

European Committee for Homeopathy



HOMEOPATHIC DRUG PROVING GUIDELINES

PROVINGS SUBCOMMITTEE

EUROPEAN COMMITTEE FOR HOMEOPATHY

ECH Homeopathic Drug Proving Guidelines

The ECH Proving subcommittee aims to re-establish the understanding for the need to conduct drug provings within the homeopathic community and to attract those who are interested in provings.

The subcommittee is now pleased to present the Homeopathic Drug Proving Guidelines. They are based on the structure and contents of the Guidelines for Good Clinical Practice of the International Conference on Harmonisation (ICH), and reprocessed and amended for the requirements of homeopathic drug provings. Their aim is to lay down a framework outlining the minimum criteria which have to be covered in a protocol for a good homeopathic proving. It integrates criteria for quality control of provings with respect to the completeness of documentation (according to a defined check list) and continuing education for doctors and supervisors involved in provings.

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TABLE OF CONTENTS

	Page
Introduction	1
History and structure of International Conference on Harmonisation (I.C.H)	2
Complete Table of contents Guideline E6: Guideline for Good Clinical Practice (GCP)	4
E6.1: Glossary, amended for Homeopathic Drug Proving	5
E6.4: Investigator, amended for Homeopathic Drug Proving	9
E6.5: Sponsor / Monitoring, amended for Homeopathic Drug Proving	10
Homeopathic Drug Proving Protocol based on an amended version of ICH Topic “E6.6: Clinical Trial Protocol And Protocol Amendment(s)”, including:	11
Case Report Form (CRF), amended for Homeopathic Drug Proving	25
Appendices	
• Checklist for Proving Substance or Remedy	
• Curriculum Vitae of Principal Investigator (Example)	
• Internet Addresses	

INTRODUCTION

Homeopathic drug proving is essential in the development of the homeopathic art of cure. It provides a necessary tool to find the most appropriate remedy for the patient.

Homeopathy here is defined as the use of single remedies according to the Law of Similars. The most important part of the Materia Medica consists of provings, together with toxicological reports and clinical experience. There is a great need for further well conducted Homeopathic Drug Provings.

One of the goals of ECH-Subcommittee Drug Provings is to promote and integrate provings into education and teaching programmes. However, provings have been conducted in manifold ways, with an enormous variation in quality.

What is a decent qualitative proving? A small question, a difficult answer, which would require a lot of research. Only little research has been done so far due to the inadequate financial resources for research in homeopathy. Many theories, methods and protocols have been established and published. Meanwhile ethical and legal requirements have become more and more important (Declaration of Helsinki, ICH-Guidelines, come into operation in January 1997). So, ICH-Guidelines are rather young, compared to homeopathy, but up to date they are admittedly the standard guidelines for clinical research worldwide.

The ECH-Subcommittee Drug Provings will try to create a protocol for provings, taking into consideration both homeopathic principles and ICH-guidelines, and communicate it to people who want to conduct provings in the different European countries. It is not the intention of this protocol to impose rules for elaborating provings, but to explain what can be done and to show what the consequences are, if different approaches are followed.

In the previous years the subcommittee has been working on a "Minimum standard for homeopathic drug proving protocols", but this standard is very limited and only contains general statements. This is why it has been decided to elaborate the Minimum Standard in a booklet, which should stimulate people to do well conducted provings. We elaborated a booklet considering every aspect of a homeopathic drug proving (H.D.P.).

A homeopathic drug proving is nowadays considered to be a clinical trial. Accordingly the I.C.H. Guidelines for Good Clinical Practice (GCP) have to be applied and also methodological and legal consequences have to be considered, e.g. legal requirements for clinical trials have to be met. Although conventional trials are very different from H.D.P's, it is important to follow the frame of GCP, because many items in the I.C.H.-guidelines are necessary and useful for Homeopathic Drug Provings as well. Therefore the structure of the booklet is based on the I.C.H. Topic E6 (E = Efficacy). NOTE FOR GUIDANCE ON GOOD CLINICAL PRACTICE (CPMP/ICH/135/95). These guidelines are available from Internet (see Appendix; Internet addresses).

Only items which are relevant to Homeopathic Drug Provings are commented on and listed. However it is indispensable that the full text of the ICH-Guideline E6 has to be studied before doing a proving. Also guidelines E3 and E8 are very helpful and important.

Additionally it is necessary to comment on the terminology, which is used for conventional clinical trials. Several terms like "Sponsor", „blinding“ and „placebo“ need further explanation. Due to the fundamentally different approaches of conventional clinical trials and homeopathic drug provings, these terms are used in a different sense. Some short hints are given below but more extensive explanations are provided in the corresponding topics in the text of the guidelines (e.g. protocol 6.4.3 and glossary)."

Sponsor

According to the glossary in the EU-GCP-Guidelines E6/1.53, the sponsor is the one responsible for the total trial or homeopathic drug proving: "An individual, company, institution, or organisation which takes responsibility for the initiation, management, and / or financing of a clinical trial". This is to say that the principal investigator in a Homeopathic Drug Proving automatically also takes the role of the sponsor. The sponsor does not necessarily give money for the proving, but is always responsible for the proving.

Placebos / Blanks

Whereas the meaning of „placebo“ is different in conventional clinical trials and H.D.P's, it is proposed to use „blanks“ as an own term for „homeopathic placebos“, as described under 6.4.3 in the protocol.

For those, who are not familiar with the International Conference on Harmonisation, a chapter about History and structure of I.C.H. has been added.

SHORT HISTORY OF THE INTERNATIONAL CONFERENCE ON HARMONISATION (ICH)

The impulse to initiate ICH arose from the need to have an independent international evaluation of medicinal products, before they are allowed on international markets. The International Conference on Harmonisation (ICH) has been the leading power in formulating guidelines for clinical research within the last 5-10 years. The birth of ICH took place in Brussels in 1990.

At the first meeting of the Steering Committee of ICH the *Terms of Reference* were agreed and it was decided that the Topics selected for harmonisation would be divided into *Safety*, *Quality* and *Efficacy* to reflect the three criteria which are the basis for approving and authorising new medicinal products.

The European Agency for Evaluation of Medicinal Products, EMEA, which was founded in 1993, has constituted the Committee for Proprietary Medicinal Products (CPMP) to prepare the Good Clinical Practice – Guidelines, as marked here (on the Tab.1, Structure of ICH).

This committee has worked out the Guidelines and they have come into operation in Jan. 1997. So, they are rather young, compared to homeopathy, but for the time being they are accepted as the standard guidelines for clinical research worldwide.

Homeopathic Drug Proving are part of – *non conventional* – clinical research and if homeopathy shall be recognized as a scientific drug therapy, we will have to discuss these guidelines. Otherwise, the homeopathic community stays in a ghetto, in a homeopathic ivory tower.

Additionally, there are many items in the GCP – Guidelines, which are equally useful for Homeopathic Drug Proving.

In the following guidelines only the most important chapter for the methodology of provings, the chapter 6 of guideline E6, „Clinical Trial Protocol and Protocol Amendments“ is elaborated extensively.

In 2000, the Steering Committee of ICH has launched following Revised ICH Terms of Reference:

- To maintain a forum for a constructive dialogue between regulatory authorities and the pharmaceutical industry on the real and perceived differences in the technical requirements for product registration in the EU, USA and Japan in order to ensure a more timely introduction of new medicinal products, and their availability to patients;
- To contribute to the protection of public health from an international perspective;
- To monitor and update harmonised technical requirements leading to a greater mutual acceptance of research and development data;
- To avoid divergent future requirements through harmonisation of selected topics needed as a result of therapeutic advances and the development of new technologies for the production of medicinal products;
- To facilitate the adoption of new or improved technical research and development approaches which update or replace current practices, where these permit a more economical use of human, animal and material resources, without compromising safety;
- To facilitate the dissemination and communication of information on harmonised guidelines and their use such as to encourage the implementation and integration of common standards

Source: History and Future of ICH

<http://www.ifpma.org/ich8.html>:

The Future of ICH - Revised 2000, Statement by the ICH Steering Committee on the occasion of the Fifth International Conference on Harmonisation, 9-11 November 2000, San Diego

ICH INTERNATIONAL CONFERENCE ON HARMONISATION

ICH - Parties

- **EU European Commission - European Union**
- **EFPIA European Federation of Pharmaceutical Industries and Associations**
- **MHLW Ministry of Health, Labor and Welfare, Japan**
- **JPMA Japan Pharmaceutical Manufacturers Association**
- **FDA US Food and Drug Administration**
- **PhRMA Pharmaceutical Research and Manufacturers of America**

Observers act as a link with non-ICH countries and regions

- The World Health Organisation (WHO)
- The European Free Trade Area (EFTA), represented by Switzerland
- Canada, represented at ICH by the Drugs Directorate, Health Canada

IFPMA **International Federation of Pharmaceutical Manufacturers Associations**

representing the research-based pharmaceutical industry and other manufacturers of prescription medicines in 56 countries throughout the world. Closely associated with ICH, to **ensure contact** with the research-based industry, **outside the ICH Regions**.

IFPMA has - as a non-voting member - two seats on the ICH Steering Committee and **runs the ICH Secretariat** in Geneva.

Administration of ICH

• **Steering Committee**

- 2 representees from each of 6 parties + 2 of IFPMA + 1 representee of observers

Topics for harmonisation **Safety, Quality and Efficacy**

• **Secretariat** located in **Geneva**, Tasks:

- Preparation and Documentation of meetings of Steering Committee.
- Run by **IFPMA**

EMA European Agency for Evaluation of Medicinal Products

founded by EU-Council July 1993 Start Jan. 1995

Located: **London**

Organs:

a) Administrative Council

b) **3 committees**

b1) CPMP

b2) CVMP

b3) COMP

c) Director, Mr Thomas Lönngren

d) Secretariat

CPMP - Committee for Proprietary Medicinal Products

Chosen by EMA.

Members: 2 representees of each member state of the EU.

For Austria:

Prof. Heribert Pittner – Bundesmin. Soz. Sicherheit

Prof. Josef Suko – Pharmakol. Inst. Uni Wien

Tasks:

- Technical and scientific support for ICH-activities

- Working out of CPMP-ICH-GCP-Guidelines

(Come into operation Jan. 1997).

E6 GUIDELINE FOR GOOD CLINICAL PRACTICE

Complete table of Contents

This table of contents states all items, which are specified in the E6 Guideline for Good Clinical Practice to give an idea of the complete realm of this guideline.

To fully understand this text, as already stated in the introduction, it is indispensable to have the complete text of Guideline E6 at hand !!!

The complete wording of the Guideline is available by Internet download, as indicated in the appendix.

E6.6 CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S) has been reprocessed for the needs of homeopathic drug provings, as indicated below.

Those, topics of E6 which have not been discussed (as stated in the introduction), are put in [...].

