possible, randomized; **any other design shall be justified**. Inclusion of a large number of subjects in a trial must not be regarded as an adequate substitute for a properly controlled trial.* [Reviewer's emphasis]

Clinical statements concerning the efficacy or safety of a medicinal product under normal conditions of use which are not scientifically substantiated cannot be accepted as valid evidence [9].

*The view of the Medicines Commission [of the UK] ... which the licensing authority accepts is that evidence of efficacy which has **not** been cleared as acceptable to us should not be used in promotional material for products which have been granted reviewed licences* [10].

Alternatives to clinical trials?

An obvious point is that evidence of clinical efficacy is required for herbs only when medicinal claims are made.

Discussion by legislators of the exact status of herbs **not licensed as medicines** and making no claims on their labels, whether this is as foods, "diet integrators" [11] or otherwise will not involve the im-

position of new requirements for efficacy.

It has also been suggested in the UK that the extent of evidence required is in direct proportion to the clinical severity of the indication claimed for the medicine.

The [UK Committee for the Review of Medicines] has advised that when manufacturers make claims for the treatment of major conditions the claims must be capable of substantiation by the results of clinical trials in the same way as would claims for new medicines before the Committee on Safety of Medicines. If, however, claims are restricted to the symptomatic relief of self-limiting conditions the CRM has advised the licensing authority that it may be unreasonable to demand controlled trials.

Nevertheless, the CRM does expect a pharmacological rationale and bibliographic evidence of efficacy [12].

The only exceptions for medicines considered in the recent directive would have the effect of removing them from the General Sale List.

When, in respect of particular therapeutic indications, the applicant can show that he is unable to provide comprehensive data on the quality, efficacy and safety under normal conditions of use, because:

- *the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or*
- *in the present state of scientific knowledge comprehensive information cannot easily be provided...*

marketing authorization may be granted on the following conditions:

- a) the applicant completed an identified programme of studies within a time period specified by the competent authority, the results of which shall form the basis of a reassessment of the benefit/risk profile;*
- b) the medical product in question may be supplied on medical prescription only...*
- c) the package leaflet and any medical informa-*

tion shall draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects [13].

The use of clinical evidence from other license applications is generally allowed, provided safety data is available.

If the medicinal product is already authorized in other countries, information shall be given in respect of adverse drug reactions of the medicinal product concerned and medicinal products containing the same active ingredient(s), in relation to the usage rates if possible. Information from worldwide studies relevant to the safety of the medicinal product shall be included [14].

Methodological discretion

In view of the fact that conventional controlled clinical trials are notoriously expensive to run and involve clinical infrastructure not always available to phytomedicine manufacturers, other proposals for establishing evidence have been made.

They include proposals for non-controlled studies, comprehensive field data and case reports, physiological monitoring, and quality-of-life and functional assessments that are genuinely appropriate to the material, and could at the very least improve on existing standards for bibliographic evidence. They provide the basis for substantial but less expensive clinical evidence to be offered with licensing applications.

It is not however the suppliers of herbal medicinal products who can determine how they establish their case. Discretion as to the validity or credibility of any research method rests with three main bodies, the licensing authority, the ethics committee and the independent author of the expert report.

1) The **licensing authority's** position has been set out above and reiterated in the establishment of the European Agency for the Evaluation of Medicinal Products [15]: the EMEA is

to adopt "transparent" procedures, to give detailed reasons for all negative decisions, to grant appeal rights and to publish decisions [16]. It will interpret the regulations, in conjunction with medical and scientific advice, so as to establish

a standard by which clinical trials are designed, implemented and reported so that there is a public assurance that the data are credible, and that the rights, integrity and confidentiality of subjects are protected [17]

2) The **ethics committee** is an essential referee in all research involving human subjects. It has a mandatory role in protecting the interests of subjects and other study participants. The role of the ethics committee is also firmly entrenched in the appropriate legislation.

