Best Practices for Testing and Control of Homeopathic Starting Materials in Batch Manufacturing

Homœopathic Pharmacopœia Convention of the United States (HPCUS)

HPCUS Expert Panel on CGMP Gaps for Homeopathic Drug Products

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Introduction

This White Paper, *Best Practices for Testing and Control of Homeopathic Starting Materials in Batch Manufacturing,* discusses the interpretation and application of 21 CFR Part 210: Current Good Manufacturing Practice in Manufacturing Processing, Packing, or Holding of Drugs and 21 CFR Part 211: Current Good Manufacturing Practice for Finished Pharmaceuticals to homeopathic drug product components. This includes, but is not limited to, the topics listed under 21 CFR 211 Subpart E—Control of Components and Drug Product Containers and Closures.

Compliance with the Homeopathic Pharmacopeia of the United States (*HPUS)* Homeopathic CGMPs is an essential part of manufacturing and marketing homeopathic drug products in the United States.

Not every 21 CFR requirement is mentioned in this paper; it is written from the perspective that the majority of the 21 CFR Part 211 requirements are basic expectations, well understood, and already consistently practiced industry-wide by homeopathic product manufacturers. The paper's focus is on those areas where the manufacture of homeopathic drugs necessitates different approaches that are more appropriate to, and relevant for, these products than are commonly practiced in the manufacture and marketing of allopathic drug products. This White Paper considers the suitability of definitions that have been developed for allopathic drug products when they are applied to homeopathic drug products with unique manufacturing requirements; and in turn provides recommendation to help rectify areas of confusion arising from definitional and manufacturing differences in an effort to clarify these gaps for both regulators and manufacturers of homeopathic drug products.

Scope

The scope of this White Paper includes GMPs relevant for manufacturing of batch-processed commercially distributed products; it does not address the topics or details addressed in USP chapters <795> Pharmaceutical Compounding-Nonsterile Preparations, <797> Pharmaceutical Compounding-Sterile Preparations, or <825> Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging.

- *Starting materials* and *packaging components* for drug products produced through batch manufacturing are in scope, while extemporaneously compounded drug products are excluded from the scope of this White Paper. The reader is directed to USP chapters <795> Pharmaceutical Compounding-Nonsterile Preparations and <797> Pharmaceutical Compounding-Sterile Preparations for extemporaneously compounded drug products
- *Starting materials* and *packaging components* for drug products intended for oral and topical administration are in scope. Because of the additional concerns for control of microbiological quality and viral inactivation, future best practices will be considered for dosage forms administered by other routes.
- Starting materials of chemical, botanical, or mineral origin are in scope. Specific substances of zoological origin are currently beyond the scope of this guidance.

Key Terms (*Complete Glossary located at the end of this draft*)

The terms "raw material" and "starting material" are colloquially used interchangeably. It is useful to recognize that in the context of the *HPUS*, a "starting material" is that item which is used to prepare the first attenuation (*i.e.*, the first homeopathically prepared dilution). A “raw material” is used to prepare a “starting material” but is not itself used to make homeopathic attenuations directly. By example, 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 of Ferrum phosphoricum.

The Council on Pharmacy (CoP) of the HPCUS has recommended aligning the terminology used in this White Paper with the FD&C Act, implementing regulations, and FDA guidance documents (*e.g.*, ICH Q7). The use of consistent terminology is important for effective communication and to reduce confusion and/or ambiguity. While the reader is advised to refer to the complete glossary located at the end of this document, several key terms are discussed herein. Exceptions and points of differentiation between the terminology used in these sources is discussed below. Specifically, in this paper the substance(s) of interest to which a homeopathic drug product (HDP) is labeled will be referred to as the *homeopathic starting material.* Refer to Figure 1 and the discussion that follows. Special attention should be paid to the following terms:

- Raw Materials
- API Starting Materials and Homeopathic Starting Material
- Active Pharmaceutical Ingredient and Drug Substance
- Intermediate
- Attenuation

