HPCUS Proving Guidelines

Homœopathic Pharmacopœia Convention of the United States

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1 Foreword

The following guidelines are presented to help monograph sponsors for homeopathic medicines design and conduct a Proving for their monograph submission that will meet the standards for approval; and to help guide reviewers who examine monograph submissions to ensure that expected standards of quality are being upheld. Published literature on homeopathic provings was considered in the development of these guidelines.\(^{(1-8)}\) A glossary is placed at the end of this document to provide definitions of terms used within these guidelines. Periodic review and revision of these guidelines will occur as needed. Please use the online version available at [www.hpus.com](http://www.hpus.com) as the current reference.

These guidelines contain two specific types of criteria: standard requirements and best practice recommendations. Standard requirements are recognized by language that is definitive, such as “should” or “will include”, while best practice recommendations will use more permissive qualifiers such as “is recommended”. For monograph approval, the submitted Proving must meet all standard requirements. Deviations from best practice recommendations are permitted, but should be accompanied by an explanation by the sponsor. If a monograph sponsor expects their proving to deviate from these guidelines, questions for clarification may be submitted in writing to the Editor (HPCUS).

Monograph reviewers are instructed to ensure the following criteria are met for Provings:

- Compliance with the Proving design & execution requirements (Sections 2–6)
- Proper analysis to evaluate the sufficiency of the Proving results (Section 7)
- Compliance with all legal, ethical, and publication requirements (Section 8–9)
**Standard** = A requirement that must be met for approval of the monograph. Non-compliance with these requirements will likely cause non-approval of a monograph. Any proposed deviation from these requirements must be approved by the PRC prior to initiation of Proving. Standards may be periodically updated as needed. Standards contained within these guidelines for Provings are recognizable by language that implies a required element, placement in the left column of the document, and appearance in the text as regular font.

**Best Practice Recommendation** = Suggested method or practices or particular point that will need to be considered when conducting a Proving. Elements of Provings that comply with current best practice recommendations will be considered within compliance standards. Elements of a Proving that fall outside of current best practice recommendations, while not immediately disqualifying, should be accompanied by the reasoning for such a departure to help expedite the monograph review process. Best practices will be updated as community research standards continue to evolve. Best practice recommendations contained within these guidelines for Provings are recognizable by language describing the element as “recommended”, placement in the right column of the document, and appearance in the text as italicized font.

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## 2 Personnel Qualifications & Training

### 2.1 Principal Investigator

The Principal Investigator has a minimum of 5 years of homeopathic clinical practice experience. Prior experience with Provings is recommended. The Principal Investigator has experience or publication that demonstrates a working knowledge of Human Clinical Research.

### 2.2 Project Coordinator / Administrator

Utilization of a Project Coordinator / Administrator to enhance communication, coordination, and control of the Proving is recommended.

### 2.3 Proving Subject Supervisors

A minimum of 200 hours of homeopathic training to include case-taking, case-analysis, and case-management skills is required. Quality assurance and record-keeping training of Supervisors is recommended prior to Proving.

A minimum of 1 year of homeopathic clinical practice experience or the equivalent in clinical homeopathic training for case management and follow-up of active clinical subjects is required.
2.4 Ethics Training

Ethics training is required for all personnel to the extent necessary to achieve Ethics or Institutional Review Board Approval (9).

Ethics training shall include:

a) Training is required for Principal Investigator and Project Coordinator (if used).

b) Documented Training courses on Ethical Issues in Human Research must meet National Institutes of Health criteria or update of similar course within past 3 years (10) (Program examples include: Collaborative Institutional Training Initiative, Harvard School of Public Health course, NIH Protecting human research participants course, or similar).

Recommended for all Supervisors.
In the development of these guidelines, various references were consulted including those standards that have been established by the Homeopathic Pharmacopeia of the United States (HPUS), the United States Food and Drug Administration (FDA), the International Conference for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), the Homeopathic Medicinal Product Working Group (HMPWG) of the European Union (EU) Heads of Medicine Agency, and the EU-Notice to Applicants (NTA) guidance on Homeopathic drug manufacture \(^{(11), (12)}\).

For monograph submission, Good Manufacturing Practices (GMP) should be followed throughout the production process for manufacture of the Investigational Proving Substance (IPS) used in the Proving. Information specific to Provings regarding the IPS as described in the following guidelines should accompany the Provings Report (see section 10 (Appendix A)).

### 3.1 Investigational Proving Substance Manufacturer Information

Name

Address

Contact name

A means of contact

### 3.2 Identity of IPS

Sufficient information to identify the unique substance used in the IPS must be provided.

Name of the substance including any scientific nomenclature, common name, and synonyms commonly used are to be included.
3.3 IPS Manufacturing Process

The sponsor must provide a statement confirming that the IPS was manufactured in a manner consistent with Good Manufacturing Practices and the process described in current HPUS guidelines.

3.4 Toxicology

The sponsor must provide a summary of the available toxicology to include the following:

a) The sponsor must provide a summary of known toxic effects of the IPS.

b) References to source information on toxic effects should be included.

3.5 Prior Clinical Information

Sponsors are recommended to provide a summary of any available clinical information on the IPS. Such information may include:

a) A summary of clinical case reports for the use of IPS in homeopathic or other forms.

b) A summary of published research on the IPS in homeopathic or other
3.6 Prior Proving of the IPS

If referenced, such Proving information should be made available to any HPCUS review committee upon request.

*Any available prior Proving information on the IPS is recommended to be referenced in the current submission.*
4 Design / Methods

4.1 Overall Study Design and Plan

Research design type must be described and justified in detail.

While retrospective information may be placed in the introduction, toxicology section, and/or pre-Proving information, all data for Proving analysis will be prospective in nature.

Number of Centers involved in a Proving will be noted (mono- or multi-center are equally acceptable).

4.2 Controls

If blinding to substance identity for both subjects, supervisors, and principal investigator is not possible, use of control (placebo) is required.

The control used should be indistinguishable by the subjects and supervisors from the medication and vehicle of the verum medication.

In randomized controlled Provings, a minimum of 20% of the Proving subjects at the initiation of the proving should receive control (placebo) to help minimize bias in the Proving.
4.3 Selection of Study Population

A Proving will be conducted with the widest range of subjects possible.