[The ethics committee is] an independent body, constituted by medical professionals and non-medical members, whose responsibility is to verify that the safety, integrity and human rights of the subjects participating in a particular trial are protected, thereby providing public reassurance... [18]

Subjects must not be entered into the trial until the relevant Ethics Committee(s) has issued its favourable opinion on the procedures and documentation [19]

One of its implicit charges is to reject, in advance, in the interests of the subjects involved, any proposed study which it considers not rigorous enough to answer the question it sets out to address.

It is unethical to enlist the co-operation of human subjects in trials which are not adequately designed [20].

3) The author of the **expert report** has an important role before the licensing authority.

In accordance with Article 2 of Directive 75/319/

EEC, expert reports must be provided on the chemical, pharmaceutical and biological documentation, the pharmacotoxicological documentation and the clinical documentation respectively.

The expert report shall consist of a critical evaluation of the quality of the product and the investigations carried out on animals and human beings and bring out all the data relevant for evaluation...

Each expert report shall be prepared by a suitably qualified and experienced person... The professional relationship of the expert to the applicant shall be declared [21].

The pertinence of the different trials to the assessment of safety and the validity of methods of evaluation shall be discussed in the expert report [22].

Role for experts in phytotherapy?

The European Agency for the Evaluation of Medicinal Products, through its component committee the Committee for Proprietary Medicinal Products (CPMP) is charged with calling in experts to assist in the evaluation of particular scientific questions that may arise [23]. It is further stated that Member States will provide “up-to-date lists of experts with particular competence in the various areas of evaluation of medicinal products” [24]. Since the establishment of the EMEA the Working Group on Herbal Medicinal Products [see paper by Keller in this journal] has moved to address regulatory issues that affect herbal medicinal products.

The questions that appear to need addressing in reviewing the rules of evidence for efficacy for herbal medicinal products include:

1. The practical implication of the definition of a **clinical trial**, and **Good Clinical Practice (GCP)** to the licensing of herbal medicinal products.
2. The requirement for appropriate pharmacotoxicological guidelines for licenced herbal medicinal products.

3. The composition and terms of reference of **ethics committees**.

References

- 1 The Rules governing Medicinal Products in the European Community Volume III: Guidelines on the quality safety and efficacy of medicinal products for human use, 1989, [ISBN 92-825-9619-2], pp. 119-168 ; and
Good Clinical Practice for Trials on Medicinal Products in the European Community: from the CPMP Working Party on Efficacy of Medicinal Products, 1990, [III/3976/88-EN], pp. 2 and 11-29
- 2 Future system for the free movement of medicinal products in the European Community. pp 21 and 38
- 3 The Rules governing Medicinal Products in the European Community Volume III: Guidelines on the quality safety and efficacy of medicinal products for human use, 1989. pp. 118 and 167-168
- 4 The Rules governing Medicinal Products in the European Community Volume III: Guidelines on the quality safety and efficacy of medicinal products for human use, 1989.: Part 4 Clinical documentation
- 5 *ibid* : Part 4 Clinical documentation
- 6 *ibid* : Part 2 Chemical, pharmaceutical and biological testing of medicinal products
- 7 *ibid* : 4A: General requirements
- 8 Commission Directive 91/507/EEC: 4C: Presentation of results
- 9 *ibid* : 4F: Clinical efficacy and safety
- 10 DHSS letter to BHMA 21st January 1986
- 11 Diet Integrators: A discussion paper **from the European Commission**. III/3767/91
- 12 CRM Update (1986) British Medical Journal, 292, 333.
- 13 Commission Directive 91/507/EEC: 4G: Documentation for application in exceptional circumstances
- 14 *ibid* : 4H: Post-marketing experience

