# Best Practices for Unique Aspects of Finished Product Testing for Homeopathic Drug Products

Homœopathic Pharmacopœia Convention of the United States (HPCUS)

HPCUS Expert Panel on CGMP Gaps for Homeopathic Drug Products

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## Introduction

The Federal Food, Drug, and Cosmetic (FD&C Act or the Act) recognizes as "official" homeopathic drugs which are the subject of a monograph in the Homeopathic Pharmacopeia of the United States (*HPUS*). Like all drug products, homeopathic drug products (HDP) must be packaged in accordance with section 502(g) of the Act and must be manufactured in conformance with current good manufacturing practices (CGMP), as required by section 501(a)2(b) of the Act and Part 211 of the Code of Federal Regulations (CFR).

21 CFR § 211.165 addresses "Testing and release for distribution" and describes several requirements, including testing of each drug product batch for conformance to final specifications. Also included are requirements for sampling plans, specification, and test methods to be appropriate and documented.

Specifically, 21 CFR § 211.165(a) requires the following:

*"For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release….*

Some HDP's contain such low levels of chemical constituents that the quantitation and detection of these components are unattainable, creating a situation where the required testing for identity and strength is impossible to perform. For this reason, greater emphasis must be placed on the overall control strategy for the HDP.

This document assumes the reader is familiar with the quality management system concept and model as described in the ICH guidance Q10 Pharmaceutical Quality System.[1] A control strategy is a planned set of controls derived from current product and process understanding that assures process performance and product quality. Specifications and testing are part of an overall control strategy, making up part of a firm's Quality System. More details are discussed in the *Control Strategy* section of this paper.

When applied to homeopathic drugs, with their generally extremely low levels of active ingredients finished HDP testing poses challenges. The finished product testing requirement was part of FDA's 1978 revamping of the original CGMP regulation.[2] In response to comments filed by the American Association of Homeopathic Pharmacists (AAHP), FDA proposed to amend the regulation to exempt homeopathic drugs from the finished product testing requirement. At the same time, FDA also said that:

*"Pending the receipt of comments on this proposal, and the agency's final decision on this matter, this interim enforcement policy will remain in effect. If the agency determines not to*

[1] International Conference on Harmonization. ICH Q10 Pharmaceutical Quality Systems. 2008 (https://database.ich.org/sites/default/files/Q10%20Guideline.pdf)
[2] 43 FR 45014 et seq. (Sept. 29, 1978).

*adopt this proposal as a final rule, it will so announce in further rulemaking notices that are published in the Federal Register."*[3]

FDA took no further action on the petition. In 2003, FDA proposed to withdraw certain proposed rules that were published in the FEDERAL REGISTER more than five years before. FDA stated that these proposals were no longer considered viable candidates for final action. The finished product testing exemption for homeopathic drugs was among those FDA proposed to withdraw because of the passage of time. This "housekeeping" decision to abandon the proposal would mean that homeopathic drug manufacturers would be required to comply with the active ingredient finished product testing rule. The AAHP submitted comments in opposition to FDA's intention to withdraw the proposed rule, arguing that the passage of time had done nothing to change the correctness of the AAHP's and FDA's earlier position.

In the FEDERAL REGISTER of November 26, 2004, 69 FED. REG. 68831, FDA rejected the Association's comments and withdrew the proposed exemption. In rejecting the AAHP position, FDA said that:

*"There **may be instances** where testing of a homeopathic product for identity and strength of the active ingredients prior to release for distribution would be appropriate and consistent with protection of the public health."* (Emphasis added.)

Thus, notwithstanding the language of the CGMP regulation, FDA's latest word on the subject would appear to be that finished product active ingredient testing for homeopathic drugs is required only when the agency finds that it is "appropriate and consistent with protection of the public health."

The primary purpose of this White Paper is to help elucidate feasible approaches that ensure the quality and safety of homeopathic drug products whose active ingredient(s) and components are often present in concentrations that are magnitudes more dilute than current levels of detectability. Recommendations for control strategies and specification testing are provided as well.

## Notes on Definitional Distinctions

As more fully explained in the companion White Paper titled *Best Practices for Testing and Control of Homeopathic Starting Materials in Batch Manufacturing*, the term *starting material* has significantly different connotations in homeopathic and non-homeopathic drug manufacturing. To minimize potential confusion, in this paper the substance(s) of interest to which an HDP is labeled will be referred to as the *homeopathic starting material* (See Glossary); the term *starting material* will not be used in order to avoid confusing the reader who may not be familiar with homeopathic terminology. Hopefully, this concise compromise in terminology provides a clear and uniform understanding of the various substances of interest that are involved and their role in the attenuation process.

[3] 48 Fed. Reg. 14003, 14004 (Apr. 1, 1983).

## Scope

The scope of this White Paper is limited to those homeopathic drug products with the following parameters:

1. Only HDPs that may appropriately be available (or provided) over-the-counter;
2. Only HDPs that are available as oral and topical products only, and
3. Only HDPs that are prepared from chemical, mineral, and botanical substances.