- E6.1** Glossary, (amended for Homeopathic Drug Provings)

- [**E6.2**] The principles of ICH GCP

- [**E6.3**] Institutional Review Board/Independent Ethics Committee

- E6.4** Investigator

- E6.5** Sponsor / Monitoring

- E6.6** Clinical Trial Protocol And Protocol Amendment(s)
Reprocessed as:
„Homeopathic Drug Proving Protocol Based On An Amended Version Of ICH Topic E 6.6, Guideline for Good Clinical Practice (Note for Guidance on Good Clinical Practice)“
including: Case Report Form (CRF), amended for Homeopathic Drug Provings

- [**E6.7**] Investigator´s Brochure

- [**E6.8**] Essential Documents For The Conduct Of A Clinical Trial

E6.1 GLOSSARY

NOTE: This glossary contains only those items, which have been subject to change according to the needs for HDPs. The complete text is available by download of the Guideline E6 from internet, as indicated in appendix 'Internet addresses'.

Terms not existing in ICH-guidelines, are amended in alphabetical order and marked by an asterix (*).

1.1 Adverse Drug Reaction (ADR)

In homeopathic drug provings a conventional ADR will not occur, because there are no toxicologic effects of the proving substances, since they usually are administered in high dilutions.

* Adverse Proving Symptom

An adverse **Proving Symptom is defined as a symptom, which is likely to be caused by the administration of the proving substance and adversely affects the well being of a volunteer, disturbs the normal daily routine and may require the withdrawal of the volunteer from the homeopathic drug proving. It will be recorded on the Adverse Event Form, attached to the Case Report Form (CRF) of each volunteer.

* Proving Symptom

Proving symptoms are defined as those changes of the mental, emotional or physical state of the volunteer, which are likely to be caused by the administration of the proving substance and are out of the ordinary patterns of reaction of the volunteer, shown during the taking of the case history. Proving symptoms are generally temporary symptoms, lasting for several hours or days.

1.2 Adverse Event (AE)

Any untoward medical occurrence in a volunteer administered a proving substance and which does not necessarily have a causal relationship with the action of the substance. An adverse event (AE) can therefore be any unfavourable and unattended sign, symptom or disease temporally associated with the administration of a proving substance, whether or not related to it.

1.4 Applicable Regulatory Requirement(s)

Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products (proving substances).

A homeopathic drug proving is legally considered to be a clinical trial.

1.10 Blinding / Masking Placebos / Blanks

Whereas the meaning of „placebo“ is different in conventional clinical trials and HDPs, it is proposed to use „blanks“ as an own term for „homeopathic placebos“, as described under 6.4.3 in the protocol. In Homeopathic Drug Proving blinding is not restricted to getting the substance or not, but also to the identity of the substance, because the administration of the proving substance is not a treatment, but will produce proving symptoms, which may affect the whole organism.

1.12 Clinical Trial / Study

The aim of a homeopathic drug proving is not the proof of efficacy but to gain knowledge about the innate character of a drug, the “remedy picture”, which is more an aspect of quality, than of quantity. Thus a homeopathic drug proving is an investigational clinical trial designed to gather information on the potential areas of application for homeopathic remedies.

1.13 Clinical Trial / Study Report

The report of a homeopathic drug proving requires specific items, which are not mentioned in the ICH Guideline for Structure and content of Clinical Study Reports. Therefore a specific structure for Homeopathic Proving Reports has to be applied.

* Healthy volunteer

The volunteer has to be healthy in the sense of being free from important physical or psychic symptoms and does not consider himself to need medical treatment. The investigator too – after having taken the case history and done clinical examination – does not see an indication for medical treatment.

*** Homeopathic Drug Proving – Definition**

A homeopathic drug proving (HDP) is done by the defined administration of a proving substance in a non-toxic dilution, prepared according to a homeopathic pharmacopoea, to healthy persons (volunteers, provers).

The proving substance causes reversible symptoms on the physical, mental and psychic level of volunteers, which are systematically observed and recorded by the volunteer(s) and the investigator(s). This is done in order to use it as a homeopathic remedy according to the principle of similarity in a sick person.

1.27 Independent Ethics Committee (IEC)

To review Homeopathic Drug Provings, an IEC which also includes homeopathic professionals is necessary.

1.33 Investigational Product

*A proving substance (drug), prepared according to a Homeopathic Pharmacopoeia or a placebo / blank administered or used as a reference in HDP.

1.34 Investigator (see diagram at the end of Glossary)

* **Investigator in HDP** (In homeopathic literature also referred to as: Observer; Supervisor; Proving doctor): A person responsible for the direct contact with the volunteer(s). He reviews the diaries (journals) together with each volunteer in order to clarify and if necessary amend the symptoms.

* **Principal Investigator** (In homeopathic literature also referred to as: Master Prover; Coordinator; Director of Proving)

Is responsible for the conduct and organization of the Homeopathic Drug Proving following GCP-Guidelines, e.g. contact with Independent Ethical Commission and the report of severe adverse events, storing of study documents.

* **Volunteer** (In homeopathic literature also referred to as: Prover) Person who takes the proving substance and reports any symptoms that occur by keeping a diary and direct contact with the investigator.

* **Law of similars** see under Principle of similarity

1.38 Monitoring

Usually monitoring is not applicable in Homeopathic Drug Provings because of the small number of volunteers, taking part in a proving.

*** Potentized Medicines**

Medicines processed in a specific way, namely by succussion or trituration of serial dilutions. The diluting procedure specific for homeopathy is called potentisation or dynamisation. With steps of 1 part plus 99 parts of excipient, i.e. centesimals or “C”-potencies are obtained. The number of steps usually defines the degree of dynamisation, e.g. “C 12” or “C30”.

*** Principle of similarity** (also stated as „law of similars“)

A substance, capable of provoking symptoms in a healthy organism, acts as a curative agent in a diseased organism in which similar symptoms are manifested (e.g. the dilution of “onion” or *Cepa allium* cures a coryza with symptoms like those that occur when cutting onions).

*** Proving symptom**

Proving symptoms are defined as those changes of the mental, emotional or physical state of the volunteer, which are likely to be caused by the administration of the proving substance and are out of the ordinary patterns of reaction of the volunteer, shown during the taking of the case history. Proving symptoms are generally temporary symptoms, lasting for several hours or days.

* **Principal investigator** see: 1.34 investigator and diagram at the end of Glossary

1.44 Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.

Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments.

1.45 Protocol Amendment

A written description of a change(s) to or formal clarification of a protocol.

1.50 Serious Adverse Events (SAE) or Serious Adverse Drug Reaction (Serious ADR)

Since Homeopathic Drug Provings are done with only non-toxic dilutions of a proving substance, it is very unlikely to have serious adverse drug reactions.

1.51 Source Data

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a Homeopathic Drug Proving necessary for the reconstruction and evaluation of it.

Source data are contained in source documents (original records or certified copies).

1.53 Sponsor

An individual, company, institution, or organisation which takes responsibility for the initiation, management, and / or financing of a Homeopathic Drug Proving.

Comment: This is to say that the principal investigator in a Homeopathic Drug Proving automatically also takes the role of the sponsor. The sponsor does not necessarily give money for the proving, but is always responsible for the proving.

1.54 Sponsor-Investigator

If the Homeopathic Drug Proving is done with several investigators, the sponsor-investigator takes the role of the principal investigator.

1.56 Subinvestigator

In Homeopathic Drug Provings usually the investigators (proving doctors) have no subinvestigators.

1.57 Subject / Trial Subject (Volunteer)

An individual who participates in a clinical trial (Homeopathic Drug Proving), either as a recipient of the investigational product(s) (proving substance) or as a control.

OVERVIEW OF TERMINOLOGY IN

GCP-GUIDELINES

HOMEOPATHIC DRUG PROVINGS

Sponsor or Sponsor- (Principal-) Investigator
over-all responsibility for the clinical trial

Sponsor or Sponsor- (Principal-) Investigator
over-all responsibility for the proving

Coordinating investigator
Head of investigators in a multi-centre trial

Coordinating investigator
Head of investigators in a multi-centre trial

Principal Investigator,
called so, if head of team of investigators

Principal Investigator (Master Prover)
(Coordinator)
(Director of Proving)

Investigator
responsible for the conduct of the clinical trial at the trial site

Investigator (Supervisor)
(Proving doctor)
(Observer)

Subinvestigator
member of the clinical trial team, supervised by the investigator

Subinvestigator
usually not a function in homeopathic drug provings

Trial subject

Volunteer (Prover)

E6.4 „INVESTIGATOR“

(see also glossary under 1.34)

Note: Only those topics, which have been commented or amended due to specific needs for Homeopathic Drug Provings are quoted here. The other topics have to be reviewed in the source document, available by Internet-Download as given in the Introduction of this paper. A number of topics given in the source document however are not relevant or applicable for Homeopathic Drug Provings.

4.1 Investigator's Qualifications and Agreements

There are different statements about the responsibility and required qualifications for principal investigators and investigators in national laws, which have to be taken into consideration.

The Declaration of Helsinki (latest version, adopted at the 52nd WMA General Assembly, Edinburgh, Scotland, Oct. 2000- / Download: Homepage of World Medical Association : <http://www.wma.net>) in article 15 states: *Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.*

For Homeopathic Drug Provings the following qualifications are considered to be adequate:
All investigators, who are in direct contact with volunteers, must have a qualified education in homeopathy, must have had at least 5 years of experience in Homeopathic practice (treating patients) and must have proven at least 3 Homeopathic remedies personally.
The principal investigator of the proving must additionally have at least 2 years of experience in HDPs.

4.1.2 The investigator should be thoroughly familiar with the appropriate use

Comment: In case of blinding of investigator and/or principal investigator they should not know, which proving substance is used.

E6.5 SPONSOR / MONITORING

E6.5 SPONSOR

Homeopathic Drug Provings are quoted here. The other topics have to be reviewed in the source document, available by Internet-Download as given in the Introduction of this paper. A number of topics given in the source document however are not relevant or applicable for Homeopathic Drug Provings.

5.12 Information on Investigational Products

In Homeopathic Drug Provings safety is assured by administering only non-toxic dilutions of the proving substances. There is no need for efficacy data, since in a Homeopathic Drug Proving efficacy is not tested.

5.13 Manufacturing, Packaging, Labelling and Coding Investigational Product(s)

5.13.3 The Investigational Product(s)

should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

NOTE: See also drug proving protocol E6.6.4.4!

5.18 MONITORING

Usually in HDP there are only small numbers of volunteers engaged, the sponsor often is a sponsor-investigator, there are little or no financial resource implications. Therefore monitoring is desirable, but often will not be feasible.

With this respect, it would be helpful to have independent peer groups for quality assurance!

In the longer term an International monitoring group for Homeopathic Drug Provings is necessary, because national monitors will not be feasible in every country due to lack of personal and financial resources.

HOMEOPATHIC DRUG PROVING PROTOCOL

BASED ON AN AMENDED VERSION OF ICH TOPIC E 6

**NOTE FOR GUIDANCE ON GOOD CLINICAL PRACTICE
(CPMP/ICH/135/95) CHAPTER 6:**

CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)

(DATE FOR COMING INTO OPERATION 17 JANUARY 1997)

EDITED BY

**Subcommittee Drug Proving
of the
European Committee for Homeopathy (ECH)**

E6.6 CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)

Table of contents

Note: To give an overview of the genuine guideline E6.6, a table of contents is prefixed here.