- 15 Council Regulation (EEC) No 2309/93 of 22nd July 1993: laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary of Medicinal Products.
- 16 Future system for the free movement of medicinal products in the European Community [COM(90) 283 final]. p23
- 17 Good Clinical Practice for Trials on Medicinal Products in the European Community: from the CPMP Working Party on Efficacy of Medicinal Products, 1990 , [III/3976/88-EN] , p. 6
- 18 *ibid* p. 6
- 19 *ibid.* p. 11
- 20 *ibid* p. 2
- 21 Commission Directive 91/507/EEC: Part 1C Expert reports
- 22 *ibid* 4F: Clinical efficacy and safety
- 23 Council Regulation (EEC) No 2309/93 of 22nd July 1993: laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products. Articles 21-22.
- 24 Future system for the free movement of medicinal products in the European Community. [COM(90) 283 final] . p. 36

2) RESEARCH QUESTIONS AND METHODS

DISCUSSION PAPER

with the ESCOP Research Committee and European Phytotherapy Research Group

The following section summarises responses to a proforma survey, as well as a series of wide-ranging discussions about research trial methodologies at meetings of the ESCOP Research Committee, later expanded to the European Phytotherapy Research Group. Its aim is to review appropriate research methods for evaluating the effectiveness of herbal medicines, rather than provide a comprehensive critique of conventional or other trial designs. Contributors to the discussion are listed at the end of the paper: they represent accomplished authors of published research literature on phytomedicines, in toxicology, pharmacognosy and phytochemistry as well as in clinical efficacy studies. This paper should be taken as a summary of contributions rather than as representing the views of any particular individuals.

It is clear from the previous section, that for the purposes of licensing a medicinal product in the Euro-

pean Union efficacy data has to be in the form of *'controlled clinical trials' and if possible, randomized; any other design shall be justified..*

In order to agree labelled and advertised claims for the efficacy of medicinal products, regulators will require to see the results of several "pivotal" trials for each application and indication, usually double-blinded, random-assignment, and controlled against placebo or other standard medicine. These should be conducted by different research teams, and if not published in peer-reviewed academic journals will need adequate review in the expert report submitted with the dossier.

If other evidence was to be submitted it might add up to a "pivotal-trial-equivalence" but this is always at the discretion of the regulator and is increasingly unlikely as a prospect. It may be more likely for rare indications or for treatments where it is otherwise difficult to set up adequate controlled trials.

There may seem little scope therefore for arguing the merits of less conclusive research methods in this context. Nevertheless there are features of phytomedicines that call for other research approaches, and there should always be a role for supportive efficacy and effectiveness data in applications for marketing authorisations. In occasional cases it may indeed be possible to upgrade the value of some of the alternatives by rigorous method and articulate presentation of the case.

Pivotal Trials

Controlled clinical trials

For researching over-the-counter (OTC) label indications for discrete medicinal products, in which individual responses to remedies are not the critical issue, the double-blind controlled clinical trial is clearly the most appropriate method.

In addition as the “patient” is in many cases not being diagnosed professionally and is determining his or her own treatment and prognosis, self-assessment questionnaires are often an appropriate measure of progress. These are not expensive to administer. Also as this is often “out patient” medicine research costs can be saved as close clinical supervision need not be always necessary throughout the trial.

There are however practical problems in pursuing good clinical research in herbal medicine.

1) Herbal medicine in the west can boast few teaching hospitals or research institutes, nor support from public resources. Industrial investment has been limited to a few larger manufacturers used to working in a pharmaceutical culture. In most parts of the sector the necessary infrastructure is lacking. Neither can the costs of undertaking research studies easily be justified commercially: it is difficult to patent herbs and the size of the market for any individual product is only occasionally comparable to that for any patent-

able conventional drug.

