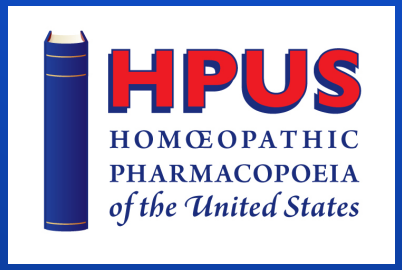

Progress on Developing a Guideline for Validation of Dilution Process for Preparation of Hahnemannian Liquids

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HPUS
HOMŒOPATHIC PHARMACOPOEIA of the United States

Introduction

Establishment of Homeopathy

- Homeopathy was founded by Samuel Hahnemann (1755-1843), raised in Meissen, Germany.
- Students of Hahnemann founded the first homeopathic medical school in the United States in the early 1800s. Gram, 1826, Allentown Academy 1838 (nb Phila College of Phcy 1821).
- Mark Twain writing in *Harper's* magazine (early 1890) credited the establishment of homeopathy for dispatching the outmoded practices of Robert James' *Medicinal Dictionary* (1743–1745). [Robert James, English physician 1703–23 March 1776]

Growth of Homeopathy

- In the 1970 the ethos of natural is better, as a reaction to the excesses of better living through chemistry began to surface. (Rachel Carson “Silent Spring” (1962), Love Canal (1977))
- Effect of CPG 400.400
- Growth of the mass market for homeopathic products has been accompanied by the industrialization of homeopathic frug product manufacturing.

Industrialization

A series of technical evolutions linked to the industrial revolution that affect how goods are made, from production to processing and distribution.

- **Production:** Growing the plants and animals, mining the minerals, synthesizing the chemicals.
- **Processing:** Transforming the raw materials into what is recognized and purchased.
- **Distribution:** Getting the drug product to where the practitioner or patient will obtain it in its ready to use form. This might involve transporting material to a nearby store front, or it might involve many stages. For instance, trucked to a large retailer's warehouse, trucked again to a local distribution facility, and finally delivered to a retail location.

So How Did We Get Here?

- In 1972 FDA established the OTC Drug Review process to evaluate the safety and effectiveness of hundreds of thousands of OTC drug products that were on the market at that time.
- During the comment period to the proposed rulemaking, the American Institute of Homeopathy (AIH) request that homeopathic products be excluded from the OTC review.
- FDA commissioner Alexander M. Schmidt, M.D. (10th commissioner of the FDA), indicated in the preamble to the 1972 regulations, that homeopathic products would be excluded based on their uniqueness, and would be reviewed as a separate category after the OTC review was completed.

In the intervening time homeopathic practitioners and manufactures have relied on the HPUS and FDA‘s 1988 Compliance Policy Guide (CPG) 400.400 titled “Conditions Under Which Homeopathic Drugs May Be Marketed.”

In discussions with the FDA in 2018 and 2019, the Board of Directors of the Homoeopathic Pharmacopeia of the United States determined that substantial work was required to increase the level of harmonization between the practice of homeopathic pharmacy and current FDA guidelines and expectations.

Five key domains were identified.

1. Active Pharmaceutical Ingredients (API)
2. Product Release
3. Validation of Dilution Process for Preparation of Hahnemannian Liquids
4. Validation of Dilution Process for Powders
5. Dosage Form Manufacture – Discrete Solid Oral Dosage Forms

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Purpose

Industry and regulators agree that we must assure the quality and the safety of homeopathic drug products.

The objective of these efforts is to develop pharmacopeial guidelines that will help large scale manufacturer align the practice of homeopathic pharmacy and current FDA expectations, by providing sufficient practical information to firms to achieve the desired outcome without prescribing a particular set of actions.

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Challenges

The Number of Monographed Drugs in HPUS

At least 1,310 products are listed in the HPUS. These products contain a wide range of substances, including ingredients derived from plants (botanicals), healthy or diseased animal or human sources (sarcodes and nosodes), minerals and chemicals. Further these products may be used at multiple levels of dilution and/or in combination with other HPCUS listed items.