Limitation of Proving subjects from ages 18 years to 75 years is recommended.

Inclusion of male and female subjects to ensure that representative data on both genders can be collected is recommended.

The location and setting of the Proving should be noted.

4.4 Inclusion / Exclusion Criteria

Criteria must be established to exclude certain subjects from the Proving to help minimize health risks, to remove potentially confounding factors from the Proving, and to ensure that subjects are capable of providing accurate information while recording their subjective symptoms.

Exclusion of subjects <18 or >75 years of age is recommended. If such subjects are included, this must be accompanied by a suitable rationale and Ethics or Institutional Review Board approval.

Criteria must be defined before Proving initiation and subject selection and approved by Ethics or Institutional Review Board.

Exclusion of pregnant subjects is recommended, unless extenuating circumstances suggest inclusion necessity and Ethics or Institutional Review Board approves of inclusion.

Exclusion of mentally incompetent subjects or individuals with inability to give an adequate history is required.

Exclusion of subjects with serious mental-emotional disorders (Psychosis, Major Depression, Bipolar Disorder or similar) is...
4.5 IPS Characteristics

Attenuation or concentration will be selected to ensure safety of test subjects based upon the maximum dosing possible during the Proving.

Attenuations lower than 12C should not be used if the safe human dose of IPS is not known.

Use of a vehicle, preparation, or route of administration that does not adhere to HPUS guidance requires HPUS approval prior to monograph submission.

Attenuations greater than 30C are not recommended for Provings.

IPS is recommended to be prepared and administered in a manner adhering to the HPUS.
4.6 Randomization

Process for randomization will follow international Good Clinical Practice standards \(^{(15),(16)}\), to ensure unbiased allocation to verum and control groups prior to distribution of Proving substance, if control (placebo) utilized.

4.7 Dosing Frequency

Timeline for repetition of dosing shall be established prior to Proving initiation as approved by the Ethics or Institutional Review Board. A test medication dosing frequency greater than three times daily is not recommended.

4.8 Criteria for Non-Repetition of Dose

Non-repetition criteria shall be explicitly defined in the Proving protocol prior to initiating the Proving.

Non-repetition criteria will include the initial development of proving symptoms by a subject (requires definition in the protocol). Criteria for non-repetition of dose are recommended to include stopping test medication dosing in subjects with no discernible response after 1 week.

4.9 Blinding

Blinding to treatment allocation when placebo control is utilized should include all of the following:

a) Principal Investigator
b) Proving Coordinator

c) Supervisors

d) Subjects (Provers)

Blinding to substance under study should include the maximum number of the following permitted by Ethics or Institutional Review Board:

a) Principal Investigator

b) Proving Coordinator

c) Supervisors

d) Subjects

e)

Un-blinding should only occur:

a) During the Proving, for individual subjects, in the event of a Serious Adverse Event. (see Section 6.3 for required elements of un-blinding process)

b) If the PI or Ethical / Institutional Review Board determines un-blinding is medically necessary for subject safety reasons.

c) After all data is locked into a final, unalterable database following the final evaluation of all subjects and correction of any subject entries.
4.10 Therapeutic Intervention during Proving

All medical and other therapeutic interventions in subjects that occur during the Proving must be recorded.

Investigator will make a determination on any such intervention during the Proving to determine if such treatment is likely to have substantially altered the validity of subsequent Proving symptoms in the subject. Events related to such treatment must be handled according to Adverse Events process within Section 6 of these guidelines.

4.11 Number of Subjects / Sample Size

Sufficient sample size must be selected to ensure that a minimum of 10 subjects receive verum and complete the proving per protocol.

Subject withdrawal rates greater than 10% are sub-optimal and must be accompanied by specific explanation.

Proving sample size is recommended to include at least 20 subjects.

4.12 Subject Replacement

Subjects who withdraw or are removed prior to the administration of the IMP should be replaced; subjects who withdraw after IMP administration—but before the data code is un-blinded—may be replaced.
4.13 Supervisor and Subject Interaction

Face to face subject evaluations are required during intake and exit visits.

Subjects must be provided instruction and the means for emergency contact with the supervisor.

Additional face-to-face or telephonic interactions with subjects during the Proving are recommended at least weekly.

Subject education is recommended to include the following:

a) How to record symptoms
b) Reporting adverse events
c) Interim contact procedure

4.14 Definitions to be Included in Proving Timeline

Run-in period (including Pre-Proving data collection)

Test period

Subject reporting / interview frequency and duration

Run-in period recommended to last at least 7 days.

a) Subject reporting / interview frequency and duration recommendations:

b) Subject interview is recommended to be at least weekly.

c) Duration of subject reporting is recommended to span at least 6 weeks.
4.15 Follow-up period

Final follow up of subjects is recommended to extend at least 3 months.
5 Data Collection and Record Keeping

Data collection during Provings must be gathered carefully and clarified to ensure proper interpretation of Proving symptoms reported by subjects as information from Provings is translated to clinical practice.

Raw data is generated during the Proving from two primary sources:

- Subject reporting
- Examiner / Investigator-gathered data including data from:
  - questioning / interviewing
  - observation
  - biometric testing (if performed)

Data collection and recording occurs in several steps:

- Before the test substance administration to establish a baseline for interpretation of any symptoms that arise during the test period.
- During the test period, to record the subject’s experience in their own words.
- During or after the test period, but before all raw data is sealed, to ensure completeness of symptom data, clarification of any ambiguous symptom data and addition of any objective or test findings.

5.1 Data Labeling

Raw data should be limited to symptoms reported by the subjects, clarifying inputs from the investigating team that result from interactions with the subjects and any collected objective data on the subjects. To enhance transparency of the Proving, data
sets should be labeled according to their source and source of entry.

Subjects shall record all mental, emotional, and physical symptoms in their own words in the diary format as prescribed before Proving initiation (hereafter referred to as Subject Diary or Subject Entry).

Supervisor and/or Principal Investigator (hereafter referred to as Supervisor or Investigator) inputs occur during or after the Proving period as a result of direct interrogation or examination of the subject, and should help ensure completeness of symptoms and clarify raw data to reduce errors in interpretation.