- 2) The indications often claimed for phytomedicines include many without robust outcome measures. As many are destined for the self-medication OTC market they are by definition directed at lesser degrees of morbidity where hard measures are elusive. By contrast most synthetic OTC medicines on the market have “switched” from prescription status and have acquired their efficacy evidence on harder clinical indications and in hospital or similar settings. Without hard or acceptably validated outcome measures, with more variable and lower grade symptoms among the patient population, with a greater likelihood of self-limiting or other spontaneously changing conditions, clear treatment effects are thereby harder to establish: the result is often the need to recruit large patient samples and to devise particularly artificial exclusion criteria to constrain sample variability. All this places extra logistic demands on those wishing to set up effective clinical trials for these products.
- 3) Herbs are complex medicines, occupying an unusual position as being medicines with many of the characteristics of vegetables. Being a complex of pharmacologically-active chemicals the whole package will have different properties from that of any single constituent acting alone. Knowing the action of the latter will not itself be predictive on the effect of the former, particularly if the experimental evidence is based on work done on laboratory animals. It is therefore rare to find the satisfactory preclinical evidence often required by ethics committees for approvals of major clinical studies.

Further limitations of the controlled clinical study are noted by the practitioner, the phytotherapist. Such practitioners will often emphasise more strongly than in conventional medicine the individuality of their treatments and often mix a number of individual herbs in a prescription. They point out

that conventional clinical trials involve the homogenisation of the patient population so that only an average effect is confirmed. Clinical trial data will help with, but still not answer, the basic question “is this drug going to be good for this patient?” It is also likely that genuinely important benefits for a minority of the population will be overlooked.

There are also certain cases where satisfactory blinding will always be difficult. In particular it will always be impossible to blind for the effects of bitters or other prominent tasting agents on oral consumption - these have played important parts in the claims of traditional herbal medicine. There will always be a role for the good single-blind study, especially if other elements are rigorously controlled.

Nevertheless the controlled clinical trial is a notably flexible instrument. With an adequate investment structure a significant section of the herbal medicinal market could be clearly evaluated in the public interest. The increasing rate of publication of rigorous clinical trials on herbal products in the scientific literature highlights the potential for a stronger evidence base in conventional terms.

Provided that the main research effort is directed towards generating new controlled clinical data it is however valid to ask whether other questions about the effect of phytomedicines may be addressed by other approaches.

The measurement of transient clinical effects

There is one particular application of the controlled clinical trial that could be particularly appropriate for assessing the impact of traditional herbal treatments: observing physiological responses to treatments in human subjects rather than direct effects on morbidity.

Traditional views of herbal remedies emphasise their primary influence on transient body functions eg. they are classed as diaphoretics, expectorants, cir-

culatory stimulants, diuretics, digestive stimulants, laxatives and so on. In other words, contrary to common belief, many herbs may have almost immediate results on the body. It is possible to devise methods by which such effects can be detected. Activity on biological markers, physiological functions and tissue or fluid constitution can be monitored directly in healthy or morbid populations and could provide much useful information on the effects on the body of herbal products. With advances in non-invasive monitoring technologies it is possible to conceive of important trials in human subjects, both in observational and controlled studies.

Against such ideas it has been pointed out that measures of efficacy tend to be based on a medicine's effects on morbidity or mortality. “Surrogate parameters” may be acceptable but would restrict possible indications as labelled claims. It would need to be argued in each individual case, with the support of other medical evidence, that a verified effect in changing some physiological parameter would be likely to have an effect on morbidity or mortality.

Supporting Clinical Evidence

Historical controlled trials

The fact that phytomedicines often derive from a long tradition of use has led many to consider ways to apply historical use to modern research. The prospects for this have been reviewed elsewhere during the preparation of this paper*.

Historical controls are harder to establish as reliable:

baseline and clearly defined outcome data to establish treatment effect are usually absent;

there is almost never concurrent comparisons recorded between treatments;

analyses of historical control studies have

* Schneider B. Established methods for the clinical assessment of the efficacy of phytotherapy. ESCOP European Phytotelegram 1996; 6, 26-33

shown that the placebo effect is consistently underestimated.