- 6.1 General Information
- 6.2 Background Information
 - 6.2.1 Name and description of the investigational product.
- 6.3 Trial Objectives and Purpose
- 6.4 Trial Design
 - 6.4.2 A description of the type and design of trial to be conducted
 - 6.4.2.1 Determination of the clinical phase
 - 6.4.3 A description of the measures taken to minimize / avoid bias
 - 6.4.4 A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s).
- 6.5 Selection and Withdrawal of Subjects
 - 6.5.1 Subject Inclusion criteria.
 - 6.5.2 Subject Exclusion criteria
 - 6.5.3 Subject withdrawal criteria
- 6.6 Treatment of Subjects
- 6.7 Assessment of Efficacy
- 6.8 Assessment of Safety
- 6.9 Statistics
- 6.10 Direct Access to Source Data/Documents
- 6.11 Quality Control and Quality Assurance Procedures
- 6.12 Ethics
- 6.13 Data Handling and Record Keeping
- 6.14 Financing and Insurance
- 6.15 Publication Policy

Supplements

Amendments in Homeopathic Drug Proving Protocol:

- *Case Report Form (CRF)*
- *Appendix 1 „Checklist for proving substance or remedy“*
- *Appendix 2 Curriculum Vitae Investigator*
- *Appendix 3 Internet Addresses*

HOMEOPATHIC DRUG PROVING PROTOCOL

Introduction

The methodology of Homeopathic Drug Proving (HDPs) has been and still is extremely variable. Important items like identity and source of the remedy, application of placebo (blanks) or not, etc., are often not stated in reports of provings. In many cases it is not possible to find out if any protocol at all has been followed in the conduct of the proving. To meet today's standards of methodology, it is inevitable to describe precisely the materials and methodology of Homeopathic Drug Proving.

Therefore the Subcommittee Drug Proving of the European Committee for Homeopathy agreed to provide a proposal for proving methodology and protocols, including several concrete examples.

To have a structure, which is internationally accepted and easily accessible (by internet download), it has been decided to take ICH-Guideline E6, chapter 6 as a basis for the protocol. The text of Guideline E6, Chapter 6 has been modified according to the needs of Homeopathic Drug Proving.

Notes:

1) As repeatedly stated elsewhere, for the sake of understanding the following Drug Proving Protocol, it is **indispensable** to have at hand the original text of the **ICH-Guideline E6, chapter 6**, which can be downloaded as pdf-file from the Internet Homepage of the International Conference on Harmonisation (ICH) under >> www.ich.org << (Go to Guidelines - Efficacy-E6 - chapter 6).

2) In the following text, the original wording of the ICH Guideline E6 Chapter 6 is marked by a black line at the margin of the text.

Amended text is written in *"italics"*.

3) The original numbering of the items from E6 chapter 6 is kept, however some items have been left out, because usually they are not needed in Homeopathic Drug Proving. Accordingly some numbers will be missing. Please look at the original text of the guideline.

4) Some items, not existing in the Guideline E6, but necessary for Homeopathic Drug Proving (HDPs) have been added as sub-items, marked by letters from "A ...Z".

5) This proposal of a protocol is not to be considered as strict rules, but will ensure that all relevant items necessary for a proving are taken into account. It will help to obtain comparable results from provings, which are made in Europe and elsewhere.

E6.6 The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate pages, or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an investigator's brochure.

6.1 General Information

6.1.1 Protocol title, protocol identifying number and date.

6.1.2 Name and address of sponsor and monitor (if other than sponsor).

6.1.3 Name and title of the person(s) authorized to sign the protocol and the protocol amendments for the sponsor (i.e. principal investigator).

6.1.4 Name, title, address and telephone number(s) of sponsor's medical expert for the trial (*if applicable*).

6.1.5 Names and title of the investigator(s) (*Proving doctors*), who is (are) responsible for conducting the trial (*proving*) and the address and telephone number(s) of the trial site(s) (*only applicable, if different groups are taking part in the proving*).

6.1.6 Names and addresses of other institutions involved in the trial (i.e. pharmacies).

6.2 Background and substance Information

6.2.1 Name and description of the investigational product(s) (*proving substance*).
Exact information about the proving substance is mandatory to guarantee reproducibility as well for the manufacturing process as for re-Provings. To ensure that all specifications are given, it is recommended to use a:

„Checklist for Proving substance or remedy“ - see Appendix 1

6.2.2 A summary of findings from *previous provings on the substance, if available. Specify literature references and check if statements, asked for in the “Checklist” are given.*

6.2.3 Summary of the known and potential risks and benefits, if any, to human subjects.

Risks

The substance administered to each volunteer will be a homeopathic preparation or a blank (placebo see also 6.4.3) which has been potentized i.e. to a C12 or C30 potency with a dilution of 1×10^{-24} resp. 1×10^{-60} . The toxicity of these preparations is considered to be extremely low, however it is expected that reversible Proving symptoms will be experienced by the Volunteers after administration of the Proving substance. Proving symptoms are defined as those changes of the mental, emotional or physical state of the Volunteer, which are likely to be caused by the administration of the remedy and are out of the ordinary patterns of reaction of the volunteer, shown during the taking of the case history. Proving symptoms are generally temporary symptoms, lasting for several hours or days. Proving symptoms might adversely affect the well being of a volunteer. This risk will be covered by an insurance for the Volunteers, provided by the sponsor (responsible for the Proving, see glossary 1.53).

Benefits

The Proving symptoms obtained are used for therapeutic purpose or treatment after the Proving according to the law of similars and thereby are beneficial for a great number of patients.

6.2.4 Description of and justification for the route of administration, dosage, dosage regimen and treatment (*administration of a Proving substance*) period(s).

Note: *The administration of a Proving substance is not a “treatment” as in conventional trials, because there is not one or several specific effects intended to be seen by applying the Proving substance. Proving symptoms may occur on the physical, psychic and mental level of a volunteer.*

Example of description:

The Homeopathic remedies used in this drug proving will be administered orally as opened capsules, the content of which is applied sublingually. The experience of more than 200 years of HDPs has shown this way of administration to be effective. As soon as proving symptoms occur, the intake of the remedy will be stopped, to prevent adverse drug reactions.

6.2.5 A statement that the trial (*Proving*) will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

6.2.6 Description of the population to be studied.

6.2.6.A Recruitment of Volunteers

It is recommended to state, how volunteers had been recruited (e.g. students of Homeopathy, lay people gained from newspaper advertising). Thus, at the end, it can be concluded if different methods of recruitment lead to different results in provings.

6.2.6.B Ethnic origin of Volunteers

The ethnic origin of the Volunteers should be documented in their individual case taking forms.

6.2.6.C Location of the Proving

It may seem as an exaggeration to ask for the ethnic origin of the Volunteers and the location of a Proving, but already Hering, one of the most sophisticated homeopaths from the past emphasised the influence of the location of a Proving on Proving symptoms as follows:

„Who has learnt to compare the (drug)-provings, must become aware of all volunteers, living at the very same place, proving the same remedy, note more similar symptoms [...] than those living at a distance. The journals of volunteers living far away report symptoms being strikingly different, which but are similar among themselves, if there are several volunteers living at that other place. The reports of volunteers have the same colouring at the same place.“ [Herings Medizinische Schriften (Gypser, K.-H. Hrsg.). Bd.III. Burgdorf, Göttingen 1988, 1187-1188.; translation from german by the authors]

Examples:

- *Volunteers will be male and female healthy individuals, from different social groups between 18 and 70 years old, living in Brussels, recruited by newspaper advertising.*
- *Volunteers are german male and female homeopathic doctors, working in different cities of Germany, between 26 and 78 years old.*

6.2.6.D Language

Example: The case taking, filling in of diaries (journals) and reporting of symptoms will be done in german language.

In case a proving is conducted in different countries as a multi-centre study, it has to be determined, in which language the study report will be written. Usually it will be in English, but it should be stated before the beginning of the proving. It also has to be stated, to which extent symptoms will be translated for the report and if the text of the original wording and language of a symptom shall be cited, or not. For the sake of being able to trace back a proving symptom to its ultimate origin, it must be kept in original language and wording of the Volunteer, who experienced it. How it could be feasible to reach this goal with respect to translations has to be discussed. But it should be discussed so that the sentences out of which the proving symptoms have been collated will at least be documented in their original wording by the director of the proving.

6.2.7 References to literature and data that are relevant to the trial (Proving) and that provide background information for the trial (Proving).

Examples:

- *For references to literature and appendices see “supplements” under 6.16*

Comment: *As a Homeopathic drug Proving from a legal point of view is a clinical trial, the protocol may be judged e.g. by members of ethical committees not familiar with Homeopathy. Therefore a general information about Homeopathy has been included.*

- *The following introduction is given to provide background information for people, who are not familiar with homeopathy:*

The founder of Homeopathy is Samuel Hahnemann (1755-1843), who performed his first drug Proving in 1790 with China bark.

Homeopathy is a system of medical practice, aimed at methodologically improving the level of health of an organism by the administration of proven potentized ** medicines, which are individually selected in accordance with the law of similars ***.*

** a proven substance = one which has been pharmacologically tested on healthy human beings during a Homeopathic drug Proving;*

*** potentized = processed in a specific way, namely by succussion or trituration of serial dilutions. The diluting procedure specific for homeopathy is called potentisation or dynamisation. With steps of 1 part plus 99 parts of excipient, i.e. centesimals or “C”-potencies are obtained. The number of steps usually defines the degree of dynamisation, e.g. “C 12” or “C30”;*

**** law of similars = a substance, capable of provoking symptoms in a healthy organism, acts as a curative agent in a diseased organism in which the same symptoms are manifested (e.g. the dilution of “onion” or Ceba allium cures a coryza with symptoms like those that occur when cutting onions).*

In traditional clinical trials phase I, the main goal is to give evidence of a specific effect, i.e. reduction of blood pressure or anxiety etc.. A generalized statement about the realm of action is given. The effect is rated by statistical methods and mostly is related to placebo or an established therapy. Homeopathic drug provings historically are the first systematic, experimental approach to detecting changes in healthy volunteers after exposure to a drug.

The concept of homeopathic drug provings has been outlined by S. Hahnemann in his Organon of Medicine, §§ 105-142 (Appendix 1) and assumes that a remedy, given to a healthy person, affects the organism of a human being and that the alterations in the organism are shown by individual symptoms in mind, intellect and body of the volunteer. The range of enquiry is not a predetermined field, but all symptoms in the realms of mind, intellect and body are registered and documented. In Homeopathy, the individual symptoms are the most important. Not the diagnosis of the illness, but the pattern of symptoms, the “disease picture”, which matches best the “remedy picture”, leads to the choice of the remedy and to cure.

The aim of a Homeopathic drug Proving is to gain knowledge about this innate character of a drug, the “remedy picture”, which is more an aspect of quality, than of quantity. We prove a substance not for the proof of an effect, but in the sense that we test its qualities.

Thus a Homeopathic Drug Proving is an investigation which is designed to gather information on the potential areas of application for Homeopathic remedies.