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Challenges (continued)

- From many of the 1,310 HPUS listed products, there are many available homeopathic potencies.
- Historic variability in production batch sizes.
- The uniqueness of homeopathic products.

How Are Homeopathic Products Unique?

Starting from substances derived from the mineral, herbal and animal worlds, following a well-defined procedure, The techniques of preparation of these drugs include the dilution of the raw material, in hydroalcoholic solutions or in other excipients, and the potentization of the product into different grades.

- Raw Materials / Starting Materials
- Minerals and Chemicals
- Plant Material
- Animal or Human Derived Source Material

Active Pharmaceutical Ingredients (API)

Guideline to establish the requirements for receiving, testing and storing the Active Pharmaceutical Ingredients used for manufacturing homeopathic products.

Receiving, testing and storing a homeopathic drug product's intermediate products, the tincture, or the starting material is an important part of overall cGMP practice. It is at this stage that the prevention of mix-ups and control of foreign materials or objectionable micro-organisms is first performed.

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A guideline will not specify the manner of performing the recommended activities but will establish that consideration be given to the activities and justification established when the recommendations are not considered appropriate.

- **Guideline:** One or more non-binding recommendations.
- **Policy:** A statement of intent, which is implemented as a procedure or protocol.
- **Procedure:** (standard operating procedure, SOP) set of step-by-step instructions compiled by an organization to help workers carry out complex routine operations in compliance with established policy.

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Scope of an API Guideline

This guideline should encompass the topics listed under 21 CFR 211 Subpart E—Control of Components and Drug Product Containers and Closures.

- 21 CFR 211 Sub Part E is straight forward to interpret for raw materials of chemical origin.
- Raw materials of Botanical origin also align with USP <561> *Articles of Botanical Origin* and/or E.P. monograph: *Herbal Drugs for Homeopathic Preparations (2045)*.
- Raw materials of zoological origin also align with 21 CFR 1271 Sub Parts C and D *Human Cells, Tissues, And Cellular And Tissue-Based Products.*

Correspondence Between Homeopathic GMP and 21 CFR 211.84

§ 211.80 - General requirements.

§ 211.82 - Receipt and storage of untested components, drug product containers, and closures.

§ 211.84 - Testing and approval or rejection of components, drug product containers, and closures.

§ 211.86 - Use of approved components, drug product containers, and closures.

§ 211.87 - Retesting of approved components, drug product containers, and closures.

§ 211.89 - Rejected components, drug product containers, and closures.

§ 211.94 - Drug product containers and closures.

§211.80 General Requirements

Subpart E—Control of Components and Drug Product Containers and Closures	Chemical	Botanical	Sarcode	Nosode	Needed in the HPUS Guideline
(a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures; such written procedures shall be followed.					• Procedures for quarantining unapproved materials. • Inventory management practices (FIFO). • Written procedures required / sufficient detail.
(b) Components and drug product containers and closures shall at all times be handled and stored in a manner to prevent contamination.	3.6 5.8	3.6	3.6	3.6	
(c) Bagged or boxed components of drug product containers, or closures shall be stored off the floor and suitably spaced to permit cleaning and inspection.	3.6				• Prohibition from storing on the floor. • Wood pallets.
(d) Each container or grouping of containers for components or drug product containers, or closures shall be identified with a distinctive code for each lot in each shipment received. This code shall be used in recording the disposition of each lot. Each lot shall be appropriately identified as to its status (i.e., quarantined, approved, or rejected).					• Inventory management, tracking & tracing. • Recordkeeping to support recall, withdrawal, and/or investigations. • Silent on the topic of withholding unapproved materials from use (manufacture at risk/ mfg. under quarantine).

