Utilizing a Quality by Design Model for Hahnemannian Dilutions in the Manufacture of Homeopathic Drug Products

Homœopathic Pharmacopœia Convention of the United States (HPCUS)

HPCUS Expert Panel on CGMP Gaps for Homeopathic Drug Products

16 January 2024

Posted for Public Comment.
Public Comment Period Ends April 22, 2024

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Introduction

This White Paper is one in a series published by the Homoeopathic Pharmacopoeia Convention of the United States (HPCUS) to address conceptual difficulties and concerns for infeasibility of implementation of certain sections of 21 C.F.R. Part 211 when considering the homeopathic manufacturing process. Its purpose is to propose science-based methods to achieve compliance with otherwise inapplicable or inappropriate CGMP requirements consistent with the spirit of the regulation and the limits of available science as they apply to certain unique aspects of homeopathic drug manufacture. The suggested methodology considers the limits of available science as they apply to these unique aspects of homeopathic drug manufacture and provides recommendations that will meet the needs of both regulators and manufacturers.

The Food and Drug Administration's regulation establishing Current Good Manufacturing Practice for Finished Pharmaceuticals, 21 C.F.R. § 211.1 *et seq*., provides, that, "*For each batch or 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.*" 21 C.F.R. § 211.165(a).

For those products where measurable levels of the homeopathic starting material (see glossary for homeopathy specific definition) exist in the finished homeopathic drug product (HDP), the requirement can be achieved. However, the homeopathic model primarily relies on ultra-low levels of starting materials in the finished HDPs. Indeed, the levels of starting materials present in most HDPs are below what might be considered a therapeutic dose for an allopathic drug and well below thresholds of concern for safety. As such, HDPs (and their associated homeopathic product intermediates) often contain levels of homeopathic starting materials that are orders of magnitude below the limits of detection (LOD) of conventional analytical chemistry. To insist that HDPs with such extremely low levels of starting materials require the same type of testing as allopathic drugs is to undermine, perhaps fatally, their ability to comply with CGMP and the recognition that the U.S. Congress has repeatedly accorded to homeopathic drugs.

Furthermore, in the preamble to the 1979 CGMP regulation, FDA itself formally acknowledged the uniqueness of homeopathic drug products by proposing to exempt them from finished product testing.[1] Even when FDA revoked that proposal twenty years later, as part of an agency effort to clean up unfinished rulemaking proposals, the agency said, in response to comment opposing the revocation, that routine finished product testing for homeopathic drug products did not appear to be necessary: "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. For example, in instances where a product includes an active ingredient that at certain levels could be toxic or otherwise pose a public health concern, ***finished product testing may be appropriate*** because the testing could identify a potentially significant manufacturing or labeling error. Since requiring this testing

[1] Human and Veterinary Drugs, "Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding," *43 FR 45077*, Preamble, Section XIII: Packing and Label Control, Paragraph 357.

when necessary to protect the public health is consistent with FDA's mandate, we are withdrawing the proposed rule." 69 Fed. Reg. 68831, 68834 (Nov. 26, 2004)(emphasis added).

Unfortunately, FDA has never provided any guidance as to those situations in which "finished product testing **may be** appropriate." (Emphasis added). Rather than continue with this uncertainty regarding testing, this paper proposes a relevant science-based method using the principles of Quality by Design approach (hereinafter referred to as Homeopathic Quality by Design or HQbD) that obviates the need for finished product testing in situations where such testing is impossible or impracticable.

Notes on Definitional Distinctions

In contrast to allopathic drugs where the active ingredient is understood to be the easily measurable chemical or biological substance (*i.e.*., the active pharmaceutical ingredient (API)), the homeopathic active ingredient is the attenuation that comprises the *final* HDP, less (a) any inactive ingedients ncecessary to complete the dosage (*e.g.*, tableting components, ointment base(s), etc.) and (b) the container closure system. Here, the attenuation is understood to mean the HDP that results from the succussion and dilution of the starting material in accordance with homeopathic CGMP. For allopathic drugs, API and the drug product are defined as different entities with specific regulatory meanings and corresponding CGMP. In contrast, only the homeopathic attenuation (prior to the addition of any inactive ingredients) is considered the active ingredient for homeopathic drugs. Further, the homeopathic substance used to make the HDP may best be referred to as the *homeopathic starting material* in HDP manufacture.