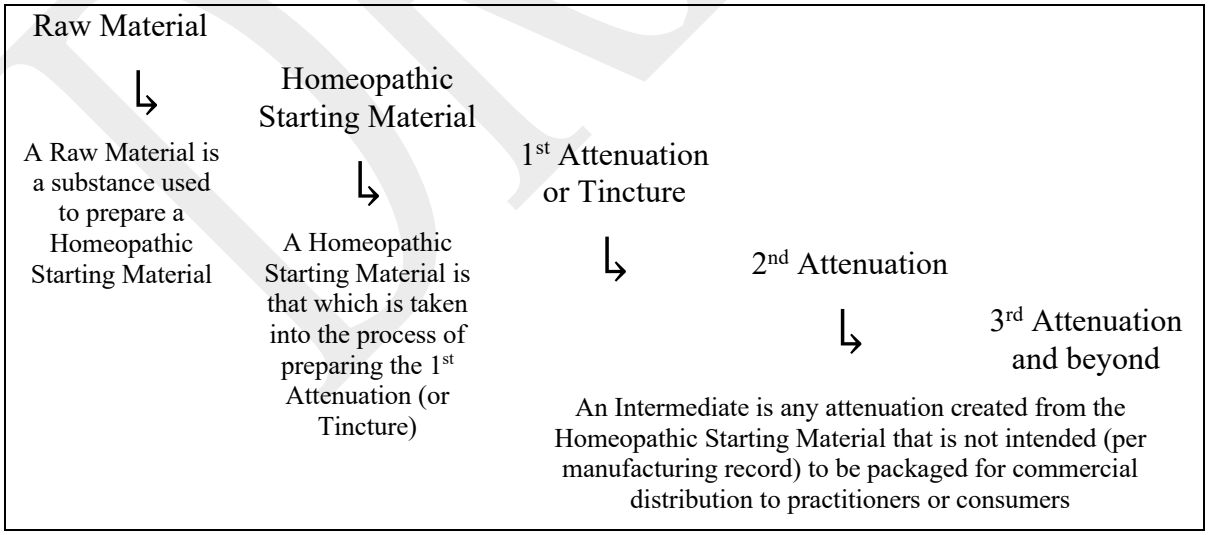

Figure 1: Relationship of raw materials, starting materials, and intermediates and their identification as active pharmaceutical ingredients/drug substances.

Raw Materials – ICH Q7 defines Raw Material as a general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs. From ICH Q7 "raw materials" may be subjected to processing steps which do not fall under the requirements of the Q7 guidance, whereas once a "starting material" (colloquially *registered starting material (RSM)*) is designated in the sequence of manufacturing steps, the requirements of the Q7 guidance apply.

In the manufacturing of homeopathic products, a raw material is a substance used to prepare a starting material, it is not itself used directly as a homeopathic drug product. It should be noted that requirements of the *HPUS*' *Expanded Homeopathic Good Manufacturing Practices* includes provisions applicable to raw materials.

Homeopathic Starting Material – In the manufacture of allopathic drugs, an API starting material is designated and justified during the development and commercialization process. The designation of the API starting material marks the point in the synthesis of the drug substance where GMP processing begins.

In contrast, the starting material for a homeopathic drug is defined by the *HPUS* which provides no latitude for designating a starting material other than that identified in the *HPUS* monograph. CGMP control of manufacturing begins with the introduction of the Homeopathic Starting Material to the homeopathic manufacturing process; along with any requirements of the *HPUS*' *Expanded Homeopathic Good Manufacturing Practices* provisions applicable to raw materials/starting materials. For homeopathic starting materials that are not obtained directly from natural sources such as ascorbic acid USP (used to make homeopathic *Ascorbicum Acidum*), CGMP control of the homeopathic manufacturing process would begin (for example) with the ascorbic acid USP as the starting material.

The Homeopathic Starting Material is ***that which is taken into the process of preparing the first attenuation*** (solution or trituration). The homeopathic starting material may or may not result from processing of a precursor raw material; many Homeopathic Starting Materials are obtained directly from natural sources (*e.g.*, harvest of plants or plant parts) with no change in the natural material prior to its use as a homeopathic starting material.

Once the *HPUS* attenuation process (which may occur multiple times) is completed, the resulting attenuation is designated as a homeopathic drug product or as a homeopathic intermediate, depending upon its intended subsequent use. Homeopathic intermediates are not labeled for sale to physicians and the public. Therefore, whether a homeopathic attenuation is an intermediate or a finished drug product is determined by the declared intention of the manufacturing process, as found in the batch production record and reflected on the product label.