§211.82 Receipt and Storage of Untested Components, Drug Product Containers, and Closures

Subpart E—Control of Components and Drug Product Containers and Closures	Chemical	Botanical	Sarcode	Nosode	Needed in the HPUS Guideline
(a) Upon receipt and before acceptance, each container or grouping of containers of components, drug product containers, and closures shall be examined visually for appropriate labeling as to contents, container damage or broken seals, and contamination.					Not specifically stated.
(b) Components, drug product containers, and closures shall be stored under quarantine until they have been tested or examined, whichever is appropriate, and released. Storage within the area shall conform to the requirements of §211.80.					Silent on the topic of withholding unapproved materials from use (manufacture at risk/ mfg. under quarantine).
[43 FR 45077, Sept. 29, 1978, as amended at 73 FR 51932, Sept. 8, 2008]					

§211.84 Testing and Approval or Rejection of Components, Drug Product Containers, and Closures

Subpart E—Control of Components and Drug Product Containers and Closures	Chemical	Botanical	Sarcode	Nosode	Needed in the HPUS Guideline
(a) Each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit.					• No clear statement on withholding unapproved materials. • 5.4 Vendors must provide COA, Cert of Mfg., Cert of Conformity, identity. • 5.4.1 Typically release on vendor's COA + ID test. If so, COA must be complete, a less complete COA is acceptable if the facility will test.
(b) Representative samples of each shipment of each lot shall be collected for testing or examination. The number of containers to be sampled, and the amount of material to be taken from each container, shall be based upon appropriate criteria such as statistical criteria for component variability, confidence levels, and degree of precision desired, the past quality history of the supplier, and the quantity needed for analysis and reserve where required by §211.170.	5.5.1	6.7	7.7.1.1	8.6.1.1	• All reference 211.84

§211.84 Testing and Approval or Rejection of Components, Drug Product Containers, and Closures

Subpart E—Control of Components and Drug Product Containers and Closures	Chemical	Botanical	Sarcode	Nosode	Needed in the HPUS Guideline
(c) Samples shall be collected in accordance with the following procedures:					
(1) The containers of components selected shall be cleaned when necessary in a manner to prevent introduction of contaminants into the component.	x				Not explicitly stated.
(2) The containers shall be opened, sampled, and resealed in a manner designed to prevent contamination of their contents and contamination of other components, drug product containers, or closures.	x				Not explicitly stated.
(3) Sterile equipment and aseptic sampling techniques shall be used when necessary.	x				Not explicitly stated for chemicals.
(4) If it is necessary to sample a component from the top, middle, and bottom of its container, such sample subdivisions shall not be composited for testing.	x				Not explicitly stated for chemicals.
(5) Sample containers shall be identified so that the following information can be determined: name of the material sampled, the lot number, the container from which the sample was taken, the date on which the sample was taken, and the name of the person who collected the sample.	x				Not explicitly stated for chemicals.

Subpart E—Control of Components and Drug Product Containers and Closures	Chem.	Bot.	Sarcode	Nosode	Needed in the HPUS Guideline
(6) Containers from which samples have been taken shall be marked to show that samples have been removed from them.	x				Not explicitly stated for chemicals.
(d) Samples shall be examined and tested as follows:					
(1) At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.	3.9.1 5.4.1	3.9.1	3.9.1	3.9.1	Specificity - requirement for validation without an explicit connection to what standard is used to asses validation. Is validation an autonomous laboratory activity or does it require oversight of the quality unit?
(2) Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.					• Ambiguous regarding the applicable standard. Most often the hierarchy appears to be HPUS for HPUS materials, USP for USP materials, but substitution of E.P. or "Other official compendia" is stated. • "Where an assay is indicated in a compendium as being required, assay results must assure conformance with he assay requirement" - How is this not confused with a requirement to meet all requirements of all compendia? • "Official compendia" (current revision of the United States Pharmacopeia, National Formulary, AOAC INTERNATIONAL, Book of Methods or in other recognized standard references) • Unclear to what specification conformance must be demonstrated. A compendial grade material meeting compendial requirements when tested using the compendial methods is a clear case, the other situations are ambiguous and invite specification shopping • Accepting vendor COA needs to be based of vendor certification (proof of reliability) Collaborative testing 3, 5, 7 10 batches and 1 batch/yr. there after or every 25 batch for high volume materials…