A second significant difference in terminology applies to the divergence of allopathic and homeopathic drug manufacture. For allopathic medicines, the starting material is what is used to synthesize a chemical API and thereby, any starting material appearing in the API (and drug product) is considered an impurity. In contrast, raw materials may be used in homeopathic drug manufacture; if so, they are processed to become a homeopathic starting material. The homeopathic starting material is utilized to make the first attenuation (liquid or powder) or tincture, which is then carried through the attenuation process to prepare the desired HDP[2]. To reiterate, neither the raw material nor the starting material are considered the active ingredient, but rather the active ingredient is the HDP that results from the attenuation of the homeopathic starting material[3]. As opposed to allopathic drug products, when preparing the first and

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[2] An example is given in the companion White Paper *Best Practices for Testing and Control of Homeopathic Starting Materials in Batch Manufacturing*: *e.g.,* iron(II)-sulfate heptahydrate and disodium phosphate dodecahydrate are *raw materials* used to prepare a precipitate (*i.e.,* a mixture of ferrous phosphate octahydrate, ferric phosphate hydrate, and some hydrated iron oxides) which is the *homeopathic starting material* for making the homeopathic attenuations (by the process of de-concentration and trituration/succussion) of *Ferrum phosphoricum*.

[3]As noted in the companion White Paper titled *Best Practices for Testing and Control of Homeopathic Starting Materials in Batch Manufacturing* in the section describing an Intermediate as: "… a homeopathic intermediate is any attenuation manufactured from the homeopathic starting material that is not intended to be packaged as a homeopathic drug product per the manufacturing batch record and is not commercialized.…""

subsequent homeopathic attenuations there is only a de-concentration and trituration/succussion process (but no chemical transformation/synthesis). Thus, the presence of the starting material in the HDP would not be considered an impurity.

These definitional differences should not stand in the way of relevant chemical exercises designed to validate various aspects of HDP manufacturing and their impact on quality. Therefore, to minimize confusion, in this paper the substance(s) of interest to which an HDP is labeled will be referred to as the *homeopathic starting material.* The generally accepted term *starting material* (without the homeopathic modifier) will not be used simply to avoid conflating separate meanings which are appliable in different circumstances, and which may not be immediately clear to a reader unfamiliar with homeopathic terminology. This convention in terminology is concise and allows for a clear and uniform understanding of the various substances of interest that are involved and their effective role in the attenuation process.

The working definitions for drug products between allopathic medicines and HDPs remain compatible. For example, with "Arnica Montana 30C"; Arnica Montana is the *homeopathic starting material* and Arnica Montana 30C (in its container closure) corresponds to the *drug product*.

For further clarification, the *homeopathic starting material* is that form of material or substance that first enters the homeopathic manufacturing process in the preparation of the first attenuation (liquid or powder) step or a tincture. A *homeopathic raw material* might be necessary to create the *homeopathic starting material* (see example in footnotes). Except in very unusual circumstances, botanical materials are *homeopathic starting materials* directly used to manufacture as a homeopathic tincture (*e.g.*, *HPUS* Class C)[4]; similarly, many chemical substances are also homeopathic starting materials directly used to manufacture homeopathic solutions (*e.g.*, *HPUS* Class A)[5], or triturations (*e.g.*, *HPUS* Class F).[6] Homeopathic *raw materials* and *homeopathic starting material* controls are the subject of a companion White Paper titled *Best Practices for Testing and Control of Homeopathic Starting Materials in Batch Manufacturing.*

Scope of the Guidance

The technical approaches presented herein do not propose any HDP manufacturing process change(s). The technical approaches provide a data-based framework in support of a reasonable verification of the dilution process as takes place in Hahnemannian attenuations. This verification has utility in providing relevant data to show that the dilution process during

[4] See https://www.HPUS.com/submitting-monograph/guideline-for-manufacturing-homeopathic-medicines-2/botanicals/class-c-and-class-d-botanical-tinctures-general-information/ (*Accessible by subscription*).

[5] See https://www.HPUS.com/submitting-monograph/guideline-for-manufacturing-homeopathic-medicines-2/chemicals/class-a-and-class-b-preparations-of-solutions/ (*Accessible by subscription*).