5.2 Data Management

Principal Investigator will ensure that raw data entry will be linked and locked to the source of data:

a) Data entry category permission is linked to the appropriate level of input (i.e. subject entries only by subjects, supervisor entry only by supervisors, etc.).

b) Continuity of subject data must be guaranteed (i.e. all data entered for a given subject remains tied only to that subject).

c) All data entered by subjects and supervisors must remain intact as

Electronic formats for data collection are recommended. Written formats are acceptable.
originally entered.

1. Modifications or clarifications must be entered as new data and marked as such.

2. Clarification of raw data entry by members of the investigation team should occur prior to final sealing of data.

d) Once diary information and supervisor inputs are complete, data should be marked as sealed and no further changes to sealed data can be permitted.

Principal Investigator will ensure adequate protection of all Protected Health Information (17). If applicable, criteria for the exclusion of any raw data from the data collection process must be established prior to Proving initiation.

It is recommended NOT to exclude raw data.

5.3 Subject Diary

Subjects shall record all mental, emotional, and physical symptoms in their own words in the diary format as prescribed before Proving initiation. Emphasis should be placed upon the inclusion of all physical, emotional and mental sensations or symptoms that occur.

Initial subject diary entry on a daily basis for
at least one week is recommended prior to administration of the test substance to help establish baseline health characteristics.

The time period during and shortly after test substance administration is considered a critical period for data collection.

a) Diary entry shall be at least daily while test substance is administered and for at least 2 weeks after last dose.

b) Diary entries are recommended to continue until all new symptoms or changing symptoms stop occurring.

c) Subject diary entries for new or newly changed symptoms that occur more than 6 weeks after test substance administration are not recommended.

d) Final subject diary entry should occur at the final follow up of the Proving and should be labeled accordingly.

5.4 Supervisor / Principal Investigator Inputs

Supervisor / Principal Investigator Inputs are limited to information derived from any of the following sources:

a) Clarification of a symptom reported by the subject after questioning (subjective information to enhance the completeness or clarity of a
symptom).

b) Direct examination (such as a physical finding like a rash, or other observations such as the behavior of the subject), if conducted

c) Biomarker testing (such as weight, blood pressure, laboratory analysis, etc.), if conducted

Prior to IPS administration, a case history shall be conducted on each subject. A full homeopathic interview and examination of each subject is recommended to help develop a clear homeopathic picture of the subject’s baseline state of health.

This shall be conducted in a face-to-face encounter to include:

a) Age

b) Gender

c) Ethnicity

d) Past medical history including hospitalizations, surgical operations, and clinically important birth or genetic defects

e) Present medical history including current medications, other clinically important therapeutic interventions, medication allergies, and current medical conditions in active treatment

f) Prior mental, emotional or physical symptoms or ailments that resulted
g) Clinically important symptoms experienced within the past 3 months including notation of strong modalities, peculiar symptoms, or characterizing symptoms.

After test substance administration, Proving data should be collected in accordance with the Proving protocol.

Supervisor input may include objective or subjective information as noted above in this section.

Interactions in person, or via telephone and/or voice or video linkup with subjects during the Proving, are recommended to take place at least weekly during the observation period.

Supervisor shall review all subject diary entries as part of their periodic interview during the Proving period. Investigation and clarification of symptoms should be performed to increase precision of subject reported symptoms. Specific information should be solicited and recorded to include (when present):

a) Body location
b) Time of occurrence
c) Duration
d) Frequency of recurrence or periodicity
e) Severity (using a Likert or ordinal
scale defined before Proving initiation)

f) Concomitance with other symptoms

g) Influence of any environmental, physiologic or behavioral factors (also called modalities) upon the symptoms that increase or decrease the severity.

h) Identifiable potential etiologic factors determined by either temporal or presumed causative relatedness to onset of a symptom.

Specific investigation of any symptoms that resemble past complaints, that have recurred or changed after the administration of the test substance, should be conducted to determine severity, duration and frequency relative to status prior to the test period.

Investigation and recording by the supervisor of any observed clinical findings whether or not they were recognized by the subject is recommended.

Pertinent biometric markers including physical examination, laboratory testing, radiologic examination, or other testing may be performed according to Proving design parameters or at the need of the subject. All such objective biometric data should be obtained and recorded by personnel other than Proving subjects.

Pre-defined symptom classification criteria for all subject reported symptoms is
Data Categories or Labels for recording are recommended to be utilized for all reported symptoms according to their relationship to the test substance administration (recommended labeling is included in parentheses):

a) New (N)

b) Existing, Unchanged (within expected range of frequency, duration and severity) (U)

c) Changed Existing, Unexpectedly Better / Improved (qualify according to frequency, duration, or severity) (C+)

d) Changed Existing, Unexpectedly Worse (qualify according to frequency, duration, or severity) (C-)

e) Past, Unexpected Recurrence (R)

In person evaluation by the Supervisor or Principal Investigator should be conducted at the final evaluation or exit point of the Proving for each subject.

5.5 Record Keeping

Trial record storage will comply with all applicable regulations.
6 Safety Assurance

FDA and ICH-GCP have established guidelines for adverse event definitions for clinical trials in humans. Adverse Events (AEs) are any untoward medical occurrence in subjects who are administered a pharmaceutical product during a clinical trial, irrespective of whether there is a causal relationship with the product.

Subjects in Provings are expected to develop a range of transient symptoms when taking the Investigational Proving Substance (IPS). Such symptoms are essential to the evaluation and description of clinical usefulness of the test substance. Because of the investigatory nature of Provings with respect to new medicinal substances being tested, the exact range of symptom type and severity may not be predicted prior to Proving initiation.

Within the context of Provings, any symptom or condition that occurs in a test subject during the Proving and is clinically unexpected is considered an AE. If an AE fulfills at least one of the criteria listed in Section 6.3 below, it is defined as a Serious Adverse Event (SAE). The establishment of appropriate protocol definitions and procedures will ensure the appropriate identification and handling of AEs, while avoiding inappropriate reporting of Proving symptoms as AEs. For a visual representation, see the Figure 1 below:
A further aspect of AE reporting is the assessment of the possible categorization as an Adverse Drug Reaction. If a causal relationship between the test substance and the AE is at least a reasonable possibility, the AE becomes an Adverse Drug Reaction. And if the causal relationship between the IPS and the SAE is at least a reasonable possibility, then the SAE becomes a Suspected Unexpected Serious Adverse Reaction (SUSAR).