## Relevance of Significant Attenuation

One of the unique aspects of many HDPs is the presence of only minute levels of detectable components. The FDA has previously acknowledged that factors such as potency, absorption, bioavailability, and other measures of effectiveness are not applicable to homeopathic drugs[4]. Therefore, to help ensure quality and safety, testing of finished HDPs is designed to ensure the following:

1) the absence of chemical impurities;
2) all components of the HDP are below safety related thresholds; and,
3) consideration for the relationship between safety concerns and detectability.

In evaluating safety related thresholds, please be aware that the determination of the Lowest Permissible Attenuation for OTC use listed in an *HPUS* monograph includes a 100-fold safety margin to better assure finished product safety especially in the rare circumstances when the safe dose is quantitatively proximate to the limit of detection. The reader is referred to a companion White Paper titled *Utilizing a Quality by Design Model for Hahnemannian Dilutions in the Manufacture of Homeopathic Drug Products* as it provides a detailed methodology for ensuring that the homeopathic starting material(s) are present in the HDP at their labeled attenuation(s).

[4] Federal-Register VOL. 43, NO. 190 - FRIDAY, SEPTEMBER 29, 1978, p. 45,058 (Comment 357)

## The Safety and Detectability Priority Matrix

The relationship between safety concerns and detectability is presented graphically in Figure 1 as a safety and detectability priority matrix. The figure divides the space into quadrants representing the extremes of safety concerns and detectability. Moving from Left to Right, one sees increased Detectability. Moving from Bottom to Top, one sees increased Safety Concern.

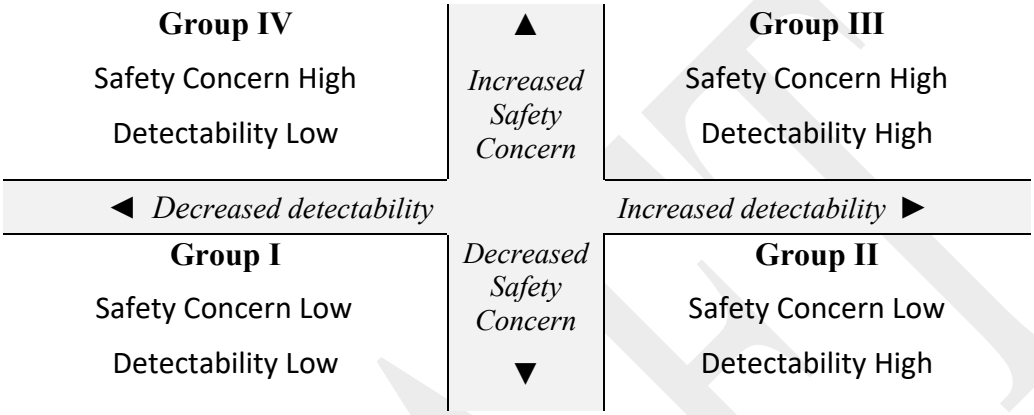


Figure 1:Safety and Detectability Priority Matrix.

The Safety and Detectability Priority Matrix helps visualize when testing is justified (risk/benefit). Safety (vertical axis) is a measure of the severity of any potential harm. A typical risk assessment would place likelihood of a potential risk occurring along the horizontal axis, but the probability of manufacturing errors or mix-ups, to a first approximation, is taken to be random, or equally weighted along the axis. Because of this, detectability is substituted for likelihood on the horizontal axis. For example, in Group I, the ability to detect any components related to the homeopathic starting material is negligible; simultaneously, the constituents of the homeopathic starting material present an imperceptible concern for toxicity.

### Detectability

Detectability is difficult to define rigorously because it is both a question of possible as well as practical. For example, with a 12C (or 24X) attenuation of a low molecular weight substance in pure form, such as natrum muriaticum (homeopathically prepared sodium chloride), a 1 g sample theoretically has only a 1 in 4000 chance of containing a single NaCl formula unit. Thus, it is not possible to detect components of HDPs at attenuations of 12C (or even further attenuated) by any means. For many homeopathic starting materials, the individual chemical constituents have molecular weights higher than that of natrum muriaticum; thus, their molar concentrations are more dilute. Many homeopathic starting materials are not pure materials (*e.g.*, HDPs derived from botanical sources), which also renders their constituents more dilute than the example of natrum muriaticum. While single-molecule detection represents the ultimate goal of ultrasensitive chemical analysis, at present it is neither possible nor practical to utilize for

homeopathic starting materials which have been taken through many attenuation steps. Well before such a theoretical limit is reached, several practical limitations are encountered, which, among other factors, include lack of available technology or skill/expertise, and/or prohibitive cost.

FDA has acknowledged that the ability of advanced scientific methodology to detect substances at ever-decreasing concentrations is not a guarantee of enhanced safety. The Delaney Clause of the 1958 Food Additives Amendment to the Act prohibited FDA from approving any food additive or animal drug which was found to induce cancer. While this appears on the surface to be a simple task, the true complexity of application became apparent when the agency needed to consider approval for a reportedly carcinogenic animal drug (diethylstilbesterol) which was claimed to leave no residue in meat.[5] As analytical technology improved, the ability to detect increasingly vanishing concentrations of the drug lead FDA to adopt a process whereby it was only necessary to test for a concentration which produced a lifetime cancer risk of less than 1-in-1-million.[6] This was the agency's operational definition of no residue. In short, it required testing only to the level that FDA considered safe.