[6] https://www.HPUS.com/submitting-monograph/guideline-for-manufacturing-homeopathic-medicines-2/attenuations/class-f-solid-attenuations-triturations-method/ (*Accessible by subscription*).

attenuation is (or is not) following arithmetic predictions relative to the homeopathic starting material content. In addition to providing a testable framework for the attenuation process, the approach discussed in this paper also allows for the assessment of variability associated with human technique, equipment, environment, etc. on the accuracy and precision of the attenuation step. It is meant to inform and support appropriate HDP manufacture.

As explained in the companion White Paper titled *Best Practices for Testing and Control of Homeopathic Starting Materials in Batch Manufacturing,* there are many circumstances in which neither intermediate nor final HDP identity testing can be performed due to the extreme de-concentration levels achieved through a series of attenuation steps. The technical approaches described below provide a reasonable and attainable alternative approach based on the scientific principles of Quality by Design methodology. If the observed homeopathic starting material concentration is aligned with the arithmetic prediction (with reasonable minor variability) at measurable attenuations, then there is greater assurance that the label claim attenuation is met when the HDP is at an attenuation too dilute to feasibly measure the homeopathic starting material content. The greater assurance the data provides is helpful in demonstrating to the public, health care providers, and regulatory authorities that label claims in terms of attenuation are met.

This paper refers to the diluted homeopathic starting material in relation to its concentration. We note that in general, "content" may be viewed as either the "concentration" within the system or the "total content" within the system. For clarity, when referring to the attenuation procedure as described herein, this paper refers to "concentration" as the parameter of substance being measured. The scope of this paper is only in reference to the Hahnemannian attenuation process itself and not to the final dosage form presentation of the HDP.

Development of a Homeopathic Quality by Design (HQbD) Model for the Homeopathic Dilution Process.

QbD approaches have been used in the development of approved drug products for over a decade.[7,8] QbD allows for the science-based and risk-managed manufacture and distribution of drug products produced under conditions of ingredient quality and processing that may not have been manufactured or tested during the development program. This is one key benefit of QbD: to help to ensure the availability of quality medication by leveraging scientific principles which justify manufacturing flexibility in terms of safety and quality. A design space in part considers the quality performance of the product that is manufactured in the region within the tested extrema of various manufacturing parameters.

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[7] FDA Guidance Document Q8, Q9, & Q10 Questions and Answers -- Appendix: Q&As from Training Sessions (Q8, Q9, & Q10 Points to Consider) August 2012 accessed 01042024 online at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q8-q9-q10-questions-and-answers-appendix-qas-training-sessions-q8-q9-q10-points-consider

[8] FDA Guidance for Industry Q8(R2) Pharmaceutical Development; November 2009 ICH Revision 2 accessed 01042024 at https://www.fda.gov/media/71535/download

Further, there is no prohibition against data-based extrapolations as part of a design space based on scientific expectations and which shows no change in mechanism or interaction with other quality parameters over the range(s) actually tested. A classic example is the extrapolation of available stability data to support expiry periods longer in duration than the actual stability interval tested.[9]

While not incorporating all recognized QbD principles, the HQbD model is constructed and tested per QbD tenets and provides valuable and useful information regarding the accuracy and reproducibility of the attenuation process used in HDP manufacture. Specifically, like in the QbD paradigm, a case is made that a rational science-based assessment of attenuation quality can be extended to conditions (*i.e.*, attenuations) that are either not directly measured or measurable as noted in the companion White Paper titled *Best Practices for Identity Testing and Control of Homeopathic Starting Materials in Batch Manufacturing*. This then provides support for HDP label claims for labeled content (as Decimal [X] or Centesimal [C] attenuations) of homeopathic starting materials of interest in HDPs.

This paper presents a scientific approach that better satisfies 21 CFR 211.165a for HDPs and which is based on a QbD methodology. This new procedure allows for a risk managed assessment of the HDPs' labeled identity and strength at attenuations where the actual amount of the homeopathic starting material in the HDP is not feasible or practicable to measure directly. The goal of the model exercises is to show, with data, that the Hahnemannian attenuation (dilution) process has sufficient accuracy and precision to assure that the labeled concentration of homeopathic starting materials (corresponding to the labeled X or C potency) in the HDPs are appropriate and correct despite containing concentrations too low to measure by conventional means.

[9] *see* ICH Q1E Evaluation of Stability Data, Section II.C; accessible at https://www.fda.gov/media/71722/download

HPCUS's Proposed Alternative Approach to Identity and Strength Testing of Homeopathic Products (HDPs).