Subpart E—Control of Components and Drug Product Containers and Closures	Chem.	Bot.	Sarcode	Nosode	Needed in the HPUS Guideline
(3) Containers and closures shall be tested for conformity with all appropriate written specifications. In lieu of such testing by the manufacturer, a certificate of testing may be accepted from the supplier, provided that at least a visual identification is conducted on such containers/closures by the manufacturer and provided that the manufacturer establishes the reliability of the supplier's test results through appropriate validation of the supplier's test results at appropriate intervals.	3.8	3.8	3.8	3.8	• Accepting vendor COA needs to be based of vendor certification (proof of reliability) Collaborative testing 3, 5, 7 10 batches and 1 batch/yr. there after or every 25 batch for high volume materials… • 3.8 Supplier qualification program, quality agreement, prequalified in addition to audited 3.9.1 Testing & Evaluation of API • 3.9.2 Testing of Excipients • 3.9.1 (active) 3.9.2 (excipients) to be tested to a compendia with compendial methods, or a suitable validated method if no compendial method exists
(4) When appropriate, components shall be microscopically examined.					
(5) Each lot of a component, drug product container, or closure that is liable to contamination with filth, insect infestation, or other extraneous adulterant shall be examined against established specifications for such contamination.					ophthalmic, parenteral products
(6) Each lot of a component, drug product container, or closure with potential for microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use.					Cardboard dust, oral liquid, ophthalmic, parenteral products
(e) Any lot of components, drug product containers, or closures that meets the appropriate written specifications of identity, strength, quality, and purity and related tests under paragraph (d) of this section may be approved and released for use. Any lot of such material that does not meet such specifications shall be rejected.					No explicit statement

§211.86 Use of Approved Components, Drug Product Containers, and Closures

Subpart E—Control of Components and Drug Product Containers and Closures	Chemical	Botanical	Sarcode	Nosode	Needed in the HPUS Guideline
Components, drug product containers, and closures approved for use shall be rotated so that the oldest approved stock is used first. Deviation from this requirement is permitted if such deviation is temporary and appropriate.					Inventory management (FIFO)

§211.87 Retesting and Approved Components, Drug Product Containers, and Closures

Subpart E—Control of Components and Drug Product Containers and Closures	Chemical	Botanical	Sarcode	Nosode	Needed in the HPUS Guideline
Components, drug product containers, and closures shall be retested or reexamined, as appropriate, for identity, strength, quality, and purity and approved or rejected by the quality control unit in accordance with §211.84 as necessary, e.g., after storage for long periods or after exposure to air, heat or other conditions that might adversely affect the component, drug product container, or closure.					• Retesting of APPROVED materials following a deviation / excursion • Systems to record, track, conclude and analyze deviations and other "events"

§211.89 Rejected Components, Drug Product Containers, and Closures

Subpart E—Control of Components and Drug Product Containers and Closures	Chemical	Botanical	Sarcode	Nosode	Needed in the HPUS Guideline
Rejected components, drug product containers, and closures shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.					No explicit statement.

§211.94 Drug Product Containers and Closures

Subpart E—Control of Components and Drug Product Containers and Closures	Chemical	Botanical	Sarcode	Nosode	Needed in the HPUS Guideline
(a) Drug product containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements.					Non-reactive statement included for storage of API, silent on drug product
(b) Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.					Silent
(c) Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use. Such depyrogenation processes shall be validated.		6.5.2 6.5.3.3			Statements for Harvested botanicals (Sect 6), but not drug products.
(d) Standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures.					Silent - specific to parenteral and ophthalmic products

§211.94 Drug Product Containers and Closures (continued)