An additional issue involving limits of detectability is any requirement to demonstrate that the finished HDPs contain the labeled quantity of the active ingredient. Here, homeopathy diverges from allopathic medicine in an important way. To oversimply, 10 mg of an allopathic active ingredient is presumed to be twice as potent as 5 mg. However, for homeopathic medicines, experts observe that the primary determinants of medication effect are the nature of the homeopathic starting material and the number of attenuations which the homeopathic starting material has undergone rather than the quantity of homeopathic starting material in the final (or finished) product. In short, from a homeopathic standpoint, what matters is that a 12X homeopathic starting material has been diluted and succussed 12 steps, not that a specific quantity of homeopathic starting material is present as a result of the attenuation process.

Thus, for homeopathic drugs, a 12X HDP containing 10 ppb of the homeopathic starting material is not necessarily therapeutically different than a 12X HDP containing 2 ppb. At allopathic dosages, of course, a five-fold difference could likely have significant differences in therapeutic effects and generate safety concerns; for homeopathic medications -- provided the amounts of homeopathic starting material are safe due to the de-concentration resulting from the repeated process of attenuation -- such a difference in the concentration of homeopathic starting material would be unlikely to affect treatment outcomes or be of quality concern to the medical provider.

For the purposes of testing HDPs, the HPCUS deems modern spectroscopic and chromatographic analysis practical, but considers more advanced techniques (*e.g.*, LC/MS, LC/MS/MS) beyond what is practical or necessary for routine quality control use, especially in relation to the concept of requiring testing only to the level that is considered safe. HPCUS believes this to be consistent with the expectation that manufacturers will use technologies and

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[5] Merrill, Richard A. "Food Safety Regulation: Reforming the Delaney Clause" in Annual Review of Public Health, 1997, 18:313-40.

[6] Food and Drug Administration. 1977. Criteria and procedures for evaluating assays for carcinogenic residues in edible products of animals. Fed. Regist. 42:10412–37.

systems that are sufficiently sensitive to comply with the CGMP regulations without requiring testing that provides no additional useful data. Further, HPCUS accepts as reasonable that no regulatory body would apply more stringent criteria for the limit of detection and limit of quantification to homeopathic products than those corresponding to approved allopathic drug products. Throughout this White Paper, the terms *testing when feasible* and *feasibility* will be used to communicate that testing is appropriate when it is both theoretically possible to obtain a valid result and falls within the working ranges of modern spectroscopic and chromatographic analysis when performed by a person skilled in the art.

## Safety

With regard to safety, the *HPUS* stipulates minimum margins of safety for each official HDP as described in the respective monograph and in the *Table of Lowest Permissible Attenuations and Class of Manufacture.*[7] These OTC attenuation levels include a 100-fold margin of safety.[8]

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[7] Accessible at https://www.hpus.com/table-of-attenuations/ *(Accessible by subscription).*

[8] Safety concerns focus on three aspects, all of these are addressed by the lowest permissible attenuation which includes a 100-fold margin of safety, in conjunction with labeling statements.

The 100-fold margin of safety means: a 10 kg child would have to consume, at one time, one hundred 30 ml (1 oz) bottles containing the Lowest Permissible Attenuation (a.k.a. "dilution") stated in the respective monograph in order to be exposed to the minimum quantity which might exhibit an adverse event.

1) Accidental ingestion of a large, unexpected bolus amount (for instance, a young child ingesting an entire OTC retail package, such as the entire contents of a 30 ml bottle): a usual dose (for instance: a homeopathic liquid) is usually in the range of 10-15 drops, which equals $^{1}/_{3}$ to ½ of an ml, or $^{1}/_{60}$ to $^{1}/_{100}$ of a single 30 ml bottle. The 100-fold safety margin utilized in the calculation of the lowest permissible attenuation, as noted above means the usual dose is actually $^{1}/_{6,000}$ to $^{1}/_{10,000}$ of the amount which might cause an adverse exposure. Thus, the accidental ingestion of a single unexpected bolus amount is $^{1}/_{100}$ of the amount which might cause an adverse exposure. (Larger retail packages may change the calculations but not by any order of magnitude.)

2) Daily exposure for acute use (as mass exposure x number of doses per day): the Lowest Permissible attenuation primarily applies to OTC products, which are labeled with a limit on the number of times to be used during the day without conferring with a health care practitioner. At four times per day (a common "high" number of daily doses for homeopathic products) the total daily dose is still $^{1}/_{1,500}$ to $^{1}/_{2,500}$ of the amount which might cause an adverse exposure. In conjunction with labeling statements, the lowest permissible attenuation provides a significant safety assurance.

3) Chronic or maximum exposure (as daily exposure x number of days of therapy): the Lowest Permissible Attenuation primarily applies to OTC products, which are labeled with a limit on the number of days to be used before stopping and without conferring with a health care practitioner. Calculating on the basis of four doses per day with a maximum 15-day limit, the chronic exposure for an OTC product would be $^{1}/_{100}$ to $^{1}/_{166}$ of the amount which might cause an adverse exposure. A separate Lowest Permissible Attenuation is given for Rx-Only homeopathic products; while a narrower margin of safety is utilized for these, it is based on the common understanding that prescription products (irrespective of being homeopathic or non-homeopathic) are utilized under the care, supervision and monitoring of a health care provider, and their use has benefits that outweigh potential risks.