The label claim *strength* (*i.e.,* homeopathic attenuation) of a homeopathic drug product is often impossible to determine by direct measurement owing to the extreme de-concentration of the homeopathic starting material resulting from the repeated attenuation process. However, direct measurements (data) at intermediate attenuations, coupled with science-based reasoning established through fundamental scientific principles and rigorous procedures can provide compelling verification of the homeopathic starting material identity and strength (as an attenuation factor) as appearing in HDP labeling in cases where they may be impossible or impracticable to directly measure.

As discussed above, QbD is a rational development approach to reasonably assure (with corresponding low risk of failure) quality product performance across an array of interacting quality and processing conditions (a design space). Such a design space is wider, including compositions and processing conditions for the drug product, than may have been actually tested but the relevant quality and processing conditions are at an established low risk for failure. Through appropriate QbD design, drug products may be manufactured under conditions which may not have been evaluated during development. This outcome is a regulatory benefit of QbD approaches with no additional risk to safety.

In the case of dilute homeopathic products, the design space concept is greatly simplified owing to the nature of homeopathic product manufacture and the constraints applied by the *HPUS*. It is known that the attenuation and mixing processes are critical. Other factors (*e.g.*, temperature, equipment, etc.) and ingredient quality are fixed by the manufacturer minimizing those influences and interactions on attenuation process accuracy and repeatability. Thus, the key feature of this HQbD approach is the ability to indirectly verify strength in very dilute homeopathic attenuations from carefully controlled and evaluated strength determinations at measurable intermediate attenuations encountered during HDP manufacture.

Using HQbD principles, it can be shown that at label claim attenuation factors too low to directly measure, it is feasible to demonstrate, with significant safety, that label claims of high attenuation are reasonably and realistically met (with corresponding reasonable variability) using a science and data-based model such as described herein. This model is a valid and more realistic interpretation of 21 CFR § 211.165(a) than the current impossibility situation previously described or FDA's temporizing language.

The cornerstone of the approach proposed herein as a remedy for the impossibility of performance problem for applicable HDPs is to develop a focused design space for identity and strength determinations as part of a QbD approach. This approach proposes to evaluate the homeopathic starting material concentration from the first relevant attenuation of the homeopathic starting material through a series of successive intermediate attenuations approaching the limit of quantification (LOQ, usually corresponding to 4X to 6X attenuation). Concentration will be determined using reasonable contemporary analytical methods, for example HPLC, or GC. These design-space-like results are then used to provide documented and

verifiable support for applicable HDPs meeting label claims for identity and strength with high assurance when they are attenuated to immeasurably low concentrations of the homeopathic starting material.

Routine analytical chemistry methods such as those mentioned above, when applied to drug product analyses, are used ubiquitously and globally for regulated drug analyses. Routine methods for identity and strength testing are typically able to quantify substances at the ppm level. As with most other routine determinations of identity and strength for drugs, ppm level quantification is usually more than adequate for purpose, as well as being feasible, cost effective, and sustainable: collectively taken as *practicable*. For further discussion of practicable tests, see the companion White Paper titled *Best Practices for Identity Testing and Control of Homeopathic Starting Materials in Batch Manufacturing*.

It is also impracticable to apply this detailed method to every monographed homeopathic product in the *HPUS*. Using substances that a) are prepared according to the *HPUS* Hahnemannian Attenuation process[10] and b) challenge the technical aspects of that process better demonstrates robustness of the Hahnemannian Attenuation across a broad range of homeopathic starting material types. These will be discussed in a subsequent section. Further details and constraints of the attenuation assessment model are provided below.

Model Constraints

The following constraints apply to the alternative model described herein for verification of identity and strength testing in finished HDPs, which is the basis for validating the Hahnemannian Liquid Attenuation Process:

1) The model described herein applies to liquid Hahnemannian attenuation methods only.

2) The aliquot method is linked to the attenuation method. Aliquots for attenuation and for analytical testing from attenuations should be conducted in a manner which ensures that the sample accurately represents the whole uniformly.

3) The tested serial attenuations will be in 10-fold (decimal or X) or 100-fold (centesimal or C) per attenuation with the most de-concentrated solution studied being at or near the LOQ for the substance(s) being tested, and such that at least three different serial attenuations are studied. Note that typically, a given HDP is made by either decimal or centesimal attenuation steps; not both. Therefore, the studies conducted should use one or the other attenuation ratio.