A manufacturer of homeopathic products may begin the process from the homeopathic starting material, provided they have the capability and capacity to prepare the first attenuation, or they may begin the manufacturing process from a homeopathic intermediate produced by another manufacturer.

Intermediate – ICH Q7 defines an intermediate as a material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes

an API. In contrast, 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 to the public or physicians as that intermediate.

The attenuation of a homeopathic intermediate proceeds without purification or any demonstrable molecular change. Homeopathic Intermediates may be obtained as an article of commerce for further manufacture (not to the public and physicians) or produced in-house. Note that intermediates commercially purchased may be under contract or commercial agreement.

A homeopathic intermediate would be further attenuated to produce the next sequential homeopathic intermediate or drug product. The distinction between homeopathic intermediate and drug product is not necessarily compositional but is determined by intent as recorded in the production record and on the label. As an example: Arnica 10X is processed through an attenuation step to prepare Arnica 11X, which is an "intermediate" and is not packaged as a drug product as indicated in the production record; this "intermediate" is labeled for further manufacturing and is subsequently processed through an attenuation step to prepare Arnica 12X, which is packaged as a drug product as indicated in the production record.

Attenuation – Attenuation as a noun may refer to the product of the process used to make a homeopathic medicine, while as a verb may refer to the process itself.

- **Attenuation** – (noun) *i.e.*, homeopathic attenuation: the result of the two-phase homeopathic process (serial dilution or de-concentration and vigorous mixing); can be in a liquid state or a solid (powder) state and is, in general, the homeopathic active ingredient in its entirety. 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. The first phase is 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 state 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.

Active Pharmaceutical Ingredient/Drug Substance – The use of the terms API or Drug Substance in relation to homeopathy is a significant source of confusion. ICH Q7 defines an Active Pharmaceutical Ingredient (API) (or Drug Substance) as any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. In contrast, ***in***

the homeopathic model the active ingredient is the homeopathic attenuation in its entirety because the dilution itself modulates the activity in a manner according to homeopathic principles.

The first prepared attenuation is not analogous to an API produced through a sequence of synthetic reactions. The homeopathic starting material provides a more appropriate analogy to the more conventional concept of an API.

Ensuring CGMP compliance in the control of components

The control of starting materials is crucial to product quality, and the receipt of starting materials is the first, best, and least expensive point in manufacturing to remove nonconforming materials. Conformance is based on meeting specific requirements, referred to as *acceptance criteria.* The term *specification* is often used synonymously with acceptance criteria, but formally, a specification is the combination of three items: 1) attributes to test, 2) testing methods for those attributes, and 3) an acceptance criteria for them. For some diluted homeopathic intermediates, attributes are difficult to define. Due to the degree of de-concentration, testing methods are impossible to implement. This issue is explored with proposed solutions in the section on Identity Testing of this paper.

In terms of homeopathic starting materials, areas of challenge for CGMP conformance within the homeopathic drug industry include:

1) the use of supplier test results,
2) identification testing of homeopathic intermediates, and
3) the application of retest periods.

Use of Supplier Test Results

21 CFR 211 § 211.84 stipulates that apart from identity testing, data taken from a report or certificate of analysis may be used to show conformity with a component's specifications for purity, strength, and quality, provided the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals. The validation of test results is one component of supplier qualification. It is important to recognize that the reliability of the supplier's analyses must be validated, and this must be repeated periodically.

Validation of the supplier's test results is achieved through appropriate testing. Conducting paper and/or on-site audits is often considered to be necessary but not sufficient on its own. 21 CFR §211.84 provides that, "auditing is not a complete substitute for validation of the supplier through testing." The principles of quality risk management should be followed when establishing a supplier qualification protocol. Certain risks will be intrinsic to the material, while other risks will depend on the supplier.

Where appropriate, consideration should be given to the control of residual solvents, elemental impurities, and nitrosamine impurities. These potential drug product impurities may be controlled at the raw material and/or homeopathic starting material stages in order to allow for a calculation of these in the drug product. Manufacturers may also choose to test the drug product

for all required attributes. Detailed guidance on these approaches is provided by the FDA and the USP. In the case of some intermediates, validation of the supplier's test results through testing will not be technically possible due to the degree of attenuation of the homeopathic starting material (*i.e.*, when it is an intermediate). This is discussed further in the following section (Identity Testing).