More information is accessible at

https://www.hpus.com/document/explanation-of-the-attenuation-levels-recognized-by-the-hpcus/ *(Accessible by subscription).*

HDPs for which the minimum safety has been determined to permit OTC (over-the-counter) marketing of permitted attenuations are deemed "without any safety concern."

To illustrate the concepts above, consider the widely used HDP *Coffea cruda*. The *HPUS* designates the Tincture of *Coffea cruda* (prepared from the dried, unroasted seeds [Class C]) for OTC distribution, indicating that the tincture meets the minimum margin of safety, such that it may be labeled for OTC use. In the case of the tincture, the *HPUS* provides suitable identity test; detectability is unquestioned. *Coffee cruda Tincture* would therefore fall in *Group II* of the Safety and Detectability Priority Matrix with little to no safety concern and no difficulty in detection.

Extending this example to Coffee cruda 12C (or 24X) attenuation, any concerns for safety are further removed from that of the *homeopathic starting material* by virtue of the significant de-concentration resulting from repeated attenuation steps. This attenuation, however, places the constituents of the *homeopathic starting material* far below practical limits of detection. In this case, Coffee cruda 12C falls into *Group I* of the Safety and Detectability Priority Matrix with little or no safety concern, but with insurmountable challenges for detection.

Some HDPs may have a potential safety concern that results from possible manufacturing errors/mix-ups because the first attenuation (typically 1X) contains a component that does not meet the minimum margin of safety for OTC marketing. One example is Nux Vomica which contains the indole alkaloids strychnine and brucine. Nux Vomica does not meet or exceed the minimum margin of safety until the third decimal attenuation (3X) step. Thus, the *homeopathic starting material* as well as the 1X and 2X attenuations would present a safety concern if there was a manufacturing error or mix-up.

With regards to detectability, some potentially toxic constituents may be readily detectable in the 3X attenuation. Because Nux Vomica seeds usually contain about 1.8–5.3% strychnine and brucine[9]; the 3X attenuation is therefore expected to contain detectable levels (> 10 ppm). The need for testing is based on the known toxicity of individual constituents of the *homeopathic starting material* at attenuations between 1X and the lowest permissible OTC attenuation. This testing is both possible and practical. Nux Vomica 3X would therefore fall into *Group III* of the Safety and Detectability Priority Matrix due to significant safety concerns coupled with no difficulty for detectability.

However, consider the Nux Vomica example further: a 10C attenuation. For a continuous manufacturing campaign beginning with the *homeopathic starting material*, the safety concern is unchanged due to the potential toxicity of strychnine and brucine in the 1X, and 2X attenuations. However, in the production of a 10C attenuation, these compounds are expected to be present at approximately $10^{-21}$ g strychnine and $10^{-21}$ g brucine per g of solution, which are far below 1-part per trillion ($10^{-12}$ ) in the HDP, and far below any practically achievable limit of detection. In this case, Nux Vomica 10C falls into *Group IV* of the Safety and Detectability Priority Matrix

[9] William Charles Evans, Daphne Evans, Chapter 26 - Alkaloids, Editor(s): William Charles Evans, Daphne Evans, Trease and Evans' Pharmacognosy (Sixteenth Edition), W.B. Saunders, 2009, Pages 353-415.

where safety cannot be assured on the basis of the *homeopathic starting material's* safety, but an assay cannot practically be performed.

In such a case we must ensure known potentially toxic components of the HDP are below any safety related thresholds. In this example, it is essential to demonstrate that strychnine and/or brucine are below any level of concern; this can be accomplished by limit tests which assures the safety of the HDP with regards to its *homeopathic starting material*. Further assurance is provided through a homeopathic Quality By Design (HQbD) approach which is the subject of the companion White Paper, *Utilizing a Quality by Design Model for Hahnemannian Dilutions in the Manufacture of Homeopathic Drug Products.*

## Control Strategy

ICH Q10 defines a control strategy as a planned set of controls, derived from current product and process understanding, that assures process performance and product quality. While it is not possible to give a fixed list of elements included in a control strategy, one might expect to find most, if not all, of the following:

1) Identify critical input material attributes; control these through purchase agreements, specifications, and test methods.
2) Identify critical process parameters; control these using master batch records and standard operating procedures.
3) Identify critical drug product quality attributes; control these through management of the process along with verification by testing to specifications.
4) Demonstrate control is achieved through process validation.

A comprehensive risk management approach involves three interconnected pillars:

1) control strategy to reduce risk probabilities,
2) detectability to identify risks early, and
3) consideration of the consequences of risk events.

A well-designed control strategy is of primary importance as it lowers the probability of risk-related events occurring in the first place.