However, there is little or no toxicological risk, when highly diluted substances are taken. A substance which has been potentized to a C 12 has a dilution of 1×10^{-24} whereas a C30 potency has a dilution of 1×10^{-60} , making the concentration immeasurable.

6.3 Trial (Proving) objectives and purpose

A detailed description of the objectives and the purpose of the trial (Proving).

This protocol is designed to conduct Homeopathic Drug Provings for the purpose of creating or amending a symptom list and drug picture of Homeopathic remedies.

The aim of a Homeopathic Drug Proving is to gain knowledge about the innate character of a drug, the “remedy picture”, which is more an aspect of quality, than of quantity. We prove a substance not for the proof of its efficacy, but in the sense that we test its qualities. The symptoms will be collated and communicated to the Homeopathic community so that they can be clinically verified, which among others means that a symptom, which has occurred in a drug Proving, now occurring in a sick patient is alleviated by that remedy, which produced the Proving symptom after the administration of it.

Example for amending a remedy picture: The original proving of “Petroleum” was done with a natural substance, called “Steinöl”. Today, another substance is used for preparing “Petroleum”. A re-proving will show, if the former symptoms do still occur with the “new” “Petroleum”(This has in fact been done in 1984 in Germany and has shown, that there was an astonishing correspondence of the symptoms with those of the original proving by Hahnemann).

6.4 Trial (Proving) Design

The scientific integrity of the trial and the credibility of data from the trial (Proving) depend substantially on the trial design. A description of the trial design should include:

6.4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial (Proving).

Comment: *Homeopathic Drug Provings are not mentioned in the Good Clinical Practice Guidelines of the European Community (EC). There are similarities with conventional clinical trials, but there are also fundamental differences.*

The purpose of a Homeopathic Drug Proving is not to show the efficacy, but to obtain complete individual symptoms of a drug. This has to be considered in Proving designs.

How the term “Homeopathic drug Proving” is used in this protocol, is defined as follows:

Definition

A Homeopathic Drug Proving (HDP) is a systematic observation and recording of symptoms which occur after the defined administration of a potentized drug or a druglike effective substance, not yet or not sufficiently homeopathically proved, to healthy persons (Volunteers). It is done under the responsibility of a principal investigator, if need be with the assistance of further observers.

Aim of a Homeopathic Drug Proving

The aim of a HDP is to elicit, observe and document reversible proving symptoms (see also 6.2.3 and 6.7), which are needed to use a Homeopathic remedy according to the law of similars. They are defined as those changes of the mental, emotional or physical state of the Volunteer, which are likely to be caused by the administration of the remedy and are out of the ordinary patterns of reaction of the Volunteer, shown during the taking of the case history. It serves for widening the knowledge about insufficiently proved remedies or for introducing new remedies to the Materia Medica Homeopathica.

6.4.2 A description of the type/ design of trial (Proving) to be conducted (e.g. double blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

Example

Blinding method - Double blind

Statistical design - Parallel groups

Control group - Blank (Placebo) controlled

Data collection - Diary and personal contact to proving doctor

The Homeopathic Drug Proving in total will last 5 weeks. The different steps will be described in the following chapters.

Time schedule	Week	1	2	3	4	5
Interview-Case History		X				
Inclusion/ Exclusion Criteria (6.5.1-2)		X				
Evaluation		X				
Education of Volunteers (6.4.5.A)		X				
Prelimin. observation period (6.4.5.B)		X				
Contact with Volunteer (6.4.5.C)	X	X	X	X		
Administration of Proving substance (one day)			X			
Period of observation (6.4.5.C)			X	(X)		
Post observation period (6.4.5.C)				X	(X)	
Observation for adverse events		X	X	X	X	
Processing of Data, Final report		X	X	X	X	X

6.4.3 A description of the measures taken to minimize / avoid bias, including:

- a) Randomisation
- b) Blinding

Terminology in Homeopathic research

Different meanings of the terms „blinding“ and „placebo“ in conventional clinical trials and Homeopathic drug Proving

BLINDING

In relation to HDPs, the term „blinding“ has not the same meaning as in conventional clinical trials.

In conventional double blind studies, neither the investigator nor the subject are aware, which of the groups (verum or placebo) the subject belongs to [• Hinze, C. Klinische Arzneimittelprüfung. Editio Cantor Verl., Aulendorf, 1998, S.69]. The subjects / patients and investigators are but blind only with respect to the question, if the substance is administered or not. They however do know, which kind of therapy will be administered in case of verum treatment (i.e. lowering of blood pressure).

Here again, as already mentioned under 6.2.4 it has to be stated that giving a Proving substance to healthy Volunteers is not a treatment in the conventional sense, which intends to create the same defined specific effects in a great number of patients or Volunteers. The goal of conventional trials is to prove efficacy in a collective of patients.

In HDPs however, the proving substance is not applied to create predefined effects and prove efficacy, but to describe the individual response of every volunteer to the application of the substance. Therefore in HDPs Volunteers and investigators shouldn't know the verum proving substance. They should not only be blind to the question if verum is given, but also to the question what the verum is like. In conventional clinical trials blinding always implicates the giving of placebo.

For provings, blinding seems to be meaningful, even if no blanks (placebos) are used, to reduce symptoms of anticipation. In case of a HDP without blanks, „blinding“ would be limited to what the proving substance (verum) is like.

BLANKS – a specific term for placebos in HDPs

Considering that many terms from conventional clinical research are used for Homeopathic research too, but often based on fundamentally different prerequisites, and therefore understood in a different way there is evidently a need for an own terminology in homeopathic clinical research (the term „drug proving“-„Arzneimittelprüfung“ -is used for conventional clinical trials as well as for homeopathic drug provings).

As described, the meaning of „blinding“ is different in conventional clinical trials and HDPs. In provings, blinding is useful even when no placebos are given. Here the placebos are not given to measure a placebo effect, but to raise the critical alertness of the Volunteers and eventually to find out how far the quality of „Proving symptoms“ under placebo differs from real Proving symptoms. Hence also the meaning of „placebo“ is different.

The first „placebo - controlled trial“ has been done in Nürnberg/Germany in 1835 [• Stolberg, M.: Die Homöopathie auf dem Prüfstein. Münch. Med. Wschr. 138 (1996), 364-366.]. At that time no specific term was used for the „placebos“ given in the Proving. In 1885 american homeopathic doctors used globules without Proving substance, which they called „blanks“ [Mcquire, D.J.: REPORT OF THE DIRECTORS OF PROVINGS. In: Transactions of the Thirty-Eighth Session of the American Institute of Homeopathy, held at St. Louis, June 2,3,4,5, 1885.].

Whereas the meaning of „placebo“ is different in conventional clinical trials and HDPs, it is proposed to use „blanks“ as an own term for „Homeopathic placebos“.

6.4.4 A description of the dosage regimen of the investigational product(s). Also include a description of the dosage form, storage, packaging and labelling of the investigational product(s).

Comment: Packaging has to be done in a way that contamination among the proving substances is prevented. In vitro experiments have shown contamination among verum and blanks (placebo), if they are stored in close neighbourhood without isolating. Aluminum foil has proved to prevent contamination. The single doses of Proving substances and blanks therefore should be wrapped in aluminum foil.

6.4.5 Expected duration of subject (volunteer) participation, and a description of the sequence and duration of all periods, including follow-up, if any.

(Time schedule, example see 6.4.2)

A) *Education of Volunteers*

Example: Being primarily included, the volunteers will be informed about the basic principles of Homeopathy, the sense and objectives of Homeopathic drug Proving and will be instructed, how to keep the diaries.

An extensive case history and (Homeopathic) interview will be taken (in- and exclusion criteria) in advance (see CRF).

B) *Preliminary observation period*

Example: During this phase, lasting one week, the Volunteers are required to fill out the diaries the way, they have been shown. The Proving doctor will contact each person every two or three days to test her or his compliance. Failure in keeping the diary properly may lead to exclusion from the Homeopathic drug Proving.

C) *Contact with Volunteer, period of observation, post observation period.*

Example: From the beginning of the preliminary observation period until the end of the period of observation, there will be an intense contact between the Proving doctor and the Volunteer. During the period of observation, there will be daily contact by telephone and at least two personal meetings, where the diaries are gone through and completed (§139 Organon). During the post observation period the filling in of the diaries will be continued for one week, but personal contact with the proving doctor is scheduled once at the end of the week or in case the Volunteer needs assistance.

6.4.6 A description of the “stopping rules” or “discontinuation criteria” for individual subjects (Volunteers), parts of trial (Proving) and entire trial (Proving). See under 6.6

6.4.7 Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any. (See also 6.1.5 and 6.1.7)

Here is to be stated, who produces, who provides the proving substance and blanks (placebos) and who is responsible for controlling all the steps.

Proving substance: _____ Manufacturer: _____

Responsible for allocation of proving substance and blanks (placebos) to proving doctors: _____

6.4.8 Maintenance of trial treatment, randomisation codes and procedures for breaking codes.

Example:

Randomisation

The proving substances and the blanks (placebos) will be randomized and coded for the sponsor by an independent institution (i.e. a research department of the university of Freiburg). The Volunteers will be assigned to groups A - F and according to the list will receive small boxes, each containing 6 capsules marked e.g. as “A3” or “B15” etc.

The random codes for the proving substances and blanks (placebos) will be sealed in envelopes.

The sealed random code envelopes will be kept by _____ (name of principal investigator or of proving doctor, who keeps them and is responsible for decision to open in case of adverse events).

They must be returned unopened to the sponsor/principal investigator (person responsible for the Proving, see glossary 1.53) at the end of the proving, unless the code has to be broken in case of an adverse event. If an envelope has to be opened, the time, reason and person, who opened it has to be marked on the envelope. This information will also be stated in the corresponding space of the Adverse Event Report Form.

- 6.4.9 The identification of any data to be recorded directly on the Case Report Forms, CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

There should not exist any other records of data, belonging to the Proving, than those in the personal case report form of each volunteer.

The criteria for selection and withdrawal of volunteers are to be set up by the team of investigators. The examples given below may not be exhaustive and have to be reconsidered for each single HDP.

6.5 Selection and Withdrawal of Subjects (Volunteers)

Interview – Case history and evaluation

Example: The candidates will be included or excluded according to the inclusion and exclusion criteria. All will undergo a clinical examination and will be evaluated using the Case-history form.