6.1 Adverse Events

Any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a proving and which is unexpected and clinically significant should be considered an Adverse Event.

Unexpected symptoms and signs have at least one of the following characteristics:

a) have duration longer than the proving period

b) have clinical severity greater than described in the Informed Consent

c) have clinical severity that falls within the definition of Serious Adverse Event

d) require medically necessary therapeutic intervention,

e) results in removal from the Proving

All AEs should be reported and managed according to the requirements of all applicable regulations and Ethics and Institutional Board Requirements.
A process for determination of likelihood of causation should be established prior to IPS administration.

It is recommended that the possibility of causation be determined prior to unblinding and based upon the following factors \(^{(18)}\):

a) Temporal relation to IPS administration

b) Strength of association

c) Consistency over repeated dosing within one subject or across the study population

d) Observed increase of symptoms with repetition of dose or increase in attenuation (if any in the design)

e) Coherence with known facts on the biology of disease

f) Once identity of IPS is known, causality may be reassessed based upon known biological properties of the substance (if feasible, should be done before un-blinding as to verum or placebo allocation)

Report of causation likelihood should be included for all AEs using the following labels derived from the FDA and ICH.\(^{(19)}\)

a) ‘Possibly related’ meaning there is evidence to suggest a ‘Reasonable possibility’ of a causal relationship between the drug and the adverse
b) ‘Unrelated’ meaning there is no evidence to suggest a causal relationship between the drug and the adverse event.

All AEs with a possible causal relationship to the IPS should be reported and managed as possible Adverse Drug Reactions, including:

a) Report to Pharmacopoeia Revision Committee (PRC) the following information using standard reporting categorization provided in the International Conference on Harmonization tripartite guidance on Clinical Safety Data Management E2Br (R2)\(^{(20)}\)

1. Report of causation likelihood

2. Report of adverse event timeline and outcome

   i. Death: The drug may have contributed to the death.

   ii. Not recovered/not resolved: The subject has not yet recovered.

   iii. Recovered/resolved with sequelae: The subject recovered, but with an after effect possibly due to disease, injury,
treatment, or procedure.


v. Unknown: The reporter did not know the outcome at the time the report was submitted.

b) Adverse Drug Reactions that potentially change the risk profile need to be reported to the relevant Competent Authority (e.g. FDA) and to the IRB in accordance with applicable regulations. Unanticipated adverse events which create a problem for the conduct of the trial should be reported to the IRB\(^{(19)}\).

c) Compliance with any applicable regulations

d) Reporting to the Manufacturer.

### 6.2 Serious Adverse Events

Serious adverse events are defined by the FDA\(^{(21), (22), (23)}\) as any untoward medical occurrence that at any dose:

a) Results in death

b) Is life-threatening

c) Requires inpatient hospitalization or prolongation of existing
hospitalization
d) Results in persistent or significant disability/incapacity
e) Is a congenital anomaly/birth defect
f) Or, requires medical or surgical intervention to prevent hospitalization, permanent impairment or damage

All serious adverse events must be recorded and reported:

a) To Ethics or Institutional Review board within the specified time period
b) To the Manufacturer of the IPS within 24 hours
c) And to government agency(s) in the time and manner according to any applicable legal requirements of the country(s) where the Proving is being conducted

A pre-determined written protocol should be followed for reporting and management of serious adverse events during the Proving.

6.3 Single Subject Un-blinding in Connection with Adverse Events

A system for un-blinding of a single subject status in relation to an adverse event should be established prior to Proving initiation.
Decision to un-blind an individual Proving subject in the case of an AE should be based upon therapeutic necessity.

SAEs may require un-blinding at the time of the event.

Un-blinding protocol should comply with the following requirements:

a) Maintains blinding during the Proving unless un-blinding is required;

b) Limits the number of personnel within Proving team who will have access to un-blinding information to those absolutely necessary;

c) Controls which personnel have authority to access data;

d) If individual blind is broken, records any data access including specific personnel who obtained or viewed this information, information that was obtained, date in which it was obtained, and reason for un-blinding;

e) Includes protocol for when un-blinding should occur;

f) And contains adequate “fail-safe” procedures to assure immediate access to subject data during the Proving.
6.4 Individual Subject Discontinuation from Proving

All subjects with an AE, where the therapeutic intervention has been determined by the Investigator to potentially affect the Proving, should be discontinued from the Proving. A complete record of the discontinuance and reasons should be part of the study record.

If subject is withdrawn/discontinued due to symptom reliability concerns, no further data from that subject should be included in the Proving analysis.

6.5 Event Handling Flow Chart

A flow chart for new symptom assessment to guide Study Personnel in the recognition and management of suspected adverse drug reactions (including SUSARs) should be developed. Chart 1 (below) may be used as a template.

The proposed timeframes associated with SAE reporting are recommended; variations based on local requirements may apply.
Flow chart for adverse event determination in a proving

Symptom / Observation Occurs

YES

Unexpected?

NO

Suspected
Adverse
Drug
Reaction

Enter into Trial Log

IRB Report (if Required)

Include in Submission

*Regulatory Reporting Compliance per Locale of Trial

NO

Symptom

Subject Remains in Trial

Suspected
Unrelated
Event

Suspected
Unexpected
Serious Adverse Reaction

< 24 hrs

Report to Manufacturer

7-14 days

IRB Report

Suspected
Adverse Drug Reaction

Is Un-blinding Therapeutically Necessary?

YES

Un-related:

Inclusion in Monograph Submission

NO

Premature Discontinuation of Subject from Trial

Causality Determination

Un-blinding: Verum or Placebo?

Suspected Unrelated Event

Suspected
Serious Adverse Event

Meets Criteria for Serious Adverse Event?

YES

NO

Chart 1
Data Analysis

Data compilation and analysis by the Proving team is a key factor in the translation of raw Proving data into a meaningful clinical drug picture that can be used by a prescriber. The data analysis process must be carefully designed to avoid excessive inclusion of non-specific, non-characteristic data, yet ensure that the most characteristic and dependable data for homeopathic prescribing is maintained.