### Specifications

ICH Q6A defines a *specification* as a list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described. Finished HDPs must have established (*i.e.*., pre-approved) specifications for the product's physical, microbiological, and chemical characteristics. One critical goal of a product's specification is to assure safety by ensuring consistent control of product quality. In some instances, the finished drug product specification testing described in ICH Q6A may be appropriate for homeopathic drug products, although the unique nature of HDPs may necessitate different approaches than those used for non-homeopathic drugs.

Mirroring the organization of ICH Q6A, *HPUS* provides guidance for those tests that apply universally to HDPs as well as those that apply to specific dosage forms/routes of administration. Certain tests conducted during the manufacturing process, where the acceptance criterion is identical to or tighter than the release requirement, (*e.g.*, pH of a solution) may be sufficient to satisfy specification requirements when the test is included in the specification. However, this approach should be validated to show that test results or product performance characteristics do not change from the in-process stage to the finished HDP.

## Specification testing universally applicable to finished homeopathic drug products

**Description:**

A qualitative description of the HDP should be provided. The acceptance criteria should include the final acceptable appearance of the finished dosage form and packaging. For example: "A clear liquid, devoid of visible particulates in a sealed amber glass bottle."

**Identification:**

A specific identity test should be included when technically feasible and reasonably achievable. For some homeopathic starting materials, identity testing is performed for a target analyte that is uniquely characteristic of the natural substance. The selection of an appropriate chemical marker for the active ingredient is discussed in *Assay* (below). Separate from the selection of an appropriate chemical marker for the active ingredient, identity testing for active ingredients that have already been attenuated may not be achievable due to the high level of de-concentration through multiple attenuation steps. If it is impractical to extend the limits of measurement for identity testing through sample concentration and/or application of conventional analytical technology (*e.g.*, HPLC), product identity may be demonstrated through the totality of CGMP compliant documentation of the *homeopathic starting material* identity, batch manufacturing records, in-process test results and/or process validation. Owing to the unique nature of many HDPs, testing to demonstrate that homeopathic starting materials are not present above levels of safety concern may be the only feasible approach in these cases.

When specific identity testing is not technically feasible nor reasonably achievable, a homeopathic Quality by Design (HQbD) approach should be used to assure the manufacturing process delivers the intended attenuation step. That HQbD approach is discussed at length in the companion White Paper titled *Utilizing a Quality by Design Model for Hahnemannian Dilutions in the Manufacture of Homeopathic Drug Products.*

**Assay:**

A specific assay to determine concentration (content of target analyte) should be included when there are concerns regarding safety and an assay is technically feasible and reasonably achievable. For many HDPs, such testing may not be feasible due to the high level of de-concentration that has occurred through multiple attenuation steps. If it is impractical to extend the limits of quantitation for assay testing through sample concentration and/or application of conventional analytical technology (*e.g.*, HPLC), the absence of assay testing may be justified by the following:

1) the condition that the compendial *homeopathic starting material* in its attenuated form (*i.e.*, compendial article) does not present any safety concerns (Group I or Group II in Figure 1) at its first attenuation,

***or***

2) a limit test is performed demonstrating the lot under test does not exceed established safety thresholds for the given compendial article. In cases where the compendial article is a complex mixture, assay testing requires the use of one or more target analytes that is/are representative of the compendial article. Selection of a target analyte for assay testing is the responsibility of the product owner and justification for its selection should be documented.

*Such a justification should include:*

- a discussion of the target analyte(s)'s uniqueness to the compendial article (to help ensure the absence of mix-ups),
- the detectability of the target analyte (document why the absence of detection appropriately assures that the HDP is highly dilute),
- the stability of the target analyte (which would be further demonstrated during validation), and
- the quantitative relationship between the target analyte and any compounds presenting a safety concern, as well as any other specific safety concerns.

HDPs containing compounds of known potential toxicity[10] should be assayed, or subjected to a limit test, for one or more representative compounds to demonstrate the content does not exceed established safety thresholds. When multiple compounds of concern are associated with a given compendial article, only one compound needs to be tested, provided its control also assures the control of the untested compounds. Test methods must be validated to assure detection at concentrations relevant to the applicable safety thresholds.

**Impurities:**

The HDP specification should establish limits on those types of contamination that may adulterate or that may lead to adulteration of the HDP. The *Expanded Homeopathic Good Manufacturing Practices guideline*[11] of the *HPUS* should be consulted for appropriate testing of homeopathic starting materials. Sections 5 and 6 of these guidelines address these controls for homeopathic starting materials of chemical (including mineral) and botanical origins. (Other sections of these guidelines address homeopathic starting materials with different origins but which are not within the scope of this White Paper as explained above.) These controls assure adventitious contamination is constrained to negligible limits. Comprehensive control of

[10] *e.g.*, Nux Vomica (, strychnine, brucine, aethusin, narcissine), belladonna (*i.e.,* hyoscine, hyoscyamine, atropine, and scopolamine), aconitum napellus (*i.e.,* aconitine, mesaconitine, hypaconitine and jesaconitine), gelsemium sempervirents (*i.e.*, strychnine-related alkaloids gelsemine and gelseminine) , mercury salts, lead salts)

[11] Accessible at: https://www.hpus.com/submitting-monograph/homeopathic-good-manufacturing-practices/introduction/ *(Accessible by subscription).*

homeopathic starting materials typically obviates the need for testing of the final HDP for organic impurities, solvent impurities, and elemental impurities, provided similar controls are in place for all other components of the HDP (*e.g.*, excipients, primary packaging).