6.5.1 Subject (Volunteer) inclusion criteria

Example:

- *The volunteer must be healthy in the sense that he doesn't show severe psychic or physical symptoms and does not consider himself to be in need of medical treatment. Also the Proving doctor does not see a necessity for treatment. A medical history and physical examination should confirm this.*
- *The person must be trustworthy, able and ready to express and describe his experiences during the Proving (§§126;139 Organon).*
- *There should be no plans for important life changes like moving, change of job, marriage etc. The usual habits and conduct of life should be continued.*
- *The person should not plan to begin medical treatments like dentistry, surgery or psychotherapy during the drug Proving.*
- *Age: Over 18 years.*

6.5.2 Subject (Volunteer) exclusion criteria

Example:

- *Current medical treatments or Homeopathic drugs in the preliminary observation period or during the Proving.*
- *Prescription of drugs (including Homeopathic) in the past four weeks.*
- *Contraceptive pills in the past three months. (IUP,s mark in the accounts)*
- *Surgical treatment within past two months.*
- *Pregnant, breast feeding.*
- *Under the age of 18.*

6.5.3 Subject (Volunteer) withdrawal criteria (i.e. terminating investigational product treatment / trial treatment [application of Proving substance]) and procedure specifying:

- a) *When and how to withdraw subjects (Volunteers) from trial / investigational product treatment (application). See 6.6 - Stop of intake of Proving substance as soon as symptoms occur. This but does not mean withdrawal from the trial. Not in the case of occurrence of Proving symptoms, but only in case of a severe adverse event, a Volunteer has to be withdrawn.*
- b) *The type and timing of the data to be collected for withdrawn subjects (Volunteers). If a Volunteer has to be withdrawn because of a severe adverse event, the data are kept together with those of all other Volunteers in the CRF of the Volunteer, marked as "withdrawal".*
- c) *Whether and how subjects (Volunteers) are to be replaced.*
Example: No replacement of withdrawn Volunteers
- d) *The follow-up for subjects (Volunteers) withdrawn from investigational product treatment/trial treatment. See 6.8.4*

6.6 Treatment of subjects (Administration of Proving substance to Volunteers)

Comment: *About term „treatment“ remember statements in 6.2.4 and 6.3.*

- 6.6.1 The treatment (administration of *proving* substance) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route(s)/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/ arm of the trial.

Example:

Administration of Proving substance

The Proving substances or Homeopathic remedies used in these drug Proving will be administered orally as opened capsules, the content of which is applied sublingually.

One dose approx. every two hours, max. 6 times for one day, with minimum 15 min. before or after eating. The exact time of drug intake has to be stated in the diaries. As soon as Proving symptoms occur, the intake of the remedy will be stopped.

- 6.6.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/ or during the trial.

Examples:

- *In case of severe adverse events, the investigator (Proving doctor) decides, if an antidote is given , as described under 6.8.3.*
- *Concomittant medication: None.*

- 6.6.3 Procedures for monitoring subject (*Volunteer*) compliance.

Compliance monitoring

To ensure the proper intake, the volunteer will report to his proving doctor at the end of each day of intake.

6.7 Assessment of efficacy

- 6.7.1 Specification of the efficacy parameters.

- 6.7.2 The methods and timing for assessing, recording, and analysing of efficacy parameters.

Assessment of efficacy has to be commented for HDPs.

Example:

In Homeopathic drug Proving, efficacy is assessed differently to conventional trials. Literally, it is not an assessment of efficacy, but of the of action of the Proving substance. "Assessment of efficacy" in HDPs means observing of Proving symptoms. A Volunteer ... "must note down distinctly the sensations, sufferings, accidents and changes of health, he experiences at the time of their occurrence, mentioning the time after the ingestion of the drug, when each symptom arose ..." §139 Organon [Hahnemann, S. Organon of Medicine, translated by William Boericke, B.Jain Publishers, New Delhi, 1921].

Definition of Proving symptoms

Proving symptoms are defined as those changes of the mental, emotional or physical state of the Volunteer, which are likely to be caused by the administration of the proving substance and are out of the ordinary patterns of reaction of the volunteer, shown during the taking of the case history.

The ultimate proof of whether a symptom really belongs to a remedy, however cannot be obtained while conducting the Homeopathic drug Proving, but only in a second step afterwards, by clinical verification, when the proving symptom has led to the choice of the remedy and has cured that symptom in the patient.

There are however some criteria to calculate the probability of a symptom belonging to the proving substance. They have been published by Bayr and Stübler and have been amended as shown below, under 6.9. (Amended criteria of Bayr and Stübler for assessment of symptoms)

6.8 Assessment of Safety

Note: *Descriptions of ethical considerations relating to the proving, as required under 6.12 Ethics are already given here.*

Example: Safety for the volunteers is an important prerequisite in planning of clinical trials. According to the Basic Principles mentioned in the World Medical Association (WMA) Declaration of Helsinki, adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by

The 52nd WMA General Assembly, Edinburgh, Scotland, October 2000, Chpt. 16.:

„Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not

preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.“

As stated above, under 6.2.3 - „Risks“ the proving substances are administered in extremely high dilutions, which ensures low toxicity and thereby considerable safety for the volunteers.

In Homeopathic Drug Provings, there is no conventional pharmacodynamic action of the substance to be considered, because it is administered in high dilutions, which according to experience provokes transient so called “proving symptoms”, but does not cause toxicological effects. Additionally the administration of the proving substance usually will last only for a short time, which again minimizes the probability of adverse events. All Volunteers will be informed about the objectives, potential risks, inconveniences and benefits of the trial and will sign an informed consent form before the beginning of the Homeopathic drug Proving.

6.8.1 Specification of safety parameters.

6.8.2 The methods and timing for assessing, recording safety parameters.

There is no need for defined safety parameters, because in HDP we don´t focus on single parameters as blood pressure, pain or metabolic changes etc.. All changes on the physical, psychic and mental levels are observed.

Safety for the volunteers is an important prerequisite in planning of clinical trials. According to the Basic Principles mentioned in the World Medical Association (WMA) Declaration of Helsinki, adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by

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All Volunteers will be informed about the objectives, potential risks, inconveniences and benefits of the trial and will sign an informed consent form before the beginning of the Homeopathic drug Proving.

6.8.3 Procedures for eliciting reports of and for recording adverse events and intercurrent illnesses.

6.8.3 A Adverse events

6.8.3 B Adverse drug reaction

As stated in the glossary 1.1, 1.2 and 1.50, the terms “Adverse event” and “Adverse drug reaction” are not appropriate for HDPs.

6.8.3 C Adverse proving symptom

- *Adverse events and adverse proving symptoms (see Glossary 1.1), as well as intercurrent illnesses will be recorded on the Adverse Event Form, attached to the Case Report Form (CRF) of each volunteer.*

- *The beginning will be stated and described in the diary of the volunteer.*

- *An adverse proving symptom might require the withdrawal of the Volunteer from the Homeopathic Drug Proving.*

- *The envelopes containing the trial codes will be kept within easy reach by the proving doctor or his designated assistant, only to be opened in case of a severe adverse event or a severe adverse proving symptom. If this occurs, the drug intake will be stopped immediately, the code will be broken and, in case of verum, either an antidote will be given, or the doctor in charge will take care of the Volunteer personally and organise adequate treatment.*

- *The sponsor and principal investigator will be informed within 24 hours of the investigator's / proving doctor's knowledge of the event by sending email or fax.*

6.8.4 The type and duration of follow-up of subjects (Volunteers) after adverse events.

It is recommended to state a scheme for follow-ups after adverse events:

Example:

Any volunteer experiencing an adverse event will be followed up free of charge as long as the symptom(s) exist(s), which caused the withdrawal from the proving or it is determined that the symptoms were not caused by the proving substance.

6.9 Statistics

6.9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis(es).

In conventional clinical trials statistics serve to compare verum and control groups to measure the efficacy of a treatment. In HDP there is no measurement of efficacy, but description of individual proving symptoms.

It has to be stated that the value of Proving symptoms does not ultimately depend on number of Volunteers, who had a particular symptom. Symptoms obtained in a SMALL number of Volunteers, are equally valuable.

The evaluation will not be done by conventional statistical analyses, but by compilation of the Proving symptoms in different categories, representing a certain probability to be associated with the remedy and therefore are the most important ones for further verification.

Example:

Amended criteria of Bayr and Stübler for assessment of symptoms:

A symptom will belong to the remedy with great probability, if at least one of the following criteria is met:

- 1) *Occurrence of the symptom in two or more Volunteers.*
- 2) *Objective, measurable signs and symptoms*
- 3) *Distinct intensity of the symptom*
- 4) *Occurrence of the symptom several times shortly after administration of the drug.*
- 5) *Recurrence of the symptom several times over the course of a number of days.*
- 6) *Recurrence of the symptom using different potencies.*
- 7) *Striking, singular, uncommon symptoms (§153 Organon)*
- 8) *Striking, seldom or paradox modalities and/ or concomitants of the symptom*
- 9) *Mutual pathophysiology in several symptoms (i.e. inflammation in different joints)*

[Bayr, G. and Stübler, M. (1986) Haplopappus baylahuen: Eine Prüfung mit den Potenzen D2, D3, D6 und D12. p.92. Ed. by Stübler, M. Haug: Heidelberg]

There will be a ranking of intensity, given by the Volunteers and a classification, as to whether it was an old, new, or altered symptom that was experienced.

Symptoms, which are not thought to belong to the drug picture, should also be stated, but in a separate chapter, so they are not lost, but marked in a specific manner.

In the final report, symptoms will be compiled according to the format of Clarke's Materia Medica (or Kent Repertory), English edition.

6.9.2 The number of subjects (Volunteers) planned to be enrolled. In multicentre trials, the number of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

Example:

There will be 12-15 male and female Volunteers in each Proving, three of them receiving blanks (placebo). The blank (placebo) is given to keep the Volunteers unsure, whether they got an active substance or blank.

The number of 12-15 Volunteers has been sufficient to give good Proving symptoms in former Proving, therefore this number has been chosen.

6.9.3 The level of significance to be used.

Not applicable

6.9.4 Criteria for the termination of the trial (Proving).

Example:

The HDP will be determined according to time schedule of design, no other criteria to be matched.

Comment:

In HDPs severe adverse events are very rare and, if they occur at all, are usually limited to a single volunteer. Therefore, it is unlikely that there will be any reason for a proving to be terminated prematurely. In the event of 3 or more volunteers developing severe adverse proving symptoms, the proving will be stopped.

6.9.5 Procedure for accounting for missing, unused, and spurious data.

Not applicable for HDP, because only relevant for comparing placebo and verum results for proof of efficacy in conventional trials.

6.9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).

Usually not applicable for HDP.

6.9.7 The selection of subjects (*Volunteers*) to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

All volunteers who reported symptoms should be included in analyses of symptoms. The symptoms obtained under verum or blanks (placebo) must be listed in different groups.

6.10 Direct Access to Source Data/Documents

The sponsor should ensure that it is specified in the protocol or other written agreement that investigator(s)/institution(s) will permit trial (*Proving*) related monitoring, audits, IRB/IEC review and regulatory inspection(s), providing direct access to source data / documents.

Comment: For homeopaths, easy and direct access to source data and original wording of a symptom is crucial for further research in Homeopathy, confirmation and clinical verification of Proving symptoms. Ideally a repertory should provide the information, stating from which words of which Volunteers a symptom has been derived.

6.11 Quality Control and Quality Assurance

The Case Report Form (CRF) is one of the most important documents for quality control in clinical trials and in HDP. It is the reference document for Audit and Monitoring. The entries therefore have to be complete and correctly represent the data obtained. In case of corrections, the original item must be kept legible (only cross out, not erase) and the correction must be signed with date and initials. This is useful to trace back the changes and allows eventual further inquiry. The investigator confirms the correctness of the data in the CRF by his signature. See also: Case Report Form (CRF).