Monograph reviewers are instructed to evaluate Proving outcomes and analysis according to these guidelines (see Chart 2) to ensure that an adequate Proving outcome has been achieved. An analysis process to extract dependable homeopathic prescribing indications from a drug Proving is required to contain the following dimensions (as described in information that follows):

- 1st dimension All symptoms occurring during the Proving
- 2nd dimension Proving symptoms with relative characterizing assessment
- 3rd dimension Characteristic symptoms (a highly individualized subset)

**Figure 2**

All Symptoms occurring during the Proving should be recorded according to criteria in Section 5. This group will include symptoms that are typical for the prover historically (but not related to the Proving), symptoms unrelated to the Investigational Proving Substance (IPS), symptoms due to placebo effect, and symptoms due to the IPS.
7.1 Proving Symptoms

These are those symptoms or signs that are recorded during the Proving period where causality by the IPS is possible. Symptoms that occur in a severity, duration and frequency consistent with historical tendency (i.e. Unchanged (U) symptoms) of a subject should not be reported as Proving symptoms. Likewise, care should be taken to exclude from this category any symptoms related to a cause that can confidently be determined to be external to the Proving. Proving Symptoms should be defined using qualitative criteria that have been established prior to Proving initiation, and should include:

Criteria to define a significant change in any objective measure, if such measures are used in the Proving.

Qualifiers for subjective (reported by subject) symptoms including:

a) New symptoms, not previously experienced (N)

b) Unexpected a change representing worsening or aggravation of ongoing or recurring symptoms (C-)

c) Unexpected a change representing improvement in ongoing or recurring symptoms (C+)

d) Unexpected recurrence of past symptoms (R)

(These criteria should be the same criteria used in decision-making for non-repetition of the IPS as described in Section 4.8 of these guidelines.)
7.2 Relative Characterizing Features

The following list is provided as a recommended template to use for evaluation of characterizing features of Proving symptoms:

a) New symptoms with marked or unexpected severity, duration or frequency in the subject.

b) Ongoing or recurring symptoms present during the Proving that have been unexpectedly and markedly improved.

c) Ongoing or recurring symptoms that have been unexpectedly and markedly worsened.

d) Symptoms that recur from the past but have not occurred in the 12 months preceding the Proving.

e) Symptoms that display alternation with another symptom in a single volunteer in such a way that the alternation is strongly individualizing.

f) Symptoms associated with modalities or concomitant symptoms occurring in other parts of the same prover.

g) Symptoms that involve multiple body parts or organs in a similar manner or multiple symptoms within the same subject with a similar associated modality, forming an easily recognizable pattern of
reaction.

h) Similar symptoms occurring in multiple provers. Such symptoms may be related by similar sensation, modality, or body system and can be recognized through a qualitative analysis similar to “Red-Line” symptom reporting in homeopathic literature \(^{(25)}\).

7.3 Characteristic Symptoms

These symptoms obtained in the Proving represent those Proving symptoms produced in a subject that are of particular value from a homeopathic perspective, and only include highly individualistic symptoms. Reporting Characteristic Symptoms that occur during a Proving is strongly recommended to help establish an adequate homeopathic clinical picture of the IPS. Characteristic Symptoms are one of the primary criteria used in evaluation of Proving outcomes. When reporting Characteristic Symptoms such symptoms should be reported in a binary fashion (characteristic or not). When Characteristic Symptoms are reported from the Proving, symptoms will be evaluated using the following criteria:

Strongly individualizing symptoms must be well described by the prover or observing supervisor.

Proving symptoms will be considered to be Characteristic Symptoms only when they have strong characterizing and individualizing features. These types of symptoms are often described as being highly peculiar, strange, or rare in their nature.

Characteristic Symptoms are recognizable as those symptoms that are sufficiently individualizing to allow a clinician to
reasonably consider the use of the medicine based upon that clinical feature alone.

7.4 Clinical Synopsis of the IPS

Well designed Provings create an opportunity to develop a coherent remedy picture for the IPS. A remedy picture represents the influence of the IPS upon the complex human biologic system as observed in patterns of reaction in one or more subjects. While all Proving symptoms should be considered in this process, Characteristic Symptoms play a more important role due to their specificity, individuation, and consistency with good homeopathic clinical practice.

The following elements will be considered in this part of the monograph review:

a) Quality and Number of Proving symptoms.

b) Quality and Number of reported characteristic symptoms.

c) Frequency of similar Proving symptoms or observations within a single prover, across multiple subjects in the same Proving, or if appropriate, in other Provings of the same substance.

Sufficiency of remedy picture development will be evaluated by the Pharmacopeia Revision Committee (PRC). Sufficiency determination will be determined by PRC consensus and Board of Director approval. The Proving results must attain at least one of the following:

a) Presence of 1 or more Characteristic
Symptoms

b) A discernible clinical picture emerges in one prover or across multiple provers

c) Presence of 3 or more proving symptoms with sufficient characterizing quality to provide an adequate amount of data for clinical use.

Homeopathic Provings that produce few or no Proving symptoms and few or no characteristic symptoms in subjects receiving the verum IPS may not provide sufficient indications for clinical use of the IPS. In turn, lack of sufficient clinical indications for the IPS may result in a determination of inadequacy of the Proving for the monograph.

7.5 Use of Control Results

Criteria for use of symptoms produced by subjects who receive control allocation of IPS must be established prior to initiation of Proving.

Symptoms reported by subjects who received control allocation should not be included as symptoms reported to describe the remedy picture.
noted as placebo-related symptoms.
Pharmacopeia revision committee proving quality review template

Proving Design and Execution meet minimum standards Sections I-V, VII

YES

NO

One or More Characteristic Symptoms identified in Proving Outcomes?

NO

Three or More Proving Symptoms identified in Proving Outcomes?

NO

YES

Discernible clinical symptom picture emerges in one prover or across multiple provers?

YES

NO

Symptom Analysis

NO

MORE

LESS

Marked severity, frequency or duration

Unexpected/Marked Improve or Worse

Recurrence of old symptom (>12 mo.)