*Organic Impurities:* Generally organic impurities as thought of in synthetic chemistry (related substances) should not be present in HDPs because the majority are derived from natural products. The various substances (related substances) contained in each natural product are constituents of the drug HDP, not impurities of the HDP. For homeopathic starting materials that are not obtained directly from natural sources such as ascorbic acid USP (used to make homeopathic *Ascorbicum Acidum*), impurity specifications for the HDP would not be more restrictive than those applied to the homeopathic starting material itself.

*Solvent impurities:* Solvent impurities may be controlled through appropriate testing and risk analysis for homeopathic starting materials and nonactive components following the recommendations of ICH Guideline Q3C. Testing should be performed for residual solvents when production or purification processes are known to result in the presence of such solvents. It is only necessary to test for solvents that are used or produced in the manufacture or purification of the drug substances, excipients, or HDP. Although manufacturers may choose to test the HDP, a cumulative method may be used to calculate the residual solvent levels in the HDP from the levels in the ingredients used to produce the HDP following a risk management approach. The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.[12] If the calculation results in a level equal to or below that recommended in ICH Guideline Q3C, no testing of the HDP for residual solvents need be considered. If, however, the calculated level is above the ICH Guideline Q3C recommended level, the HDP should be tested to ascertain whether the formulation process has reduced the relevant solvent level to within the acceptable amount. HDPs should also be tested if a solvent is used during manufacture other than those solvents deliberately used as excipients.

*Elemental impurities:* Elemental impurities may be controlled through application of ICH Guideline Q3D. In developing controls for elemental impurities in drug products, the principles of quality risk management, described in ICH Q9, should be considered.

*Nitrosamine impurities:* FDA recommends steps manufacturers of APIs and drug products should take to detect and prevent unacceptable levels of nitrosamine impurities in pharmaceutical drug products. Nitrosamine impurities may be controlled through application of USP <1469>.

**Microbial limits:**

[12] ICH Harmonized Tripartite Guideline. Quality Risk Management Q9, Step 4, November 2005, Available from: https://database.ich.org/sites/default/files/Q9%20Guideline.pdf

For non-sterile HDPs, there may be a need to specify the total count of aerobic microorganisms, the total count of yeasts and molds, and the absence of specific objectionable organisms. Recommendations for acceptance criteria are provided within the *HPUS* (within the *Expanded Homeopathic Good Manufacturing Practices guideline*, Sect 6.7.9).

The absence of microbial limits testing may be justifiable when it can be demonstrated that the HDP does not support microbial viability or growth.

Sterile HDPs must be free of microorganisms and endotoxins.

## Specification testing applicable to specific finished homeopathic dosage forms/routes of administration

Table 1 provides specification testing recommendations for CGMP according to specific dosage forms and routes of administration. The table does not provide information on dosage forms or routes of administration that are beyond the scope of this White Paper.

*Table 1: Specification testing for specific finished homeopathic dosage forms.*

| *Test* | Dosage Form/Routes of Administration | | |
|---|---|---|---|
| | *Oral Solid Dose* | *Oral Liquids* | *Semi-solid Topicals* |
| *Dissolution/disintegration* | *Y* | *N/A* | *N/A*[1] |
| *Hardness/friability* | *Y* | *N/A* | *N/A* |
| *Uniformity of dosage units* | *Y* | *Y* | *Y* |
| *Water content* | *Y* | *N/A* | *Y* |
| *Microbial limits* | *Y*[2] | *Y* | *Y* |
| *pH* | *N/A* | *Y* | *Y* |
| *Apparent viscosity* | *N/A* | *N/A* | *Y* |
| *Antimicrobial preservative content (Antimicrobial effectiveness testing)* | *N/A* | *Only in the absence of sufficient alcohol content* | *Y* |
| *Extractables* | *N* | *Y* | *Y* |
| *Alcohol content* | *N/A* | *Y*[3] | *N/A* |

[1] In vitro release testing may be a useful test to assess product "sameness" under certain changes in process or scale for semisolid products. There is no requirement for a validated in vitro release test.

[2] There may be a need to specify the total count of aerobic microorganisms, the total count of yeasts and molds, and the absence of specific objectionable bacteria. These should conform to *HPUS* requirements. Justification for not including testing of microbiological attributes may be developed following the decision tree (#6) of ICH Q6A.

[3]Alcohol content in oral liquids must comply with the labeled declaration; this varies from substance to substance and is impacted by attenuation level as well as formulation criteria.