By definition it is hard to correct the deficiencies in historical data. Much more promising is to start again with such observations, to generate “new” historical data by rigorously designing prospective observational studies.

Observational studies

In some cases, attempting controlled clinical studies may prove fruitless. Such cases include, for example

- rare diseases;
- where there are many clinical complexities;
- for cases where blinding is impossible;
- rigorous scrutiny of possible adverse effects.

In these circumstances careful observations of non-controlled clinical events may be the best or even only feasible source of evidence. Such research also has preparatory and didactic benefits.

There is another way in which observational studies are an appropriate method for the study of herbal medicines. A persistent tradition is that these medicines may support self-corrective functions in the body, perhaps more readily than synthetic pharmaceuticals. This is an inherently unvalidatable claim, but the modern insights into the behaviour of complex dynamic systems suggest that new perspectives on the behaviour of the human being as an ecosystem may be productive. It is apparent in this case that different research methodologies are required. These should:

- have regard to global behaviour of the system rather than particular variables in isolation;

- aim to measure quantifiable components of health, rather than of morbidity, mortality or other indicators of disease;

- involve minimal intervention.

Again observational rather than controlled studies are appropriate. Non-invasive monitoring of physiological functions may be applied, perhaps coupled with patient self-rated questionnaires, clinical observations of overall behaviour and epidemiological methods, to establish as far as possible what actually happens to living patients when they seek treatments.

Routine collection of patient and clinical data at a teaching clinic for example, including self-rating questionnaires, for general health and target conditions, perhaps combined with a number of other non-invasive observations, compared with general remission rates, are feasible. With computer technology there are precedents to show that it is possible to accrue considerable quantities of useful observational data by involving patients and practitioners in simultaneous recording of treatments and questionnaire-derived outcomes (using simple touch-screen check-box entry forms for example)

To satisfy basic standards of research rigour for observational studies however it is important formally to set up clear experimental criteria prospectively, as follows

1. A protocol with full prospective description of the study to ensure maximum rigour.
2. There should be no bias in subject selection; during a given period of time all the subjects meeting the conditions should be admitted to the project.
3. Clear description of the condition is mandatory (using quantitative and semi-quantitative parameters).
4. Only one treatment may be provided for each diagnosis at a time or only one drug may be used per indication.

5. The description of the phytomedicine must be precise; the same applies to the duration of therapy and dosage. All drugs and treatments administered to the subject concomitantly (including treatments of other diseases) must be recorded.
6. In addition to efficacy, compliance and adverse events must be documented.
7. The observations are to be made by the same person prior to and after treatment.
8. Incomplete records should be discarded.
9. It should be possible to compare empirical reports to other reports on the same subject.
10. Therefore all terms should be carefully defined and reproducible and validated standard computer or other forms should be used.

Although it is difficult to establish cause-and-effect in observational or field studies, or specifically to separate specific from non-specific treatment effects, there are a number of ways that observational studies could productively be used in herbal research. For example

to set up controlled studies by monitoring matched groups where blinding or other ideals are impracticable;

to have individual practitioners generating longitudinal case studies, with standardised report forms, to address the question usually ignored in controlled clinical studies - the effect of long term treatments;

to audit clinical practice and generate new hypotheses - with computerised data input (as above) and sufficient quantities of data even complex and multiple prescription patterns can be evaluated;

to generate safety data.

Such information however suffers from one clear problem: it is rarely subject to independent validation or review, so includes partisan judgements. Its use without supporting controlled data in determining efficacy of treatment is therefore limited. Nevertheless in combination with other trials such studies could provide very useful information.

Single case studies

The main charge against single-case studies is that they cannot credibly select out real effects from confusing variables, specific from non-specific treatment effects and so on. Further investigation of such research however shows both that it can have more credibility than might be supposed, and that it is not a soft option.