Alternation of Symptoms

Modalities or Concomitants

Consistent with prior Clinical or Proving data

Overall Impression Favors Approval

Overall Impression Favors Need for Additional Clinical Information

Overall Impression Favors Rejection

Approve

Overall Impression Favors Approval

Overall Impression Favors Need for Additional Clinical Information

Overall Impression Favors Rejection

Chart 2
8 Legal / Ethics

Proving will be designed and conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki \(^{(26)}\), and that are consistent with Good Clinical Practice and the applicable regulatory requirements \(^{(27)}\).

8.1 Ethics or Institutional Review Board

Review and approval is required for all Proving on human subjects.

8.2 Informed Consent

Documentation of Informed Consent is required for all Proving subjects, and should include:

a) Documents should meet the general requirements for Informed Consent of 45CFR 46.116 \(^{(28)}\) and 21 CFR 50.20 \(^{(29)}\)

b) Informed Consent should contain the information required by each of the eight basic elements,

c) And, if appropriate to the Proving, any of the six additional elements as listed in those regulations.

d) Be presented in a form that is understandable by all subjects.
8.3 **Subject Withdrawal Criteria**

Voluntary subject withdrawal must be permitted at any time during the Proving at the request of the subject.

Subjects may be removed at any time during the Proving so long as the criteria are adequately recorded and approved by the Principal Investigator.

Reasons for removal of a subject from the proving (either voluntary or involuntary) must be reported in the monograph submission. Removal of subject(s) by the Principal Investigator without sufficient cause will result in disqualification of the Proving.

8.4 **Insurance coverage**

Insurance coverage for test subjects sufficient to permit Ethical or Institutional Review Board approval is required.

8.5 **Financial Disclosure Certification**

Financial Disclosure certification must be completed by the Principal Investigator and Clinical Coordinator/ Subject Supervisors (if not employed directly by the Principal Investigator) including acknowledgement of any of the following (30):

Any financial remuneration by the sponsor or manufacturer of the tested medicine beyond the cost of the study.
Any grants or honoraria paid by the sponsor or manufacturer

Any proprietary interest in the tested product

Any significant equity interest in the sponsor or manufacturer
9 Monograph Report

9.1 Proving Report

This report will include information on Proving design, execution, data collection, analysis, safety, and outcomes. The report should be indexed and formatted in a manner that ensures ease of access and a high degree of usability consistent with Good Clinical Practice guidance \(^{31},^{32}\).

Some elements listed in the ICH Harmonized Tripartite Guideline for Structure and Content of Clinical Study Reports are not applicable to Provings. Excluded or modified elements are listed in the detailed template for this report (Appendix A).

Additional elements that are required by the HPCUS for Proving clinical study reports are detailed in Appendix A.

9.2 Monograph Report Submission Process

Questions regarding report format, content, or submission should be directed to the HPUS Editor prior to submission.

All monograph reports should be submitted in their entirety in final form only.

Monograph report should be submitted in electronic version using either locked
Microsoft Word or PDF format.

Monograph report should only be submitted directly to the Editor of the HPUS.
Proving Report

Monograph sponsors are instructed to follow the requirements outlined in the ICH Harmonized Tripartite Guideline for Structure and Content of Clinical Study Reports. Monograph specific requirements and exclusions from these guidelines are noted in the outline below.

• When using this template, all sections listed within the guidelines will include the requirements of the ICH guidelines, except where specifically directed by a statement of non-applicability, or by other guidance within the listed element that requests specific deviation or additions to the ICH guidelines.

• Monograph sponsors must provide adequate information within the Proving Report to demonstrate adherence to all requirements within these Proving Guidelines.

• Additionally, the Proving Report should include reasoning for any departure from recommendations that are detailed in these Proving Guidelines.

• Extrapolated or speculative commentary should not be placed into this report except where specifically requested.
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9 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN – DESCRIPTION

9.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

Information reported in this section will be limited to discussion of the following:
Percentage of controls used. Discussion of use of control data for any purpose other than bias reduction. Discussion of use of control data for any comparative analysis.

9.3 SELECTION OF STUDY POPULATION

9.3.1 Inclusion Criteria

9.3.2 Exclusion Criteria

9.3.3 Removal of Subjects from Assessment

9.4 TREATMENTS

9.4.1 Treatments Administered

9.4.2 Identity of Investigational Product(s)

Include identifying information about the IPS, manufacturer, and compliance with described manufacturing procedure submitted to the Monograph Review Committee.

9.4.3 Method of Assigning Subjects to Treatment Groups

9.4.4 Selection of Doses in the Study

9.4.5 Selection and Timing of Dose for each Subject

Homeopathic proving dosing and timing has different selection criteria than therapeutic agents used in trials for treatment outcomes. Please provide a brief description of the criteria used for timing, frequency, and repetition of doses during the Proving.

9.4.6 Blinding

9.4.7 Prior and Concomitant Therapy

Concomitant therapy with homeopathic agents is not permitted for Provings submitted for monograph review. All information in this section will refer to therapeutic agents that are not homeopathic preparations. Narrative report of any
concomitant treatment across the whole group should be included here with reference to table describing individual concomitant treatments within the demographic factors report table.

9.4.8 Treatment Compliance

Reports of treatment compliance will be limited to how delivery of each dose of IPS to prover was confirmed and recorded.

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

Not applicable

9.5.2 Appropriateness of Measurements

Not applicable

9.5.3 Primary Efficacy Variable(s) Drug Concentration Measurements

Not Applicable

9.6 DATA QUALITY ASSURANCE

9.7 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

9.7.1 Statistical and Analytical Plans

Not applicable

9.7.2 Determination of Sample Size

Adherence to Proving guidelines must be demonstrated.

9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

10 STUDY SUBJECTS

10.1 DISPOSITION OF SUBJECTS

10.2 PROTOCOL DEVIATIONS

11 EFFICACY EVALUATION
11.1 DATA SETS ANALYSED

Outcome analysis for Provings will not measure efficacy of the IPS. All other parameters of this part of the ICH guidelines should be followed with respect to the data sets used in outcome analysis.

11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

11.3 MEASUREMENTS OF TREATMENT COMPLIANCE

11.4 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL SUBJECT DATA

11.4.1 Analysis of Efficacy

Efficacy measures do not apply to Proving results and this type of analysis is therefore not applicable in Provings. Guidance on analyses types, how outcomes were measured, and the evaluation of safety as described in the ICH guidelines are to be included in the Proving Clinical Study Report.