Subpart E—Control of Components and Drug Product Containers and Closures	Chemical	Botanical	Sarcode	Nosode	Needed in the HPUS Guideline
(e) Medical gas containers and closures must meet the following requirements—(1) Gas-specific use outlet connections. Portable cryogenic medical gas containers that are not manufactured with permanent gas use outlet connections (e.g., those that have been silver-brazed) must have gas-specific use outlet connections that are attached to the valve body so that they cannot be readily removed or replaced (without making the valve inoperable and preventing the containers' use) except by the manufacturer. For the purposes of this paragraph, the term “manufacturer” includes any individual or firm that fills high-pressure medical gas cylinders or cryogenic medical gas containers. For the purposes of this section, a “portable cryogenic medical gas container” is one that is capable of being transported and is intended to be attached to a medical gas supply system within a hospital, health care entity, nursing home, other facility, or home health care setting, or is a base unit used to fill small cryogenic gas containers for use by individual patients. The term does not include cryogenic containers that are not designed to be connected to a medical gas supply system, e.g., tank trucks, trailers, rail cars, or small cryogenic gas containers for use by individual patients (including portable liquid oxygen units as defined at §868.5655 of this chapter).					Not applicable to the majority of HPUS users
(2) Label and coloring requirements. The labeling specified at §201.328(a) of this chapter must be affixed to the container in a manner that does not interfere with other labeling and such that it is not susceptible to becoming worn or inadvertently detached during normal use. Each such label as well as materials used for coloring medical gas containers must be reasonably resistant to fading, durable when exposed to atmospheric conditions, and not readily soluble in water.					Not applicable to the majority of HPUS users

Areas of Focus

Written specifications, methods, and procedures:

- Quality control specifications for chemical and microbiological tests used to release each incoming lot of component for use in manufacturing.
- Proper storage and identification. Distinctive codes/traceability.
- Status of material (approved, quarantined, or rejected).
- “At risk” manufacturing violates the precept of good quality control.

Areas of Focus

Component identity testing

- “Validating” supplier COA data. Vendor qualification & vendor certification.
- Identity testing of botanical materials.
  - Qualified botanist, technologies such as NIR, PCR.
  - Chemical testing of tinctures and attenuations with fit for purpose, specific test methods.
  - Method validation.

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Next Steps for an API Guideline

Feedback

Gather and incorporate feedback from industry and regulators through forums such as the AAHP.

Finalize Draft

Finalize, for HPCUS deliberation, the draft guideline and supporting white paper for raw materials of chemical and botanical origin.

How Are Homeopathic Products Unique?

Starting from substances derived from the mineral, herbal and animal worlds, following a well-defined procedure, The techniques of preparation of these drugs include the dilution of the raw material, in hydroalcoholic solutions or in other excipients, and the potentization of the product into different grades.

Raw Materials / Starting Materials

- Minerals and Chemicals
- Plant Material
- Animal or Human Derived Source Material

- The active ingredient of a homeopathic drug product is the homeopathic attenuation in its entirety.
- Liquid preparations consist of aqueous or hydro-alcoholic solutions, tinctures and higher attenuations, and are attenuated with succussion (see §28), generally using alcohol and/or water, in decimal or centesimal progression.
- HPCUS Section 25.2.

Homeopathic liquid attenuations are designated according to the method of scale of attenuation and the attenuation method employed. The designations, which must appear on the labels, are shown in the following table:

Designation	Scale	Method
X or D	Decimal (1/10)	Hahnemannian
CH or C	Centesimal (1/100)	Hahnemannian
CK or K	Centesimal (1/100)	Korsakovian
LM	Fifty Millesimal 1/50,000	Hahnemannian

This bottle contains Arnica montana (Leopard's Bane, Fallkraut) D6, i.e., the nominal dilution is one part in one million (10^6).

Decimal Scale of Attenuation

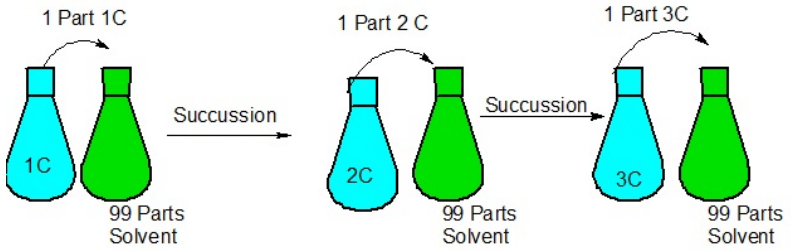
Diluting a substance
by a factor of 10 at each stage