6.12 Ethics

Descriptions of ethical considerations relating to the trial (*proving*).

See under 6.8

6.13 Data Handling and Record Keeping

Records will be kept in the original handwriting of the volunteer in the diaries (journals) filled in by the volunteers. Also notes eventually added by the investigators, Proving doctor(s) or other responsible persons will be kept within the CRF of each Volunteer. The HDP is considered to have been completed on the day of the delivery of the final report to the sponsor. After the completion of the HDP, the sponsor will provide secure space for the records to be kept as long as required by legal regulations.

Comment: *As already stated under 6.10, the data obtained in a Proving are not only necessary during Provings and for legal purposes, but equally for therapeutic use of the proven substance or remedy. Often the therapeutic effect of a remedy, applied according to the law of similars, is the more reliable, when the wording of the Volunteer in the Proving corresponds with the words of a patient.*

6.14 Financing and Insurance

Financing and insurance if not addressed in a separate agreement.

Financing:

A fee is not usually paid to Volunteers in Homeopathic Drug Provings, which are done within the Homeopathic community.

Insurance:

As already mentioned in topic 6.2.3, risks and benefits, the toxicity of these preparations is considered to be extremely low, however it is expected that reversible Proving symptoms will be experienced by the Volunteers after administration of the Proving substance. In rare cases Proving symptoms may adversely affect the well being of a Volunteer. This risk will be covered by an insurance for the Volunteers, provided by the sponsor (person responsible for the Proving, see glossary 1.53).

6.15 Publication Policy

Publication policy, if not addressed in a separate agreement.

Example: See separate agreement with sponsor.

6.16 Supplements

(NOTE: Since the protocol and the clinical trial / study report are closely related, further relevant information can be found in the ICH Guideline E3 for Structure and Content of Clinical Study Reports.)

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CASE REPORT FORM

(HOMEOPATHIC DRUG PROVING PROTOCOL)

Case Report Form

Table of Contents

	Number of pages
- CRF - General Information	1
- General considerations for the homeopathic interview and for the structure of diaries (journals)	1
- Participant Information	1
- Informed Consent Form	1
- General considerations homeopathic interview, filling out diaries	1
- Homeopathic Interview Form	5
- Information proving substance / remedy administration	1
- Volunteers Diary / Journal (Sample)	6
- Adverse Event Report Form	1

CASE REPORT FORM - GENERAL INFORMATION

The following text is cited from: Sickmüller, B.: Good Clinical Practice. Pharm Ind. 52, Nr.12(1990), citations from pp. 1477-1496, and has been commented on and amended by the authors.

A case report form is a record of the data and other information on each subject (volunteer) in a trial (proving) as defined by the protocol. The data may be recorded on any medium, including magnetic and optical carriers, provided that there is assurance of accurate input and representation, and allows verification.

Comment: As stated in the Informed Consent form, all information has to be kept confidential with respect to the identity of the donor of the information.

In order to present the results of a clinical trial adequately, it is essential that a fully comprehensive collection of information on the subject, the administration of the medicinal product being investigated and the outcome of the protocol procedures is available.

This is done, using a case report form (CRF) which should be established to facilitate observation of the subject (volunteer), and which also takes the protocol for the trial into account.

In establishing a CRF, the following items should be considered. Omissions of one or more of these items should be explained:

- a) Date, place and identification of the trial (*proving*);
- b) Identification of the subject (*volunteer*);
- c) Age, sex, height, weight, and ethnic group of the subject (*volunteer*);
- d) Particular characteristics of the subject; (e.g. smoking, special diet, pregnancy, previous treatment)
- e) Diagnosis, indication for which the medicinal treatment is administered in accordance with the protocol.

Comment: Application of a proving substance in a HDP is not a medical treatment as in conventional trials, the "indication" to administer the proving substance is to observe proving symptoms caused by the proving substance.

- f) Adherence to the inclusion/exclusion criteria;
- g) Duration of disease, time of last exacerbation (*if applicable*);

Comment: In homeopathic drug provings: make sure that the volunteer is healthy in the sense of the definition, given in the protocol

- h) Dose, dosage schedule and administration of the medicinal product; notes on compliance;
- i) Duration of treatment, *administration of proving substance*
- j) Duration of observational period;
- k) Concomitant use of medicinal products and non-medicinal interventions / therapy;
- l) Dietary regimens;
- m) Recording of the effect parameters (incl. Date, time, recorder's signature);
- n) Recorded adverse events. Type, duration, intensity, etc.; consequences and measures taken; (Adverse event report form)
- o) Reason for withdrawal (if applicable) and /or breaking of the code. (*Adverse event report form*)
- p) Following forms must be filled in, checked for signature and attached to the CRF of each volunteer:
 - P1) CRF-Informed Consent Form
 - P2) CRF-Homeopathic Interview Form
 - P3) CRF-Participant Information
 - P4) CRF-Information remedy administration
 - P5) CRF-Diary (Journal)
 - P6) CRF-Adverse Event Report Form

Participant Information Sheet

(Text is an example, has to be adjusted according to each particular proving protocol)

Study : Homeopathic drug proving of >> N.N. <<

Purpose :

The aim of this homeopathic drug proving is to constitute a homeopathic remedy picture at hand of the symptoms associated with the application of the proving substance.

The objective of the homeopathic drug proving is to find out the entire realm of action of the proving substances, with respect to both the subjective and objective symptoms.

Outline of the proving :

In this section, a summarised description of the trial will be given. There will be detailed information about the trial by the principal investigator of the homeopathic drug proving. After this there will be a personal examination and evaluation by the proving doctor and, when you meet the inclusion criteria and have signed the Informed Consent Form, the proving begins.

There will be 15 male and female volunteers taking part in each proving, three of them receiving blanks.

All participants will be trained in keeping a diary during the proving, to note down daily entries during all phases of the homeopathic drug proving. The homeopathic drug proving will last 5 weeks in total.

1) Preliminary observation period.

During this phase, all symptoms will be noted, which may occur without taking a proving substance or remedy.

2) Administration of proving substance / Period of observation.

The homeopathic preparation will be administered on the first day of this phase, following a set schedule.

You are likely to experience reversible symptoms caused by the proving substance. All symptoms that occur due to the substance are noted down in the diaries. During this phase, each participant will be in daily contact with the proving doctor, to report his/her wellbeing and symptoms.

Normally the symptoms associated with the intake of a homeopathic proving substance are not severe and will have ceased after a few days. In case of strong symptoms or adverse events, immediate appropriate care will be organised. Of course, there is an insurance covering every participant to compensate for any ongoing adverse events caused by the drug. There are also potential benefits arising out of a homeopathic drug proving, because former symptoms may be ameliorated or healed by taking the substance.

3) Post observation period. The diaries are still filled in, to see, if further symptoms occur.

Withdrawal from the homeopathic drug proving.

Every participant has the right to withdraw from the proving at any stage for whatever reason without affecting their future medical care.

Confidentiality.

The personal statements are kept **strictly confidential**, the participants will be known only by a special code in the records.

24-Hour– Emergency – Number.

In case of emergency there will be a telephone number where a doctor can be reached at any time.

INFORMED CONSENT

Study : Homeopathic drug proving of >> N.N. <<

Name of Participant: _____

I hereby confirm that I have been informed in detail about the purpose and conduct of the homeopathic drug proving. The possible risks and benefits have been thoroughly explained and all my questions or concerns have been answered. I have fully understood the purpose, goal and procedure of the homeopathic drug proving. My participation is absolutely voluntary at all stages of the study and refusal to participate or my withdrawal at any stage will not in any way subsequently disadvantage me. All personal information, given by me orally or in written form, will be treated as strictly confidential in accordance with legal requirements. Furthermore, I have been informed that all participants are insured in case any severe adverse events associated with the intake of the proving substance should occur.

If I have any questions or if any adverse events during the study, I have been provided with a 24-hour contact phone number where I can reach my proving doctor or one of his/her colleagues.

Date

Participant signature

Date

Investigator signature

General considerations for the homeopathic interview and for the structure of diaries (journals)

It has to be decided whether the homeopathic interview is taken personally by the proving doctor or if the volunteer fills in a questionnaire. The use of a questionnaire is less time consuming for the proving doctor, therefore this method will be used if a proving doctor is in charge of many volunteers.

It should be clearly stated that it is a great disadvantage for the quality of the proving, if the proving doctor cannot provide a minimum of fifteen to twenty five minutes per day for each one of the volunteers during the observation period of the proving. The way of taking the case (direct interview or questionnaire) may considerably influence the symptoms, noted for each volunteer.

There are results in clinical trials, where the efficacy of a drug has “changed”, when the effect of the same drug has been stated either in the volunteer’s own words, or by filling in a questionnaire. It has been shown in trials, performed with Flurazepam by Kohnen and Lienert [• Kohnen,R. Lienert,G,A.: Placebo-Effekte-Ein Phänomen der Untersuchungsmethode? In: Das Placeboprobem (H. Hippus et al., Hrsg.) S.49-60. Gustav Fischer, Stuttgart 1986.], that more placebo effects are reported, when questionnaires are answered, than with verbal description of effects (63% verum and 17% *placebo effects with free description*, = 46% efficacy ; versus 83% verum and 58% *placebo with questionnaire answering* = 25% efficacy, related to five quality items of sleep)[in Hippus pp. 51-54]. This could mean, for the homeopathic interview, that several of the symptoms mentioned in filling in a questionnaire may not be very reliable and that symptoms mentioned in the diaries after the administration of the remedy may be given only because they are interrogated in a questionnaire.

The consequence of this would be to analyse the symptoms given by the volunteers very thoroughly, whether given by free description or by filling in a questionnaire. This is only possible when there is close contact between proving doctor and volunteer (as Hahnemann practised it) and requires a lot of experience from the proving doctor.

If only questionnaires are filled in, it will be very difficult to judge the symptoms later and the quality of a proving will be much lower when there is no personal contact between proving doctor and volunteer during case taking and/or observation period. This point has to be stressed, because the design of a drug proving protocol depends to a great extent on this question, and a proving doctor can only see a limited number of volunteers per day, since most provings are done by doctors during their day-to-day practice.

Four suggestions for performing the case taking are briefly discussed below:

1. The proving doctor takes the case personally with each of his volunteers and *he/she* fills in the Homeopathic Interview Form of the volunteer at the case taking. Afterwards he has a second interview with the volunteer when any points can be answered, which may have been forgotten during the first interview.

Pros: The spontaneous report is not lost, no item will be forgotten.

Cons: Takes up a great deal of time.

2. The proving doctor takes the case personally with each of his volunteers and *the volunteer* fills in the Homeopathic Interview Form after having had the interview with the proving doctor.

Pros: like under 1, additionally less time consuming for the proving doctor. Volunteers may be able to write down symptoms, which they were not able to express verbally.

Cons: Takes up a great deal of time for the volunteer. Eventually problems of compliance, because the volunteer has answered most of the questions already during the personal interview.

3. The volunteer fills in the Homeopathic Interview Form before the interview and gives it to the proving doctor in advance, so that the proving doctor can read it beforehand.

Pros: The proving doctor will already know the most important items and can complete any lacking information. No item will be forgotten.