4) The liquid vehicles used for attenuation of all *HPUS* monographed products are either water, alcohol, glycerin or mixtures thereof. Selected vehicles should correspond to those used by the manufacturer / brand owner to make HDPs.

5) This model applies to attenuation evaluations for oral and non-sterile topical HDPs only. As noted in the companion White Paper *Best Practices for Testing and Control of*

[10] https://www.HPUS.com/submitting-monograph/guideline-for-manufacturing-homeopathic-medicines-2/attenuations/hahnemannian-attenuations-multiple-flask-method-of-preparation/ (*Accessible by subscription*).

Homeopathic Starting Materials in Batch Manufacturing, other dosage forms may introduce other factors that lie outside the focus of the HQbD approach as presented herein.

6) Owing to their potential complexities, also noted in the companion White Paper titled *Best Practices for Identity Testing and Control of Homeopathic Starting Materials in Batch Manufacturing,* extracts from animal tissue are not addressed at present.

7) In cases where a complex substance (*e.g.*, botanical extract) is the homeopathic starting material, a suitable fingerprint or surrogate constituent(s) may be tested for.

8) Correlating with ICH, pilot scale (one-tenth of typical commercial scale or greater) will be used in this model.

9) Commercial-like process; the same manufacturing steps (including the succussion method) will be performed in the same order and same manner using equipment that is typical for the HDP manufacturer. All manufacturing operations including attenuation and sampling for testing will be conducted at 20 °C to 25 °C.

10) The model described herein utilizes two attenuation-test substances; one surface active type substance (Benzalkonium chloride or BAC which is a consistent mixture of homologs); and salicylic acid (a well characterized, water soluble single molecule). Both substances are adequately stable, are readily available at reasonable cost; and both have straightforward published conventional analytical methods. Note that the initial attenuations for salicylic acid should be followed per the *HPUS* monograph for *Salicylicum Acidum;* since BAC is not monographed in the *HPUS*, Sections 26[11] (or 27[12]) and 29[13] using a hydroalcoholic concentration that best solubilizes the test substance. Further details of the rationale for the use of BAC and salicylic acid in this paper are discussed in the Appendix.

11) Appropriate HPLC, GC, spectrophotometric, or similar quantitative method(s) that are accurate, precise, and specific should be used. For each of these two test substances, triplicate attenuation trials are considered. For each of these trials, each attenuation will be analyzed in triplicate. In this manner, it is feasible to obtain statistically relevant information.

12) All records and documentation should include the raw data, documentation, and summary documents which clearly capture the procedure, results, and outcome for each study conducted.

[11] https://www.HPUS.com/submitting-monograph/guideline-for-manufacturing-homeopathic-medicines-2/attenuations/decimal-scale-of-attenuation-definition/ (*Accessible by subscription*).

[12] https://www.HPUS.com/submitting-monograph/guideline-for-manufacturing-homeopathic-medicines-2/attenuations/centesimal-scale-of-attenuation-definition/ (*Accessible by subscription*).

[13] https://www.HPUS.com/submitting-monograph/guideline-for-manufacturing-homeopathic-medicines-2/attenuations/hahnemannian-attenuations-multiple-flask-method-of-preparation/ (*Accessible by subscription*).

Summary of Procedures

As will be elaborated below, the two homeopathic starting materials are evaluated for attenuation (Dilution) accuracy and precision. One batch of each homeopathic starting material should be used. Figure 1 below depicts the overall study structure approach for one test substance (BAC or Salicylic Acid).

The homeopathic starting material is used in three dilution trials (black arrows for trials A, B, and C). Dilutions 1, 2, and 3 are the same for all three trials (blue arrows). Three samples (depicted as SA1…SC9) are taken at each dilution step for each trial: after the contents have come to rest, one sample is taken near the top of the container (T), a second near the middle (M), and a third sample from near the bottom (B).

Trial A	→	**Dilution 1**	→	**Dilution 2**	→	**Dilution 3**
		SA1, SA2, SA3		**SA4, SA5, SA6**		**SA7, SA8, SA9**
		T M B		**T M B**		**T M B**
Trial B	→	**Dilution 1**	→	**Dilution 2**	→	**Dilution 3**
		SB1, SB2, SB3		**SB4, SB5, SB6**		**SB7, SB8, SB9**
		T M B		**T M B**		**T M B**
Trial C	→	**Dilution 1**	→	**Dilution 2**	→	**Dilution 3**
		SC1, SC2, SC3		**SC4, SC5, SC6**		**SC7, SC8, SC9**
		T M B		**T M B**		**T M B**

Figure 1: Schematic Depiction Attenuation (Dilution) Studies for One Test Substance (BAC or Caffeine).