The criteria for validity of such trials have been well reviewed by Aldridge*: a good single case study design can be very rigorous. It includes providing as many points of view on the event as possible, clarifying operational definitions, and recycling observed data around the researchers (including the patient as co-researcher) for checking and possible refutation.

It is possible to conduct double-blind, placebo-controlled studies in a series of such individual case studies with each patient being his or her control. Standard sequences of treatment, placebo and/or control can be conducted, described as ABAB, ACABCBCB, and other complex patterns that are nevertheless attainable in everyday clinical practice.

Such rigorous exercises are best conducted in the environment of a training clinic, where there is likely to be a more overt climate of inquiry and debate, and extra administrative labour. It could allow for a useful database of reliable case-histories to be assembled over the years, as both an educational and research exercise.

* Aldridge D. Single case research designs. in Lewith GT, Aldridge D. eds. *Clinical Research Methodology for Complementary Therapies*. London, Hodder & Stoughton, 1993, 136-168

Perhaps most importantly the single case study is the raw case load of each practitioner. A routine of rigorously collating studies is a commendable continuing education exercise that may encourage practitioners to become more active in the generation of efficacy data.

Supporting Pre-Clinical Evidence

Pharmacokinetic issues

Any rationale for herbal medicine is likely to be based on the activity of many plant chemical constituents. There are fundamental technical questions raised in building a rational case for herbal therapeutics. The following might usefully form the basis of pharmacokinetic research questions which in turn could provide important information for quantifying efficacy and underpinning clinical research proposals.

In what ways are plant constituents likely to interact, in the gut and body tissues, to affect bioavailability and activity? (Obvious interactions are between essential oils, mucilages, tannins, resins, alkaloids, saponins, minerals and complex carbohydrates.)

What is known of hepatic action on plant constituents, both in terms of the results of the “first-pass effect”, as plant constituents move into the tissues from the digestive tract, and the impact of enterohepatic recycling?

Following from both the above what plant-derived constituents are likely to reach the systemic circulation (an answer to this question is an essential requisite for meaningful tissue culture experiments - see below)?

How do changes in pharmaceutical preparation affect the bioavailability and activity

of plant constituents? For example, do alcoholic extracts have significantly different actions from the aqueous extracts generally dominant in traditional practice?

With new biochemical monitoring technology it is feasible that some of these answers could be obtained non-invasively in healthy human subjects. This would provide more useful answers than the traditional reliance on animal experiments.

Cell and tissue cultures

As part of the modern move to find alternatives to animal experimentation, increasing attention is being paid to techniques for assessing the effects of drugs on cultures of cells, tissues and organs *in vitro*. Conventional drug research is switching in this direction for preliminary screening in drug discovery programmes, and there is also a move for at least initial toxicological testing.

The advantages are in the opportunity for the direct observation of the action of an agent on target cells with some reduced ethical difficulties (although the sacrifice of animals is often necessary to supply short-lived organ and tissue samples).

The problems are the limited application of such observations to the *in vivo* situation and the need to confirm any *in vitro* findings anyway; from the point of view of herbal research there is the additional problem that it is impossible at this stage to reproduce that balance of plant constituents that will actually reach internal tissues (after digestion, absorption, and the “first-pass” hepatic effect). Difficulties are increased by the desirability of using tissues most closely mimicking the real situation ie. mammalian organ cultures (rather than the easier to culture amphibian tissues, or the less sophisticated cell lines).

Nevertheless, *in vitro* techniques could provide valuable supplementary information to other research, as in the following suggested projects:

The influence of herbal extracts on epithelial tissue cultures (eg. gastric, enteric and tracheal tissues); such findings could inform pharmacokinetic calculations for herbal dosage.

Observations on the biotransformation of plant constituents using liver cultures.

Alteration in the migratory behaviour and internal metabolism of macrophages as a result of exposure to herbal extracts.

Non-specific observations (as in gerontological research) on cell migrations, length of interphase, longevity and other pointers to in vitro cell health.

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