Cons: The spontaneous report is lost. This way also takes a great deal of time, but volunteer and proving doctor have only to meet once for the completion of the interview.

4. The volunteer fills in the Homeopathic Interview Form and sends it to the proving doctor. No personal interview is done.

Pros: Least time consuming. No item will be forgotten.

Cons: The spontaneous report is lost. The individuality of the volunteer is not fully experienced by the proving doctor.

The method of case taking to be used should be stated in the protocol, together with the reasons for choosing that method.

Homeopathic Interview (Case Taking) Form

NOTE:

• It is assumed that every proving doctor will do the case taking personally with the volunteers for whom he/she is responsible for and that he/she uses this form just as a reminder. Accordingly this form is not meant to be handed out to a volunteer. It has been designed to give the proving doctor a guideline to ensure that no important information will be forgotten.

• Also, in case the proving doctor does not use this form, after the proving, ALL NOTES taken during the original case taking must be kept in the Case Report Form of each volunteer!!!

Given name(s) _____

Surname _____

Address _____ Zipcode _____

City _____ Birthdate / Place _____

Telephone (private) _____ (work) _____

Occupation _____ Retired _____

Education _____ Employed by / as _____

Married _____ Separated _____ Divorced _____ Single _____ Widowed _____

Live with : Spouse _____ Parents _____ Relatives _____ Friends _____ Alone _____

How is your general state of health ? Excellent _____ Good _____ Fair _____ Poor _____

Bodyweight _____ kg Height _____ m Blood pressure _____ / _____ mmHg (if known)

Health problems, which you have now or have had in the past.

Chief complaint: _____

Others:

1) _____

2) _____

3) _____

4) _____

When did your main health problem begin ? _____

What was your general life situation at that time ? Were there important changes on a personal level or in your external circumstances ?

Do you think, there could be a correlation with the onset of the complaint(s) and your circumstances at that time ? _____

Previous Illnesses

Childhood	When		When		When
Mumps	_____	Polio	_____	Whooping cough	_____
Measles	_____	Diphtheria	_____	Other	_____
German Measles	_____	Chickenpox	_____		

Have you had **vaccinations** : DT _____ Pertussis _____ Polio _____ MMR _____

Hib _____ BCG _____ Influenza _____ tick fever _____ Hepat.A /B _____ Other _____

Did you (or your parents) ever notice adverse reactions or illnesses after a vaccination ? _____

Have you had or do you still have any other illnesses or complaints e.g :

- | | | | | | |
|---------------------|--------|---------------|--------------------|----------------------|----------|
| Allergies | Eczema | Alcohol Abuse | Asthma | Herpes | Anorexia |
| Bulimia | Gout | Goiter | Depression | Heartburn | |
| High Blood Pressure | | Pneumonia | Psychosis | Gonorrhea | |
| Drug abuse | | Urticaria | Chronic infections | Major teeth problems | |

Hospitalizations / Surgery

Illness	Date	Hospital / Town
_____	_____	_____
_____	_____	_____

Medications

Please list all prescription medication, you are *presently* taking _____

Other like Birth Control Pills, Hormones, Thyroid replacement, Vitamins, etc. _____

FAMILY HISTORY

Please list the years of birth of your family members and the major illnesses or complaints. If they are deceased, please state the cause of death and the year, they died.

	<u>Y.o.Birth</u>	<u>Died</u>	<u>Cause of death / major illness(es)</u>
Mother	_____	_____	_____
Father	_____	_____	_____
Brother(s)	_____	_____	_____
Sister(s)	_____	_____	_____
Maternal grandmother	_____	_____	_____

Maternal grandfather _____
Paternal grandmother _____
Paternal grandfather _____
Other _____

Has anyone in your family had one of the following illnesses:

Cancer ____ Heart ____ Varicosis ____ Stomach ____ Depression ____
HBP ____ Diabetes ____ Allergies ____ Gallbladder ____ Seizures ____
Suicide ____ Stroke ____ Gout ____ Hay fever ____ Kidneys ____
Asthma ____ Venereal disease ____ Tuberculosis ____ Rheumatism ____

Mental Symptoms

Which experience in your life (pleasant or unpleasant) has affected you most deeply, i. e. are you still mourning for a relative, the death of whom you did not overcome, has there been a mortification you are still suffering from, etc. ? _____

How do you cope with your worries ? _____

What would be enough for you to make you weep? _____

How do you respond to consolation? _____

How do you tolerate having to wait ? _____

Fears

Please describe any fears that you had in childhood or you may have now, as well specific as general fears (dogs, thunderstorms, heights, confined spaces, future, being alone, etc.) _____

Under which circumstances / when do you become or have you been jealous ? _____

How satisfied are you with your professional life and / or choice of occupation?

Which kind of troubles may you get after anger, grief, lovesickness, mortification, shock, bad news or how do you react to them ? _____

What is your attitude towards death, when you are very sad? _____

What about conscientiousness, accuracy, in daily life? _____

Head symptoms

Headaches ____ Vertigo ____ Migraines ____ Dizziness ____ Seizures/ faint ____ Other ____

Eye symptoms

Infections ____ Styes ____ Skin eruptions ____ Poor eyesight ____ Other ____

Ear symptoms

Chronic ear infections – left / right ____ Ringing in the ears ____ – left / right
Hearing loss ____ Inflammations of auditory meatus ____ Other ____

Nose symptoms

Nose bleeds ____ Herpes nostrils ____ Sinus infections ____ Other ____

Face symptoms

Flushes of heat ____ Swellings of glands ____ Blushing easily ____ Other ____

Mouth/teeth symptoms

Cracked lips ____ Herpes lips ____ Aphthae ____ Gum infections ____ Other ____

Inner throat / neck symptoms

Throat pain ____ Chronic infections of tonsils ____ Hoarseness ____ Other ____

Appetite

Do you have strong desire for particular foods ? _____

Do you have an aversion against particular foods? _____

Do you generally prefer warm or cold food and / or drinks ?

Do you have loss of appetite related to specific circumstances ?

What about your consumption of : alcohol, _____ tobacco, _____
coffee, _____ black tea _____ (please give daily quantities).

Stomach Symptoms

Gas ____ Stomach ulcers ____ Heartburn ____ Pain ____
Indigestion after meals ____ Belching ____ Nausea ____

Abdomen

Pain ____ Hernia ____ Cramps ____ Bloating ____

Stool/Anus Hemorrhoids ____ Rectal itching ____ Straining at stools ____
Blood in stools ____ Diarrhoea ____ Constipation ____

Urogenital system

Painful urination ____ Frequent urination ____ Involuntary urination ____

Inflammations of bladder / kidneys ____ / ____

Male sexual organs

Prostate problems ____ Warts, condylomata ____ Pain testicles ____ Difficult erections ____

Female sexual organs

Leucorrhoea ____ Itching in the vagina ____ Difficult or no orgasms ____

Menses

When was your first menstruation ? _____ Are the intervals regular ? ____
How long do the periods usually last ? _____ Is the menstrual flow excessive /
strong/weak ? Pains during menses ? _____

Any other concomitant symptoms around the menses ?

Number of pregnancies ____ Complications during pregnancies ? _____

Number of births ____ Abortions ____ Miscarriages ____ Menopause since _____

Respiratory System

Asthma ____ Chronic cough ____ Pneumonia ____

Chest / Heart

Congestion ____ Pain ____ Herpes zoster ____

Back

Pain in scapular ____ / dorsal ____ / lumbar ____ region Injuries ____

Upper / lower limbs

Joint pain ____ Muscle pain ____ Pain in the bones ____ Numbness ____ Coldness ____

Ulcers or sores ____ Cramps in the calf ____ Nail changes ____

Skin

Itchy skin ____ Eczema ____ Skin infections ____ Urticaria ____ Moles ____ Warts ____

Herpes ____

General symptoms

How do you react to cold / hot / dry weather ? _____

How do you feel at the seaside or in the mountains ? _____

Do you feel worse or better

- in the sun
- with wind
- in the heat
- in the cold

Do you perspire easily ? _____ Do you feel cold easily ? _____

Do you consider yourself to be a warm-blooded ____ or cold-blooded ____ person ?

Is there anything which has not yet been covered and which is important for you to tell? Please note down on back page.

Information for the day of administration of proving substance / remedy

- 1) Please remember to note the substance code on the corresponding page of the day of intake in your diary.
- 2) The substance should be taken approx. every two hours for max. 6 times – only for this one day. One dose consists of the content of one capsule. The capsule is to be opened and the substance taken under the tongue. Remember to take no food for 15 minutes before and after taking the proving substance.
- 3) State in your diary the times you take each dose of the proving substance.
- 4) If you feel, a symptom may be occurring please stop taking another dose and call us.
- 5) In case you don't need all doses, please return the unused proving substance to us within the closed capsules at your next visit.
- 6) Telephone number, which connects you directly to the proving doctor or his assistant:

.....

Homeopathic Drug Proving Diary

Table of contents

General information for filling in the Diary (Journal)

Preliminary Observation Period	Page 1
Day of intake of proving substance	Page 8
Observation Period	Page 9
Post Observation Period	Page 15

Note:

The entire diary contains 42 pages (21 and the back side of each page for extra notes). Only those pages with different contents are printed here.

General information for filling in the Diary (Journal)

The quality of the symptoms gained during the proving is the essential outcome and goal of this homeopathic drug proving.

Therefore the symptoms recorded in this diary should be as specific as possible. Please note the following items, if applicable, supplemented by a statement about the intensity and duration of the symptom:

All symptoms should be recorded without compromise **in your own words**.

1) **Location and time of occurrence**

State the side of the body, if applicable and if it extends to other parts of the body.

State time of occurrence after intake of proving substance. State also, if it changes from one side to another.

2) **The kind of pain or sensation** (e.g. burning, stitching, splitting etc.)

State, if there are other experiences together with the symptom. E.g. feeling cold during headache.

3) **How did the symptom begin**, was it due to a special cause or after a certain event (e.g. bladder inflammation after sitting on a cold rock; headaches after drinking coffee)

4) **What makes the symptom better or worse ?** (cold air, heat, being inside or outside, moving, lying down, etc.)

Please state the symptoms as completely as possible, following the „ Head to Foot Scheme“, outlined in the leaflet.

Pay attention also to your surroundings. How do you react to your family members or other people around you? Do you or someone else recognise alterations in your moods and habits ?

How is your general wellbeing, how do you cope with your work, your worries ?

Are there changes in the way you react during the time of the homeopathic drug proving versus the time before?

Please make notes **every day, best is to take notes a few times a day (say 3-4 times)**, even if you think, there are no symptoms to report, but this should usually not take you more than several minutes a day.

Note also slight or inconspicuous symptoms.

Please write legibly in your diary.