Identity Testing

Identification tests are intended to ensure each component is what it is labeled to be. Paraphrasing 21 CFR 211.84(d)(1) and (2), each drug product component shall be tested for conformity with all appropriate written specifications for identity, purity, strength, and quality. Apart from identity testing, data taken from a report or certificate of analysis may be used to show conformity with the component's specifications for purity, strength, and quality, provided the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals. Suppliers of homeopathic starting materials should make available summary validation reports of sufficient detail to reasonably assure the buyer that such standards are met.

Presently, there is no exemption or alternative CGMP process to meet the identity testing requirement which requires the performance of one or more specific identity tests upon receipt of the component. The CGMP regulations are explicit that at least one specific identity test be performed upon receipt of each component. The requirement for a specific identity test requires that the test (or tests) can correctly discriminate between closely related materials when that is appropriate .

Using the terminology discussed above, the *HPUS* provides macroscopic, microscopic, chemical, and/or spectroscopic identity tests for homeopathic starting materials. Specific identity tests based on appropriate chemical, spectroscopic, or chromatographic characteristics are provided for botanical tinctures. In cases where such testing is given, provided the test is not listed as "optional," it is expected that the given test is used, although an alternate test may be used provided it has been validated by the user to achieve the same or a higher level of discriminatory power. For homeopathic starting material from extracts where a number of related compounds are expected to exist and where that homeopathic starting material is also labeled per one of those related substances, then a second orthogonal identity test may be needed to ascertain the labeled homeopathic starting material's identity. In the case of attenuations from raw materials other than botanicals (or botanicals where a mixture itself is labeled as the homeopathic starting material), a single raw material identity test (*e.g.*, a fingerprint for botanical mixtures) is typically sufficient for identifying the homeopathic starting material's identity.

21 CFR §211.84(d)(1) states "Specific identity tests, if they exist, shall be used." The contextual definition of "specific" is obtained from ICH Q2(R1). Specific means the test provides complete discrimination from closely related structures that are likely to be present as described above.

Test methods described in the Homeopathic Pharmacopoeia of the United States (*HPUS*) are provided without validation data and therefore must be validated by the user. When the

requirements of a USP-NF monograph are incorporated in the *HPUS*, the USP-NF test methods are accepted as validated, but their suitability must be verified under actual conditions of use[1].

For identity tests other than those from the current revision of the United States Pharmacopeia, National Formulary, Official Methods of Analysis of AOAC International[2], or in other recognized standard references, either modified compendial methods or developed by the firm or some other unofficial source, validation of the method must be provided by the user. In addition to specific tests for identity, the absence of specific compounds of known risk to public health may be included as part of identity testing (*e.g.*, limit of methanol in alcohol, limit of diethylene glycol, and ethylene glycol in glycerin).

While CGMP compliant identity testing is straightforward when dealing with the homeopathic starting material or the first attenuation, there may be a challenge to meet the requirement for many homeopathic intermediates. Homeopathic intermediates are made by repeated attenuation. Intermediates (and drug products) often contain exceptionally low concentrations of chemical species other than water molecules or water and ethanol molecules for hydroethanolic solutions. These aspects are discussed in the companion White Paper focused on finished HDPs, *Best Practices for Unique Aspects of Finished Product Testing for Homeopathic Drug Products* and the companion paper focused on the manufacturing process and homeopathic product quality, *Utilizing a Quality by Design Model for Hahnemannian Dilutions in the Manufacture of Homeopathic Drug Products.*

Development of alternative identity tests using instrumental techniques (gas chromatography (GC), high performance liquid chromatography (HPLC), and various molecular and elemental spectroscopies) may be possible. To develop and validate suitable alternative identity tests, the specificity of the target analyte relative to the homeopathic starting material as well as the specificity of the test method for the analyte must be considered. For example, caffeine, while a convenient target analyte is produced by numerous plants and therefore its presence is not sufficiently unique to differentiate *Ilex paraguensis* (Yerba Mate), *Cola acuminata* (kola nut), *Coffea cruda* or Caffeine USP from one another. The absence of a single specific compound can be mitigated by targeting multiple test compounds in the mixture (*e.g.*, a botanical extract) which may serve as an HPLC fingerprint for that given mixture. Once a homeopathic starting material is acceptably identified, it would be reasonable to rely on a single test for a single component to demonstrate control over the subsequent manufacturing steps (*e.g.*, process validation).