Additionally, all aspects of outcomes analysis as described in Section VI of these guidelines should be reported in this section. Specific information on criteria used for defining characteristic symptoms, Proving symptoms, and relative characterizing features should be described in detail.

11.4.2 Statistical/Analytical Issues

Not applicable.

11.4.2.1 Adjustments for Covariates

Not Applicable.

11.4.2.2 Handling of Dropouts or Missing Data

Because Provings outcomes are primarily evaluated using qualitative criteria, the effect of dropouts and missing data may be difficult to estimate. Sponsors must report all subjects that drop out of the Proving and the reasons for their leaving the Proving. Extrapolation or modeling approaches to incomplete data sets should not be included in Proving reports.

11.4.2.3 Interim Analyses and Data Monitoring

Provings design would generally not include interim analysis.
11.4.2.4 Multicentre Studies

11.4.2.5 Multiple Comparison/Multiplicity

Not applicable.

11.4.2.6 Use of an "Efficacy Subset" of Subjects

Not applicable.

11.4.2.7 Active-Control Studies Intended to Show Equivalence

Not applicable.

11.4.3 Examination of Subgroups

Such analysis is not applicable to Provings unless sample size is large.

Tabulation of Individual Response Data

Pertinent individual response data is an essential element of all Provings submitted for monograph report. Detailed response data should be formed into a table including all subjects. This table should include:

- Subject identification number
- Notation of receipt of Verum or Control
- Number of doses received
- Date of Proving initiation for each subject
- Dates and times doses received
- Date of last journal entry / data entry for each subject
- Number of Proving symptoms observed
- Number of characteristic symptoms observed

In addition a detailed record of all symptoms recorded during the Proving for each subject should be included. Each symptom recorded should include identifying
nomenclature for the type of symptom according to labeling criteria in Section IV of these guidelines.

11.4.4 Drug Dose, Drug Concentration, and Relationships to Response

Not applicable.

11.4.5 Drug-Drug and Drug-Disease Interactions

11.4.6 By-Subject Display

This information should be included within 11.4.3, if applicable.

11.4.7 Efficacy Conclusions

Not applicable. In place of Efficacy Conclusions, please add a synopsis of the outcomes from the Proving including any characteristic symptoms with descriptions and number, and a listing of the primary Proving symptoms that displayed the highest degree of characterizing features. An overall symptom picture can be presented here.

12 SAFETY EVALUATION

12.1 EXTENT OF EXPOSURE

12.2 ADVERSE EVENTS (AES)

12.2.1 Brief Summary of Adverse Events

12.2.2 Display of Adverse Events

12.2.3 Analysis of Adverse Events

12.2.4 Listing of Adverse Events by Subject

12.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

12.3.1 Listing of Deaths, other Serious Adverse Events and Other Significant Adverse Events

12.3.2 Deaths

12.3.3 Other Serious Adverse Events

12.3.4 Other Significant Adverse Events
12.3.5 Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events

12.3.6 Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

12.4 CLINICAL LABORATORY EVALUATION

12.4.1 Listing of Individual Laboratory Measurements by Subject (16.2.8) and Each Abnormal Laboratory Value (14.3.4)

12.4.2 Evaluation of Each Laboratory Parameter

12.4.2.1 Laboratory Values over Time

12.4.2.2 Individual Subject Changes

12.4.2.3 Individual Clinically Significant Abnormalities

12.5 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

12.6 SAFETY CONCLUSIONS

13 DISCUSSION AND OVERALL CONCLUSIONS

Discussions as to efficacy are not appropriate for Provings. Other findings and conclusions should be included in these sections

14 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 DEMOGRAPHIC DATA

14.2 EFFICACY DATA

Efficacy data are not applicable. Table of outcomes should be provided here. Outcomes should be tabulated by Characteristic Symptoms first, followed by those symptoms with the highest amount of characterizing qualities in a descending order according to the analysis by the Proving Supervisor. Each symptom or observation reported should be described in original language of the prover, labeled for New (N),
Improved (C+), Worsened (C-) or Recurrent (R), and described for date of onset relative to Proving initiation and dosing.

14.3 SAFETY DATA

14.3.1 Displays of Adverse Events

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

14.4 ABNORMAL LABORATORY VALUE LISTING (EACH SUBJECT)

15 REFERENCE LIST

16 APPENDICES

16.1 STUDY INFORMATION

16.1.1 Protocol and protocol amendments

16.1.2 Sample case report form (unique pages only)

16.1.3 List of IECs or IRBs (plus the name of the committee Chair if required by the regulatory authority) - Representative written information for subject and sample consent forms

16.1.4 List and description of investigators and other important participants in the study, including brief (1 page) CVs or equivalent summaries of training and experience relevant to the performance of the clinical study

16.1.5 Signatures of principal or coordinating investigator(s) or sponsor’s responsible medical officer, depending on the regulatory authority’s requirement

16.1.6 Listing of subjects receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used

16.1.7 Randomization scheme and codes (subject identification and treatment assigned)

16.1.8 Audit certificates (if available) (see Annex IVa and IVb of the guideline)
16.1.9 Documentation of statistical methods
If Used.

16.1.10 Documentation of inter-laboratory standardization methods and quality assurance procedures if used

16.1.11 Publications based on the study

16.1.12 Important publications referenced in the report

16.2 SUBJECT DATA LISTINGS

16.2.1 Discontinued subjects

16.2.2 Protocol deviations

16.2.3 Subjects excluded from the efficacy analysis

16.2.4 Demographic data

16.2.5 Compliance and/or drug concentration data (if available)

16.2.6 Individual efficacy response data
Not Applicable.

16.2.7 Adverse event listings (each subject)

16.2.8 Listing of individual laboratory measurements by subject, when required by regulatory authorities

16.3 CASE REPORT FORMS

16.3.1 CRFs for deaths, other serious adverse events and withdrawals for AE

16.3.2 Other CRFs submitted

16.4 INDIVIDUAL SUBJECT DATA LISTINGS (US ARCHIVAL LISTINGS)
Adverse Event – Within the context of a Proving, an adverse event is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a proving. It may be a new illness, worsening of a concomitant illness, an injury, or any concomitant impairment of a subject’s health (including symptoms and observed clinical effects) that is unexpected and clinically significant.