HP X or KP X

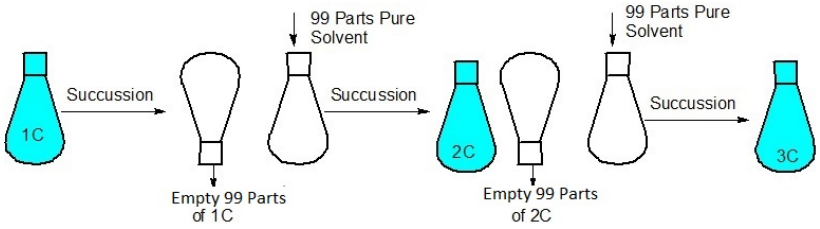
Arnica_montana_homéopathie_zoom.jpg
Source: Wikimedia Commons
License: **CC BY-SA 3.0,** license

Methods of Attenuation

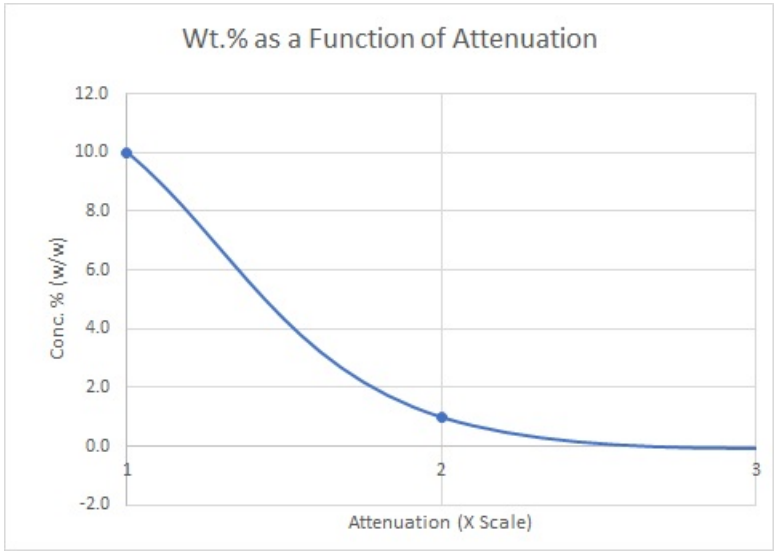
Hahnemann attenuation
(CH or C)

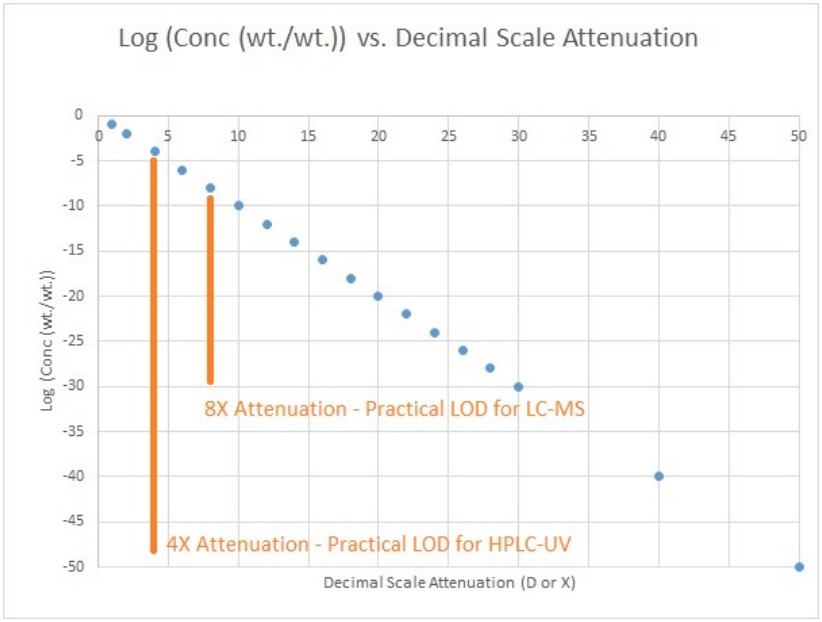


Korsakovian attenuation
(KH or K)



The Potentization Process Brings Measurable Concentrations Below Any Achievable LOQ/LOD





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How to Move Forward

The challenges associated with applying the cGMP to homeopathic products has led to slow progress in process validation by manufacturers.