## Recommendations

Based on the foregoing discussion and analysis, the HPCUS recommends the following best practices to ensure product quality and safety of Homeopathic Drug Products (HDPs)

1. Effective regulation of HDPs must include the recognition that HDPs often contain homeopathic starting material(s) and components of concern in concentrations that are magnitudes more dilute than current levels of detectability due to the dilutional aspect of homeopathic manufacture.
2. Medical professionals with a high degree of experience evaluating HDP therapeutic effects conclude that homeopathic drug product quality and effectiveness is primarily dependent upon factors such as identity, purity, and attenuation, rather than measurable quantity of homeopathic starting material in the finished product. Optimal manufacture and regulation of HDPs for quality must recognize the relevance of this distinction.
3. Adoption of the Safety and Detectability Priority Matrix discussed in this document or an equivalent tool will permit both manufacturers and regulators to evaluate safety assurance programs for different HDPs.
4. Manufactures and regulators should ensure that comprehensive risk management systems include a robust control strategy as the critical element due to issues with detectability for many HDPs.
5. HDPs attenuated below levels of detectability for homeopathic starting material(s) should remain exempt from finished product testing. However, when the homeopathic starting material is unusually toxic, poorly detectable, or has unusual physicochemical properties which challenge the assumptions of the attenuation process, or the dosage form and route of administration pose a higher toxicological safety risk from the homeopathic starting material(s) present, limit testing to demonstrate that constituents of toxicological interest are below levels of safety concern is the only feasible and appropriate approach to ensure safety.

## Glossary

**Active Ingredient(s)** – the ingredient(s) in a drug product that is intended to be pharmacologically active per 21CFR210.3.

**Active Ingredient, Homeopathic** – The active ingredient of a homeopathic drug product is the homeopathic attenuation in its entirety.

**Active Pharmaceutical Ingredient (API)** – a substance intended to produce physiological activity and incorporated into a finished drug product per 21CFR 207.1.

**Alcohol** – as defined in the *HPUS* 92.3% by weight or 94.9% by volume of ethyl alcohol ($C_2H_5OH$, m.w. 46.07) and 7.7% by weight or 5.1% by volume of water.

**Allopathy** - the treatment of disease using drugs having opposite effects to the symptoms. (*i.e.*, steroids for inflammation or anodynes for pain relief). Most conventional drugs are developed for this approach to treatment.

**Attenuation** – (noun) *i.e.*, homeopathic attenuation: the result of the two-phase homeopathic process (serial de-concentration and vigorous mixing); can be a liquid state or a solid (powder) and is, in general, the homeopathic active ingredient in its entirety (see also Active Ingredient). Historically has been referred to as potency/potencies, dilution. Due to the potential for confusion, the official designations are *attenuation* for liquids and *trituration* for solids.

**Attenuation** – (verb) *i.e.*, a homeopathic process; is the procedure utilized to make a homeopathic medicine; consists of two phases: a serial de-concentration phase in which material is de-concentrated with sufficient neutral vehicle to result in a ratio of

- 1 part material in 10 parts of total (decimal, noted by an "X" suffix) or
- 1 part material in 100 parts total (centesimal, noted by a "C" suffix).
- Ether "X" or "C" attenuations can then be repeated in a serial fashion as necessary (Analogous to the pharmaceutical process of making an aliquot series.).

The second phase is a vigorous mixing (succussion or trituration/grinding) of the entire mass at each step. This can be accomplished in the liquid or solid (powder) state. To minimize potential confusion, in the *HPUS*, the process is referred to as the "attenuation process" for liquids and "trituration process" for solids.

However, per *HPUS*, serial attenuations are prepared exclusively in either the 1:10 or the 1:100 ratio; the two proportions are not used interchangeably in the same homeopathic manufacturing series. Historically referred to as dynamization, dilution or potentization.

**Batch** – (as per 21 CFR 210.3 Definitions) batch means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.

**CFR** - Code of Federal Regulation.

**CGMP –** Current Good Manufacturing Practice.

**Complex substance** – naturally-sourced ingredients.

**Component** – a constituent part. Any matter that is intentionally introduced during drug product manufacturing, even if subsequently removed (gasses/solvents), and any material used in primary packaging. All substances used in the manufacture of a homeopathic drug are components, whether or not those substances appear in the finished product. Although ingredients are components under our definition, not all components are ingredients. Ingredient is taken to mean the natural product, the tincture, or a specified attenuation of the natural product rather than the various chemical substances contained in the natural product.

**De-concentration** – (*verb*) to decrease in concentration. In the *HPUS*, the process is referred to as the *attenuation process* for liquids and *trituration process* for solids.

**Dilution** – see attenuation (noun) (liquids) or trituration (solids).

**Drug product, homeopathic** - the homeopathic starting material in its final container/closure system. Such drug products are typically named in reference to the starting material and the final attenuation.

**Dynamization** – see attenuation (verb) (liquids) or trituration (solids).

**Excipient(s)** - an inactive substance that serves as the vehicle or medium for a drug or other active substance.

**FD&C Act (or the Act)** - The Federal Food, Drug, and Cosmetic Act, United States law.

**Finished homeopathic medicine** – see finished product.

**Finished Product** – a drug product that has undergone all stages of production, including packaging in its final container.

**Hahnemannian Attenuation** – multiple flask method of attenuation for homeopathic drug manufacture.

**HDP** - homeopathic drug product.

**Homeopathic attenuation** – see attenuation.

**Homeopathic medicine** – A drug product containing substances from the animal, vegetable, or mineral kingdoms (including specific chemicals), that are manufactured according to the complementary medical practice of Homeopathy.