Characteristic Symptom (see under “Symptom”)

Clinical Coordinator – personnel who typically coordinate subject enrollment, collection of data, control of protected health information, and other non-clinical aspects of the Proving.

Concomitant Symptom (see under “Symptom”)

Control – Placebo or physiologically inert compound that is indistinguishable from verum or active medication used in a Proving and is not expected to cause any significant mental, physical or emotional reactions in subjects due on the basis of its physical/biological properties.

Environmental Factors – include any external influence upon the body / mind such as temperature, food, emotional influence, trauma, time of day, etc.

Ethics or Institutional Review Board (IRB) – is an Institution based review board as defined in U.S. federal regulation 45CFR46.102.

Existing Symptom (see under “Symptom”)

Homeopathic Interview – specific techniques for gathering both subjective and objective data gathered according to homeopathic principles which focus upon understanding the individual’s dynamic, homeostatic balance in response to various internal and external stressors.

Homeopathic Medicinal Product – Any medicinal product prepared from products, substances or compositions called homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the HPUS and/or European Pharmacopoeia or, in absence thereof, by an officially recognized national pharmacopoeia.
Modality – An environmental or other factor related to a symptom that is associated with either increasing or decreasing the duration, severity, or frequency of that symptom (24).

New Symptom (see under “Symptom”)

Objective Data – includes any information that is obtained through observation, physical or psychological examination, or testing of subjects using an external observer. Testing may include laboratory studies, radiologic tests, psychological or other instruments, weight measures, or any other biomarker measurement.

Past Symptom (see under “Symptom”)

Peculiar Symptom (see under “Symptom”)

Principal Investigator – An individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team. The principal investigator will review and sign-off the final report.

Project Coordinator – reports directly to the principal investigator and is primarily responsible for facilitation and coordination of the clinical trial activities including financial, personnel, communication, or other related administrative duties.

Protected Health Information – individually identifiable health information, held or maintained by a covered entity or its business associates acting for the covered entity that is transmitted or maintained in any form or medium (including the individually identifiable health information of non-U.S. citizens). This includes identifiable demographic and other information relating to the past, present, or future physical or mental health or condition of an individual, or the provision or payment of health care to an individual that is created or received by a health care provider, health plan, employer, or health care clearinghouse. For purposes of the Privacy Rule, genetic information is considered to be health information.

Proving Supervisor – personnel (generally with homeopathic training) who may evaluate subjects oversee subject response to investigational medicinal product administration, clarify subjective responses, and record observable data during the Proving.

Proving Symptom (see under “Symptom”)

Randomized Controlled Trials – are studies that randomly assign individuals to an intervention group or to a control group, in order to measure the effects of the intervention.
Reasonable Possibility – Within the context of provings, the causality of adverse events by the IPS is a reasonable possibility when the presence of facts or evidence or arguments suggests a causal relationship.

Serious Adverse Reaction – Within the context of provings, an adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Suspected Adverse Reaction – Within the context of Provings is defined as any adverse event for which there is a reasonable possibility that the IPS caused the adverse event.

Suspected Unexpected Serious Adverse Reaction – An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. The event is considered a suspected serious adverse reaction if there is cause to suspect a relation to the investigational Proving Substance administration and the event, and the severity would make the event a Serious Adverse Event.

Symptom – Any change in the normal objective as well as subjective state of mind or body, as experienced by the subject, or as observed by the practitioner and/or others. (Adapted from Swayne et al) (25)

• Characteristic Symptom – Symptom produced in a Proving subject which has a high probability of being related to the test substance, and may include strong, peculiar, or highly individualistic symptoms as well as those symptoms which are strongly aggravated or ameliorated during the Proving. Additional parameters are listed in Section 7.
• **Concomitant Symptom** – Symptom associated with other symptoms in different parts of the body, or the mind, that appears at the same time or during the same disease process, e.g. a headache that occurs during diarrhea, or anxiety that occurs with stomach pain, etc.

• **Existing Symptom** – Symptom reported by subject or noted by the supervisor that was previously experienced or is experienced by the subject in an ongoing manner prior to test substance administration within the recent past and could be expected to occur during the Proving period. Note: such symptoms are often referred to as “Old” symptoms in the homeopathic Proving literature.

• **New Symptom** – Symptom reported by subject or noted by the supervisor that was not previously experienced by the subject prior to test substance administration.

• **Past Symptom** – Symptom reported by the subject to have occurred prior to the test substance administration that was resolved and would not be expected to recur during the Proving time period.

• **Peculiar Symptom** – also referred to as a Strange, Rare or Peculiar Symptom. This is a symptom which is highly individual because it is uncommon, surprising (e.g. paradoxical), or unusual in itself (e.g. a small child craving hot curry), idiosyncratic, or strikingly uncharacteristic of the complaint (e.g. a painless wound).

• **Proving Symptom** – Symptom or sign occurring during the Proving period which is possibly related to the IPS. Symptoms that occur in a severity, duration and frequency consistent with historical tendency, or can confidently be attributed to a cause external to the Proving should NOT be reported as a Proving symptom.

• **Unexpected** – Symptom or sign occurring during the Proving period that is not consistent with investigational product information. For the purposes of provings, unexpected symptoms include any symptoms or signs that have duration longer than the proving period, have clinical severity greater than described in the Informed Consent, have clinical severity that falls within the definition of Serious Adverse Event, require therapeutic intervention, or result in removal from the Proving.

**Therapeutic Intervention** – Medical or other treatment deemed medically necessary by the Supervisor for a subject during the course of a Proving other than the IPS or treatment that was ongoing prior to Proving initiation.
**Verum** – Active Medication that is used in a research trial, as opposed to the placebo or control substance.
12 References


(12) Guidance on Module 3 of the Homeopathic Medicinal Products Dossier, Homeopathic Medicinal Product Working Group, Last downloaded April 01, 2012 from online at http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-


(32) HPUS Investigational Proving Substance Report Guidelines for the Monograph Review Committee. Last downloaded April 01, 2012 from online at www.hpus.com