Development and validation of a relevant and feasible alternative identity test is consistent with the CGMP regulations for drug manufacturing. The expectation is the alternative test will be at least as reliable as the test specified in the pharmacopoeia.

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[1] 21 CFR 211.194(a)(2)

[2] Copies may be obtained from: AOAC INTERNATIONAL, 481 North Frederick Ave., suite 500, Gaithersburg, MD 20877, or from https://www.eoma.aoac.org/

When a homeopathic intermediate is too dilute to test directly, it may not be possible to carry out the tests according to monographs with standard analytical technologies or even with the use of highly advanced technologies.

Because there is presently no exemption or alternative process to meet the identity testing requirement, the regulatory requirement of 21 CFR §211.84 confronts the manufacture and marketing of homeopathic drugs with a conundrum: Congress recognizes drugs in the *HPUS*, but FDA's CGMP regulation can be seen as making their sale impossible. This conundrum is discussed in the companion White Paper focused on finished HDPs, *Best Practices for Unique Aspects of Finished Product Testing for Homeopathic Drug Products* and the companion paper focused on the manufacturing process and homeopathic product quality, *Utilizing a Quality by Design Model for Hahnemannian Dilutions in the Manufacture of Homeopathic Drug Products.*

One could envision producing homeopathic drug products only from the homeopathic starting material, but many firms engaged in providing homeopathic drugs are without the capability and/or capacity to prepare the first attenuation and therefore purchase homeopathic intermediates for further attenuation.

Therefore, the use of homeopathic intermediates as starting materials that are below any practical limit of detection cannot be ignored. These situations present a dilemma; and dilemmas require a choice between imperfect alternatives. This will also be discussed in a companion White Paper focused on the manufacturing process and homeopathic product quality, *Utilizing a Quality by Design Model for Hahnemannian Dilutions in the Manufacture of Homeopathic Drug Products.*

It is strongly expected that all available reasonable resources will be applied to achieving CGMP compliance. Only in exceptional situations, likely involving intermediates, should mitigation efforts be employed when sufficient CGMP compliance is not achievable due to infeasibility of requirements when applied to homeopathic intermediates that have been taken through several attenuation (de-concentration) steps. In such circumstances the following mitigation efforts should be included:

For each lot and shipment of the homeopathic intermediate:

- Clearly establish and document the provenance of such homeopathic intermediate back to the homeopathic starting material, including:
  - The name, address, and contact information of the supplier and each manufacturer from the procurement of the homeopathic starting material through the given homeopathic intermediate, including contractors and testing sites.
  - Copies of all test results
  - Production records
- Generate CGMP compliant data demonstrating the homeopathic intermediate's concentration falls below any practical limit of measurement or concern;
  - For products that contain ingredients associated with potential safety concerns, demonstrate the method is capable of detecting the compound(s) of concern at a concentration equivalent to the lowest attenuations at which the product may be sold for over-the-counter internal use (OTC),

  - Through specific lot analysis, demonstrate the compound(s) of concern is below the concentration equivalent to the lowest attenuations at which the product may be sold for over-the-counter internal use (OTC), and
  - Generate CGMP compliant data demonstrating the absence of foreign materials.
- For the test method(s), document the comparison of the test's limit to any safety-related thresholds (*e.g..,* Lowest Permissible Attenuation for OTC use listed in an *HPUS* monograph) for compounds of concern anticipated in the homeopathically attenuated material; the upper limit should be defined by an assay method which can then be used for the homeopathic intermediate to confirm the product's safety.

It is important to recognize that even when contracting out manufacturing, packaging, and/or labeling operations, the product owner remains responsible for ensuring that the drug product it places into commerce (or causes to be placed into commerce) is not adulterated for failure to comply with CGMP requirements. Further, contract manufacturers are responsible for the quality of drugs manufactured, packaged, and/or labeled at their facilities regardless of agreements in place with product owners. Because of this, it is expected that contract manufacturers will require that CGMP compliant identity testing for received materials be performed upon receipt whether they are shipped from the product owner, a partnering organization, or procured on the product owner's behalf. The reader is directed to the companion White Paper titled *Utilizing a Quality by Design Model for Hahnemannian Dilutions in the Manufacture of Homeopathic Drug Products* for additional information.