From Figure 1, it is observed that for each test substance (BAC or salicylic acid), all nine samples at Dilution 1 (see the Dilution 1 column in Fig. 1) may be combined into a single data set for statistical analyses. This pools three locations within the container, for three trials, at each dilution. At each step there may be very slight deviations due to normal laboratory handling. To keep any deviation from confounding results, each attenuation step is evaluated independently.

Each attenuation step will be given adequate mixing to ensure uniform distribution and then allowed to come to rest before being sampled. If the results of top, middle and bottom are tracked, it allows for a comparison of sampling location which would highlight any nonuniformity of the dilution resulting from surface activity, innate handling difficulties (*e.g.*, resinous material), or incomplete mixing.

It is worth noting that the attenuation rations (1:10 or 1:100) chosen may differ from one homeopathic starting material tested to another. However, once selected, the same attenuation ratio should be used for the three trials of that homeopathic starting material.

Using the Model

To quantitatively use this design space concept, the following calculations are recommended for each homeopathic starting material. In this paper, results are captured as percent of theoretical concentration relative to the concentration of homeopathic starting material that was used for the first attenuation step studied as part of this exercise.

Calculate the mean (M1) and standard deviation (SD1) for the 9 concentration values at Dilution 1 (all three trials). Do this for Dilution 2 to get M2 and SD2 and for Dilution 3 to get M3 and SD3. For BAC, this is the total measured concentration of all BAC related species (*i.e.*, homologues). For the purposes of this exercise, we accept that some serial accumulation of variability may occur with successive attenuations and that it is normal and unavoidable. Table 1 below provides workable estimates for the mean (M) and standard deviation (SD) that may reasonably describe limits of acceptability for the attenuation process for each homeopathic starting material studied.

Values are reported as percent of theoretical for three serial attenuations and represent multiple aspects of precision and accuracy in the attenuation process. (See text for further explanation.)

Table 1: Hypothetical Upper Limits for Attenuation (Dilution)Accuracy and Precision as Mean (M) and Standard Deviation (SD) reported as %RSD (where RSD is the relative standard deviation expressed as a percentage value of the mean value) for salicylic acid and BAC.

Dilution Number	Mean (M) of the 9 results	%RSD for the 9 results
1	93% - 107%	3
2	90% - 110%	5
3	85% - 115%	8

In addition, for the BAC trials the C12, C14, and C16 homologues are assessed separately (as a ratio of peak areas) to assess how a mixture of related substances with potentially different surface activities behaves during the dilution step of the attenuation process (Table 2). Typically, the C12 peak has the largest peak area, followed by the C14 peak, with the C16 peak typically having the smallest peak area of these three homologues.

In Table 2, the mean peak areas for the C12, C14, and C16 homologues of BAC are reported relative to the mean of the C12 mean peak area (assigned a relative value of 100). The mean peak ratios are determined from the same 9 results listed in Table 1 and Figure 1. These are then provided in the Table relative to C12 = 1

Table 2: BAC Homolog Order and Ratio.

Dilution Number	C12 : C14 : C16 Relative peak ratio as (100 : C14 : C16)
1	
2	
3	

There is no numerical limit provided on the magnitude of the ratios provided in Table 2. However, the order of the three homologue peak areas should remain the same throughout the attenuation steps and there should be no apparent trend of concern indicating that dilution results are affected by the surface activity of the BAC constituent homologues.

Managing Substantive Deviations from Near Ideal Attenuation Behavior.

If the dilution test results within the statistical limits of M and SD as described in Table 1, and the BAC homologue ratios reported in Table 2 follow the same order with no adverse trends, this is strong evidence that further attenuations conducted in the same manner should yield corresponding results. However, several possible scenarios where this is not the case are worth exploring.

If the M and SD criteria are not met at some attenuation number, or if there are apparent trends in the ratios of the three main BAC homologues the data should be examined at that dilution and evaluated to see if position (top, middle, or bottom per Fig. 1) plays a role. If values in one location are trending higher or lower, or the BAC ratio changes substantively, this provides useful information on how to correct and ultimately prevent the non-ideal mixing outcome. Once the root cause is determined (*e.g.*, human error, incomplete mixing, analytical method problem(s), surface activity, etc.) it can be corrected, and the study repeated.