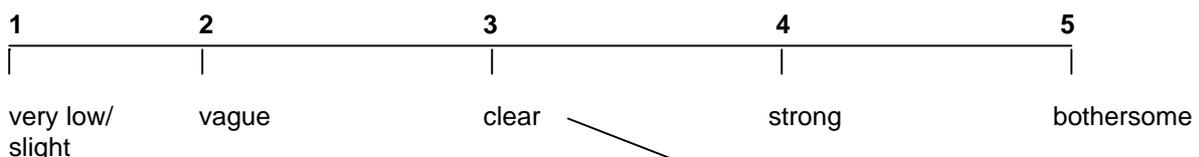
There is a total of 42 pages in this diary, two pages corresponding to each day of the homeopathic drug proving. If you need additional space, please use the back sides of the pages or contact us. The proving consists of three phases : 1) Day 1 – 7 Preliminary observation period 2) Day 8 – 14 Homeopathic Drug Proving observation period 3) Day 15 – 21 Post observation period

When you experience symptoms, please note at the end of each symptom the **category** and **intensity** as follows :

NS	New symptom -	never before experienced.
OS	Old symptom -	a symptom you had earlier and which now appears again.
AS	Altered symptom -	a normal symptom changed during the proving, e.g. usual headache experienced on left temple now appears at the right temple.
CS	Cured symptom -	old symptoms that are no longer present.

Please mark **the intensity** of each symptom beside the category, rating as follows :

Intensity of symptoms



It is helpful to mark these abbreviations by a circle. E.g.: „New, **clear** symptom“ = **NS 3**

Please fill in the remedy code from page 1 on, although the remedy is taken only on day 8.

This is to ensure the proper assignment of the symptoms.

Preliminary Observation Period

Date : _____

Code: _____

SYMPTOMS

**FOR COMMENTS
(of proving doctor)**

Head to foot scheme

Mind (mental/emotional)

Generals („I feel“-cold/warm;

Energetic/exhausted etc.)

Head

- **Eyes**

- **Ears**

- **Nose**

- **Teeth**

- **Mouth**

Throat

Stomach

Abdomen

Stool /Rectum

Urinary organs

- **Kidneys**

- **Bladder**

- **Prostate**

- **Urethra**

- **Urine**

Male / Female

sexual organs

Respiration /

Cough

Chest

Heart

Neck /Back

Extremities

Skin

Sleep

Fever

Day of intake of proving substance

Date : _____ Code: _____

Intake _____ hour:_____ hour:_____ hour:_____ hour:_____ hour:_____ hour:_____ (dose no.1) (dose no.2) (dose no.3) (dose no.4) (dose no.5) (dose no.6)

	SYMPTOMS	FOR COMMENTS (of proving doctor)
Head to foot scheme		
Mind (mental/emotional)	_____	_____
Generals („I feel“-cold/warm; Energetic/exhausted etc.)	_____	_____
Head	_____	_____
- Eyes	_____	_____
- Ears	_____	_____
- Nose	_____	_____
- Teeth	_____	_____
- Mouth	_____	_____
Throat	_____	_____
Stomach	_____	_____
Abdomen	_____	_____
Stool /Rectum	_____	_____
Urinary organs	_____	_____
- Kidneys	_____	_____
- Bladder	_____	_____
- Prostate	_____	_____
- Urethra	_____	_____
- Urine	_____	_____
Male / Female sexual organs	_____	_____
Respiration / Cough	_____	_____
Chest	_____	_____
Heart	_____	_____
Neck /Back	_____	_____
Extremities	_____	_____
Skin	_____	_____
Sleep	_____	_____
Fever	_____	_____

Date : _____

Remedy Code: _____

SYMPTOMS

**FOR COMMENTS
(of proving doctor)**

Head to foot scheme

Mind (mental/emotional)

Generals (“I feel“-cold/warm;
Energetic/exhausted etc.)

Head

- Eyes
- Ears
- Nose
- Teeth
- Mouth
- Throat

Stomach

Abdomen

Stool /Rectum

Urinary organs

- Kidneys
- Bladder
- Prostate
- Urethra
- Urine

Male / Female
sexual organ

Respiration /
Cough

Chest

Heart

Neck /Back

Extremities

Skin

Sleep

Fever

Date : _____

Remedy Code: _____

SYMPTOMS

**FOR COMMENTS
(of proving doctor)**

Head to foot scheme

Mind (mental/emotional)

Generals („I feel“-cold/warm;Energetic/exhausted etc.)

Head

- Eyes

- Ears

- Nose

- Teeth

- Mouth

- Throat

Stomach

Abdomen

Stool / rectum

Urinary organs

- Kidneys

- Bladder

- Prostate

- Urethra

- Urine

Male / Female sexual organs

Respiration /Cough

Chest

Heart

Neck /Back

Extremities

Skin

Sleep

Fever

Adverse Event Report Form

Study : Homeopathic drug proving of >> N.N. <<

Volunteer Code: _____	Code: _____	Date of birth _____	Sex _ m _ f
Randomization Envelope opened by :		Date :	Verum / Blank (Placebo)
Description of the event	occurred on: _____ duration: _____ hrs / days _____		
	Time lap after last intake _____ hrs / days _____		
Details:	<i>Example:</i>	<ul style="list-style-type: none">• Intercurrent disease• Accident• Adverse proving symptom	
	all to be described in detail		
Intensity:			

Diagnostic and therapeutic measures taken:

Hospitalization _ yes _ no

Course and outcome

of the event: completely recovered not yet recovered unknown

Other _____

Name and Tel.-Nr. of physician

being in charge of further medical care: _____

Principal investigator of the homeopathic drug proving informed about this adverse event by: _____

Date _____ daytime _____ hrs _____

Sponsor informed about this adverse event by the principal investigator of the proving:

Date _____ daytime _____ hrs _____

Other information: _____

This Adverse Event Report Form has been filled in by: _____
Investigator's name(s) and signature(s)

APPENDIX 1

Checklist for Proving Substance or Remedy

A) Identity of the substance

A.1 Exact specification of the original material (original provings are sometimes done with different basic material i.e. Apis, Petroleum, Carcininum.....). The determination/specification in the pharmacopoeia is often incomplete. Specify full latin name (i.e. Pulsatilla pratensis nigricans, Bryonia alba) and synonyms in plants, or specify exact composition of other material. If necessary, common names in country of origin. Animals: zoological identification.

Identification process done by: Name of person, who identified the plant or substance, if necessary photography.

A.2 Origin of proving substance

Range and habitat.

Description of the geographic area and physical habitat, in which the source material occurs and specific information, where it is collected.

Plants:

- locality of sampling: habitat (i.e. Arnica: above or under 600m)
- time of harvesting; during, before flowering; date
- parts used (leaves, roots, flowers etc.)

Minerals / chemical substances:

- composition
- pureness
- Mode of analysis / source

Animals / insects:

- habitat
- parts used

Nosodes:

- Exact origin and identification of source material.

B) Manufacturing process

In the pharmacopoeias several items of the manufacturing process are stated incomplete (e.g.: Pharmacopoeia of the U.S. /HPRS- 2001 – General Pharmacy p.41: for Hahnemannian attenuations is stated that the “mixture is succussed thoroughly” but not, if it is done by machine or by hand and how many times it is done).

Therefore additionally to the statements of the pharmacopoeias, the following items should be checked:

- Elapsed time from harvesting to preparation and storage of source material and potencies.

Preparation of the attenuations / potencies

- Hahnemannian potencies – Multiple flask method of preparation
Succession by hand or by machine ?
Number of succussions
- Korsakovian potencies – Single flask method of preparation
Starting from: Mother tincture, Hahnemannian, or others
Number of succussions / frequency / upstroke

Different machines are used to prepare Korsakovian potencies. Their performance varies with respect to frequency, amplitude of upstroke, power and duration of succession. Therefore the exact mode of preparation should be stated.

- Fluxion attenuations

Starting from: Mother tincture, Hahnemannian, Korsakovian potencies.
Continuous flux / discontinuous flux.

- High potencies above C1000: Which modes of attenuations (starting from Hahnemannian or Korsakovian) have been used and starting from which number of attenuation.

- Q-potencies (LM)

Hahnemann prescribes the trituration of the source material until C3 (§270 Org.6). Therefore it should be stated, if the source material has been triturated or diluted until C3.

- Preparation of blanks (placebos, inert control substance)

Proposal for 2 different kinds of blanks:

- 1) Substance vehicle only – i.e. plain globules (D.J. McGuire 1835)
- 2) Globules sprayed with non-succussed 83% alcohol.

- Samples of the source material, placebos and proving substances kept by : _____

- Manufactured by:

- Charge –No.: _____ Date of production: _____

NOTE: Details about storage and packaging see also 6.4.4.

Appendix 2 (Example)

CURRICULUM VITAE of Principal Investigator

Address

NAME

Title
Current field(s) of action

SKILLS AND EXPERIENCE

Medical practice

Locality / Site of practice
Specification of kind(s) of work with dates of beginning and ending

Administration I.e.: Member of Homeopathic Medical associations Member of other associations

Homeopathic research

I.e.: Consultant in research projects on homeopathy
Conducting of homeopathic drug provings.

Teaching

Teaching activities Supervision activities

EDUCATION

Homeopathy

Courses in homeopathy
Teachers of homeopathy

General Medicine

From - to Education in general medicine, Surgery, Internship etc.

EMPLOYMENT(s)

From – to
From – to

PUBLICATIONS AND PRESENTATIONS

List of publications, courses given etc.

APPENDIX 3

Internet addresses of important institutions

(in alphabetical order)

Adverse Drug Reaction

Reporting system, see: www.fda.gov

Formblatt Bericht über unerwünschte Arzneimittelwirkungen ist erhältlich über:

<http://www.akdae.de/> UAW-Meldung

Declaration of Helsinki – current version: The World Medical Association: www.wma.net

German version: Informationen siehe: Homepage der World Medical Association
<http://www.wma.net> (nur die englische Fassung wurde in Edinburgh beschlossen - inoffizielle,
nicht offiziell autorisierte) deutsche Übersetzung:

<http://www.bundesaerztekammer.de/30/Auslandsdienst/92Helsinki2000.pdf>

Directive on good clinical practice

Search for: Directive 2001/20/EC. It is published in: Official Journal of the European Communities.

European Committee for Homeopathy (ECH)

To contact **Subcommittee Drug Proving**s, please go to website of ECH:

www.homeopathyeurope.org ♦ Subcommittee Drug Proving

European Legislation: Search for: „Eur-Lex“ or „europa.eu.int“

European Pharmacopeia: www.pheur.org

Federal Institute for Drugs and Medical Devices

BfArM - Bundesinstitut für Arzneimittel und Medizinprodukte: www.bfarm.de

Only few documents in english

German version, search:

RICHTLINIE 2001/20/EG DES EUROPÄISCHEN PARLAMENTS UND DES RATES

GIRI Groupe International pour recherche infinitesimale

<http://www.entretiens-internationaux.mc/giri.html>

InHom:

<http://www.homoeopathie-stiftung.de/Hom-Stiftung/festschrift/Hom-Stiftung.pdf>

International Conference on Harmonisation (ICH) Homepage: www.ich.org

The ICH **E6 Good Clinical Guideline** is available from ICH-web site :

www.ich.org ♦ „Guidelines“ ♦ „Efficacy“

Comment: The ICH guidelines only exist in English.

Organon-read online:<http://www.homeoint.org/books> ♦ Hahnemann ♦ Organon ♦ English

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