**Homeopathic starting material** – The material used to manufacture the first homeopathic preparation (usually a tincture or a 1X (or first) attenuation using a 1:10 dilution, unless otherwise specified in a respective monograph). Examples include solution of a chemical / mineral with sufficient solubility; a tincture of a botanical, or a 1X trituration of an insoluble substance. (For more details, see the *HPUS Guidelines for Manufacturing Homeopathic*

*Medicines*, Sections 4 and 5 for Chemicals and Minerals, Sections 10 and 12 for Botanicals, and Section 33 and 34 for Insoluble substances).[13]

**HPCUS** - Homeopathic Pharmacopoeia Convention of the United States.

**HPUS** - *Homeopathic Pharmacopeia of the United States.*

**HQbD –** Homeopathic Quality by Design. A model for quality assurance based on the scientific principles of Quality by Design methodology.

**Impurity** – a component other than the chemical substances contained in the natural product, the tincture, or a specified attenuation of the natural product, and in addition, for a drug product, any component that is not an intentional formulation ingredient. In the case of homeopathy, impurities may include degradants and contaminants from the manufacturing process, handling, and packaging.

**Ingredient(s)** – A constituent part of the finished drug product. Note that a component that is removed during processing (*e.g.*, solvents/gasses) is not an ingredient.

**In-process material(s)** – 21 CFR 210.3(b)(9) Any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product.

**Limit of Detection** - the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value.

**Limit of Quantification** - the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy.

**Limit Test** – A quantitative or semi-quantitative test used to control small quantities below a stated level (the limit).

**Lot** – (as per 21 CFR 210.3 Definitions) lot means a batch (see above), or a specific identified portion of a batch.

**Lowest Permissible OTC Attenuation** – see *HPUS Table of Lowest Permissible Attenuations and Class of Manufacture*. *HPUS* stipulated minimum margins of safety for each official HDP as described in the respective monograph.[14]

**Mother tincture** – a term found in foreign compendia (*e.g.*, French, German), but not an official term in US homeopathy; see Tincture.

**OTC (over-the-counter) –** nonprescription.

**Primary packaging** – packaging which directly encases the drug product (product contact), to contain, preserve, and protect the drug product.

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[13] Accessible at https://www.hpus.com/submitting-monograph/guideline-for-manufacturing-homeopathic-medicines-2/introduction/guideline-for-manufacturing-homeopathic-medicines/ *(Accessible by subscription).*

[14] Accessible at https://www.hpus.com/table-of-attenuations/ (*Accessible by subscription*).

**Quality by Design (QbD) -** a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and control based on sound science and quality risk management**.**

**Quality Management System (Quality System)** – a formalized system that documents processes, procedures, and responsibilities for achieving quality policies and objectives.

**Raw material** – the term *raw material* has different connotations in homeopathic and non-homeopathic drug manufacturing:

Raw material, non-homeopathic - A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs. (ICH Q7)

Raw material, homeopathic **-** a substance used to make a starting material, but not, itself, used directly to make homeopathic drug products, (typically an item taken from the animal, vegetable or mineral kingdom).

**Residual solvents** - are organic volatile chemicals that are used or produced in the manufacture of drug product components or in the preparation of drug products. This excludes any solvent intentionally used as a vehicle or excipient (*e.g.*, alcohol).

**Specification** - a list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described (ICH Q6A).

**Specific identity tests** - the test provides complete discrimination from closely related structures which are likely to be present. The likelihood of being present should include consideration of possible mix-ups occurring at the supplier or distributor sites, as well as the possibility of economic adulteration. In the absence of a specific identity test, orthogonal testing should be performed such that the combination of test results assures the complete discrimination from closely related structures which are likely to be present.

**Starting Material** – the term starting material has different connotations in homeopathic and non-homeopathic drug manufacturing:

- *Starting material, non-homeopathic* - A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. API starting materials normally have defined chemical properties and structure. (ICH Q7)
- *Starting material, homeopathic* – defined in each monograph of the *HPUS* for making the initial homeopathic preparation.

**Succuss** – (verb – succussion, noun); performing a vigorous mixing process. One component of the manufacturing process for homeopathic drugs.

**Tincture** – the alcohol extract of the natural product (*i.e.*, an extract of the starting material taken from the animal, or vegetable kingdom). Tincture implies the product is made according to Class C, D, E, M, N, O, or P depending on the information in the individual monograph; and further

that the tincture has the concentration (or ratio of starting material to finished tincture) as shown in the *HPUS* (*Guidelines for Manufacturing Homeopathic Medicines: Section 1*).[15]

**Too Dilute to Test** – a material may be referred to as "too dilute to test" when the identify and/or quantity (as applicable) of the labeled substance(s) fall below a demonstrated detection or quantification (as applicable) limit that is achievable by an individual skilled in the art, using conventional methods (*e.g.*, HPLC, GC, etc.).

**Trituration** – the production of a homogeneous material by mixing solid component materials thoroughly, which may include particle size reduction.



[15] Accessible at https://www.hpus.com/submitting-monograph/guideline-for-manufacturing-homeopathic-medicines-2/introduction/guideline-for-manufacturing-homeopathic-medicines/ *(Accessible by subscription)*.