Applicability to HDP Intermediates in Commerce

It is a practical aspect of HDP manufacturing that, in some cases, homeopathic attenuations below thresholds of measurement for identity and strength may be exchanged in commerce. The seller (*i.e.*, the intermediate manufacturing entity) can perform similar attenuation verification exercises as described herein and then provide that information in a certificate of analysis (C of A).

Greater assurance is provided for the seller and buyer via viable and detailed C of A processes along with correspondingly healthy buyer/seller relationships. It is a pillar of FDA inspectional activities to have access to the entirety of data and information involved in the drug manufacturing process. The seller's robustly informative C of A may help to address important inspectional CGMP requirements. In cases where the C of A cannot include proprietary information, a drug master file (DMF) may be submitted to the FDA. The information in the

DMF is available to FDA staff as necessary and as authorized by letter from the DMF Holder (i.e., the seller) via a Letter of Authorization (LOA) from the DMF Holder.

Conclusions

The proposed Homeopathic Quality by Design approach provides a means to validate the Hahnemannian Attenuation (including dilution) process; this allows manufacturers and regulatory personnel to assure that identity and strength may be evaluated with very low risk to quality or safety for very dilute homeopathic products in the absence of practical direct testing**.** Strength in this case relates to the label claim attenuation (C or X) associated with conventional Hahnemannian attenuation methods applied to *HPUS* monograph products using *HPUS* designated vehicles.

The model described herein applies to oral and topical dosage forms using substances of botanical, chemical or mineral origin. Biologically sourced material and sterile products are not included in the model at this time, due to other factors and potential complexities that lie outside the focus of the HQbD approach as presently presented. The approach described herein provides a science-based and functional alternative to the current regulatory interpretation of 21 CFR 211.165(a) and it is aligned with the intention of the FD&C Act as well as with the public health needs addressed by 21CFR. Further, the model is designed to be applicable to finished homeopathic products, as well as partially attenuated intermediates used in commerce.

Detectability of allopathic levels corresponding to a gross high side attenuation failure is *easily detectable* if the product is tested for the absence of homeopathic starting material which correspond to levels below concern. This addresses severity as well as detectability of a harmful failure mode.

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. Adopt a validation protocol for the attenuation process based on a homeopathic Quality by Design (HQbD) approach. Once the HQbD process has been validated, documented manufacturing adherence to the HQbD process will provide assurance of proper manufacturing whenever the actual amount of the homeopathic starting material in the HDP is anticipated to be non-feasible or impracticable to measure directly. This model is a valid and more realistic path to compliance with 21 CFR § 211.165(a) than the current impossibility of performance situation for testing identity, strength, and purity for many HDPs.

2. Acknowledge that alternative validation approaches may also be utilized so long as a chosen alternative provides at least an equivalent measurable level of assurance of proper manufacturing. Companies choosing to use an alternative validation protocol are responsible for justifying the chosen alternative.

3. The use of the HQbD approach is currently limited to HDPs a) produced using Hahnemannian attenuation to be used in oral or non-sterile topical applications and b) manufactured from materials of botanical, chemical, or mineral origin. FDA should designate the specific HQbD approach described herein as a science-based and functional alternative to the current regulatory interpretation of 21 CFR 211.165(a) for such HDPs.

4. When a seller company supplies an attenuation(s) to a buyer company, there should be a requirement that the seller company provide to the buyer company, upon request, a Certificate of Analysis (C of A) which includes validation documentation for the attenuation process used to prepare the supplied attenuation(s).

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.

BAC – (benzalkonium chloride) a quaternary ammonium compound that acts as an antimicrobial agent by denaturing proteins and disrupting cytoplasmic membranes, which is widely used as a preservative in ophthalmology. Benzalkonium chloride NF is a mixture of alkylbenzyldimethylammonium chlorides of the general formula $C_6H_5CH_2N(CH_3)_2R]Cl$ in which R represents a mixture of alkyls, including all or some of the group beginning with n-C_8H_{17} and extending through higher homologs, with n-$C_{12}H_{25}$, n-$C_{14}H_{29}$, and n-$C_{16}H_{33}$ comprising the major portion.

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.