Application of expiration dating and retest periods

The CGMP regulations exempt homeopathic drug products from bearing an expiration date on the label and from complete stability testing (21 CFR §§ 211.137 and 211.166). FDA explained that it provided the exemption because expiration dating and complete stability testing were considered unnecessary because of the unique nature of homeopathic drugs. Both the "imprecise nature of determining extremely low levels of active ingredients for each of a large number of attenuations (dilutions) that may be prepared for each drug substance and the fact that factors such as potency, absorption, bioavailability and other measures of effectiveness did not appear to be applicable to homeopathic drugs" were specifically mentioned as the justification for the exemption[3].

Nevertheless, the exemption from expiry dating and complete stability testing is not an exemption from 21 CFR 211.87 which requires that approved components (including drug product containers and closures) be retested or reexamined, as appropriate, for identity, strength, quality, and purity and approved or rejected by the quality control unit as necessary, *e.g.,* after storage for long periods or after exposure to air, heat or other conditions that might adversely affect the component, drug product container, or closure. A finished drug product of the same homeopathic material in the same attenuation as a homeopathic intermediate does not exempt the homeopathic intermediate from the retesting or re-examination requirement. Commonly, and in

[3] Federal Register, Vol. 43, No. 190 - Friday, September 29, 1978, p. 45058.

the absence of supplier information or other verified hold time information, a period of one year is taken as storage for extended period especially for homeopathic drug products which cannot be tested due to attenuation (de-concentration) levels which are untestable with available analytical techniques. Shorter periods may be assigned when stability is known to be a concern for the homeopathic starting materials, but only when present in the homeopathic drug products within their limit of analytical detection.

Containers

The CGMP regulations stipulate that drug product containers not be reactive, additive, or absorptive to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements (21CFR211.94). This requirement is in addition to the stability testing requirements for homeopathic drug products (21 CFR 211.166(c)).

The USP provides standards (*e.g.*, <660>, <661>) and advice (*e.g.*, <1663>, <1664>) for the qualification of packaging components. FDA has provided several guidance documents[4,5] for developing adequate evidence to demonstrate each proposed container closure system and its components are suitable for its intended use. A risk-based approach to qualifying packaging components is recommended, based on the correlation between the degree of concern regarding the route of administration with the likelihood of packaging component-dosage form interactions. Thus liquid-based oral drug products containing alcohol require more characterization than oral solid dosage forms. Related to concerns regarding leachable and extractable compounds is the assessment and control of potentially mutagenic impurities. Further information on this topic can be found in the ICH multidisciplinary guideline "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk" ICH M7(R1).

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 an official definition for Homeopathic Starting Materials that recognizes the unique aspects of these materials and how they differ from conventional allopathic drug manufacture, including differences in the concept of Active Pharmaceutical Ingredient (API). Such a definition should include the understanding that homeopathic starting material is that material which is taken into the process of preparing the first attenuation (solution or trituration) or tincture.

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[4] Guidance for Industry "Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products" (February 2008).

[5] Guidance for Industry "Container Closure Systems for Packaging Human Drugs and Biologics" (July 1999)

2. Adopt an official definition of Homeopathic Active Ingredient to recognize the widely accepted homeopathic expert definition that emphasizes the combination of starting material in de-concentrated form combined with the dynamization effects of the attenuation steps (*i.e.,* the active ingredient is the homeopathic attenuation *in its entirety,* because the attenuation itself modulates the activity in a manner according to homeopathic principles but is not the finished homeopathic drug product).
3. When a homeopathic intermediate is too dilute to test directly, it may not be possible or practicable to carry out identity tests using standard analytical technologies (even with the use of highly advanced technologies). Instead, we propose an alternative identity validation procedure such as the homeopathic process based upon Quality by Design principals or Homeopathic Quality by Design process (HQbD) as described in the companion White Paper on this subject titled *Utilizing a Quality by Design Model for Hahnemannian Dilutions in the Manufacture of Homeopathic Drug Products.* This will create a pathway to compliance which can be relied upon by both regulators and manufacturers.

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.*, 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.

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

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.

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.

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).[6]

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.

Lot – (as per 21 CFR 210.3 Definitions) lot means a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits.

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) – a drug product available to consumers without a prescription from a licensed practitioner.

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

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

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

- 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.

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).[7]

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.

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