HPCUS believes process validation for homeopathic drug products should:

- Be risk-based;
- Follow the general principles contained in the Guidance for Industry: Process Validation: General Principles and Practices (Rev. 1 Jan 2011); and
- Be consistent with ICH Q9 Quality Risk Management concepts.

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Class C Botanical Tinctures

- To move forward the product validation guidance effort has focused on Class C botanical tinctures to pilot the development of a validation guidance. The level of complexity is less than other dosage forms, which favors bringing the guidance to a final form more quickly.
- In reviewing a list of the top 175 single component HPUS listed products ranked by sales volume, 100 (57%) are Class C tinctures. Sixty-five were exclusively Class C, twenty-five were also listed as Class M, nine as Class N, and one as Class O.
- Overall Class C Botanical Tinctures represent 643 individual HPCUS listed products (47%) and in many cases are then used directly, following further succession (dilution), or with an additional number of other HPCUS listed ingredients as combination products.

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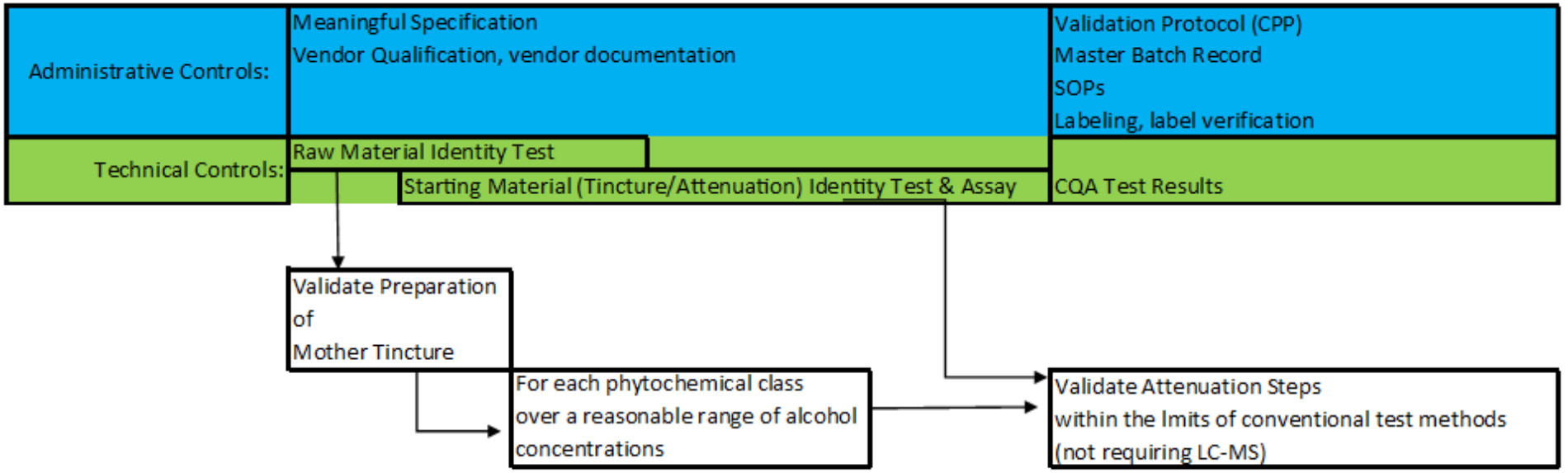
- HPCUS believes that efforts to simplify the challenges can accelerate process validation. The simplifications are in two areas.
- First is to conduct validation studies by groups where the groupings would represent similar physiochemical properties (phytochemical class), within a dosage form, under similar manufacturing conditions, using a particular set of unit operations.
- Second is to free manufacturers of any obligation to demonstrate the proportionality of further attenuation steps once test data or process validation had demonstrated any components of concern were below their respective threshold(s) of concern, in those situations where the required LOQ/LOD could not be met with conventional HPLC methods without employing sample preconcentration at a factor of 2 X 10^2 or greater (200:1).