Bespoke - made to order for a particular person or user; individually or custom made.

Bulk compounding - the creation of a pharmaceutical preparation—a drug at a scale greater than would be necessary for the unique needs of an individual patient.

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.

Design Space - the multidimensional combination and interaction of input variables (*e.g.*, material attributes) and process parameters that have been demonstrated to provide assurance of quality (ICH Q8 (R2)).

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 of 1938, as amended.

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 Intermediate — Any attenuation manufactured from the homeopathic starting material that is not intended to be packaged as a homeopathic drug product per the manufacturing batch record and which is not commercialized to the public or physicians. A homeopathic intermediate is solely used to prepare subsequent attenuations.

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).[14]

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.

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

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.[15]

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.

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.

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

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 – (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).[16]

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.

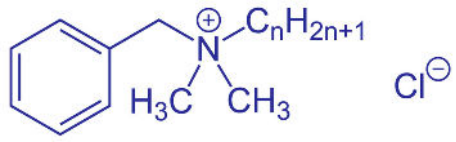
[16] Accessible at https://www.hpus.com/submitting-monograph/guideline-for-manufacturing-homeopathic-medicines-2/introduction/guideline-for-manufacturing-homeopathic-medicines/ *(Accessible by subscription).*

Appendix

Benzalkonium chloride

Benzalkonium chloride (BAC) is a surface-active substance commonly used as a disinfectant. BAC is composed of a mixture of related substances known as homologues (see structure below).

Benzalkonium chloride



BAC is also: economical to purchase, readily available in adequately high purity, relatively safe, is well characterized (including with respect to its homologues) and is straight forward to analyze using conventional HPLC methods.[17]

The series of homologues defined as BAC vary by the chain length in the alkyl chain depicted above on the quaternary nitrogen atom. The most common of the homologue series correspond to C12, C14, and C16. The C12 peak may be the most prominent peak in commercial sources of BAC.

Uniform dilution may be affected by the surface activity of the substance(s) being diluted. If a substance migrates to or away from the site where the sample aliquot is drawn, then the measured results may be substantially higher or lower than expected. Further, such deviations may or may not be reflective of the bulk solution concentration.

For this study, the total concertation of all BAC components as well as the relative ratio of homologue peak areas (C12, C14, and C16) provides important information regarding the attenuation process step. If the total BAC and relative ratio of the three main homologues in BAC follow expectations, that supports several aspects of the dilution process step as meeting expectations. These include:

1. Surface activity of the related substances in BAC do not in and of themselves cause substantial deviations in expected dilution behavior,;

[17] See: Santos, M., Li, M. & Rustum, A.M. A Single RP-LC Method for the Determination of Benzalkonium Chloride and Its Potential Impurities in Benzalkonium Chloride Raw Material. *Chroma* **71**, 499–503 (2010). Available at https://doi.org/10.1365/s10337-009-1458-4; accessed Nov. 28, 2023

2. The equipment, attenuation procedure and sampling method are not subject to surface active complications;

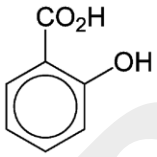
3. Mixtures of related substances with different surface activity when diluted, may meet the expected concentration owing to (1) and (2) above.

Although BAC is not used in homeopathy, the results of this study using it may be generalized as a pillar in the verification of an adequate Hahnemannian Liquid Dilution process in the overall attenuation of HDPs. This concept applies to mixtures of related substances that may also be surface active and may extend to attenuation steps where the expected concentrations fall below LODs for conventional means of analysis (see text).

Salicylic acid

Salicylic acid is also monographed in the USP and is utilized topically as a treatment for acne and other skin conditions.

Salicylic Acid



Salicylic acid is a well characterized stable single-entity molecule. It is also: not surface active and is not expected to exhibit behavior associated with surface active species (*e.g.*, accumulation at interfaces); readily available in adequate purity and at reasonable cost. It has a published USP monograph and reference standards are available from multiple common sources. It has well publicized conventional analytical spectrophotometric, colorimetric, or chromatographic methods available that are well documented and facile to carry out. Three examples are given here:

a. Direct spectrophotometric method example[18]
b. Derivatized (ferric ion) colorimetric method[19]
c. HPLC method[20]

[18] https://wjpr.s3.ap-south-1.amazonaws.com/article_issue/1523843544.pdf

[19] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7530239/

[20] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2891271/

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