#	Raw Material / Starting Material	Dosage Form Groups	Equipment train group	Formulation Type
1	Plants (botanicals)	Solutions	Powder Mixer - granulator bowl with rotor & chopper (e.g. Diosna, Fielder, etc.)	Single active ingredient
2	Minerals	Suspensions	Powder Mixer - rotating drum or cube	Multiple active ingredients
3	Chemicals	Creams	Powder Mixer - ribbon blender	Modified release
4	Healthy or Diseased Animal • sarcodes (health animal products, protoplasm of animals) • nosodes (derived from an element of a disease or from diseased tissue)	Ointments	Fluid Bed Dryer (drying process includes mixing process to ensure uniformity)	
5	Human Sources • sarcodes (health animal products, protoplasm of animals) • nosodes (derived from an element of a disease or from diseased tissue)	Tablets (via Direct Compression)	Oven Dryer (drying process does not include mixing to ensure uniformity)	
6		Tablets (via Granulation process, wet and dry)	Vacuum powder transfer system	
7		Capsules (two-piece, via Dry Mixing process)	Manual powder transfer system	
8		Capsules (two piece, via Granulation process, wet and dry	Liquid solution manufacturing & filling equipment Hahnemann dilution Korsakovian method	
9		Soft Capsules (Softgels) containing solution fills	Liquid suspension manufacturing & filling equipment	
10		Soft Capsules (Softgels) containing suspensions fills, powder mixes		

Validation Road Map



Known compounds of concern, would be used as the marker compound:

- Strychnine from Nux vomica and Ignatia
- Aconitine, mesaconitine, hypaconitine and jesaconitine from Aconitum napellus
- Gelsemine and gelseminine from Gelsemium sempervirents
- Atropine, hyocyamine and scopolamine from A. belladonna

#	Raw Material / Starting Material	Dosage Form Groups	Equipment train group	Formulation Type
1	Plants (botanicals)	Solutions	Powder Mixer - granulator bowl with rotor & chopper (e.g. Diosna, Fielder, etc.)	Single active ingredient
2	Minerals	Suspensions	Powder Mixer - rotating drum or cube	Multiple active ingredients
3	Chemicals	Creams	Powder Mixer - ribbon blender	Modified release
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8		Capsules (two piece, via Granulation process, wet and dry	Liquid solution manufacturing & filling equipment Hahnemann dilution Korsakovian method	
9		Soft Capsules (Softgels) containing solution fills	Liquid suspension manufacturing & filling equipment	
10		Soft Capsules (Softgels) containing suspensions fills, powder mixes		

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Justification for the Grouping Approach

- Phytochemical class grouping provides an effective correlation to physiochemical properties such as partition coefficients, solubility, and pKa. Successful validation of representative class members would be justification for accepting validation of the class in the absence of any contradictory finding.
- In the absence of supporting data, narrowing the groupings to specific alcohol ranges would be required.
- The method and scale of manufacturing would require standardization for accepting validation of the class.

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Justification for the Testing Approach

- Elimination of testing for compounds below their threshold(s) of concern, in situations where the LOQ/LOD of conventional HPLC methods, employing sample preconcentration at a factor of up to 2 X 10^2 (200:1) would allow the use of conventional technology currently employed in the homeopathic industry and lessen the financial implications of such testing in situations where the additional testing provided no additional assurance of quality.
- Overall, the justification for the use of these simplification strategies is the lower risk generally associated with homeopathic medicines.

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Personal Observations

Unless otherwise specified in the HPUS, percentage variance is understood as an 'absolute' variance (a “55% alcohol” specification allows for an alcohol content ranging from 40%–70%).

The description of the manufacturing process is adequate but allows significant variability in parameters which could be correlated to critical quality attributes. Manufacturing process design needs to be coupled with process validation.

- Alcohol concentration
- Time
- Temperature
- pH

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Next Steps for a Validation of Dilution Process for Preparation of Hahnemannian Liquids Guideline

Feedback	Gather and incorporate feedback from industry and regulators through forums such as the AAHP.


QUESTIONS