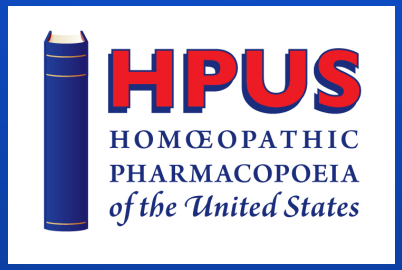

Initiative to Develop Guidelines for HPUS and Homeopathic Manufacturer

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HPUS
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Introduction

- Pharmaceutical quality is the foundation that allows patients and consumers to have confidence in the safety and effectiveness of their medications.
- Achieved through guidelines from FDA and ICH, in harmonization with detailed instructions from Pharmacopoeia.

Introduction

- The homeopathic drug industry relies on provisions of the Homeopathic Pharmacopoeia of the United States (HPUS) to ensure patient safety.
- Also relied on FDA's 1988 Compliance Policy Guide (CPG) 400.400 titled "Conditions Under Which Homeopathic Drugs May Be Marketed" to delineate those conditions under which homeopathic drug products may ordinarily be marketed, including conditions regarding ingredients, labeling, prescription status, and current good manufacturing practice.

Introduction

- In October 2019, FDA announced the withdrawal of CPG 400.400 simultaneously with the issuance of the revised draft guidance, “Drug Products Labeled as Homeopathic Guidance for FDA Staff and Industry”.
- The draft guidance describes how the agency intends to apply a risk-based enforcement approach to the manufacturing, distribution and marketing of homeopathic drug products.
- FDA intends to apply the draft guidance’s general approach to prioritizing regulatory and enforcement action, which involves risk-based prioritization in light of all the facts of a given circumstance.

Purpose

- HPCUS has taken the initiative in developing and establishing guidelines and whitepapers to ensure sufficient level of harmonization between the practice of homeopathic pharmacy, HPUS and FDA's guidelines and expectations.
- Five key categories were identified to ensure a uniform quality program across all sites of homeopathic manufacturers.
- Guidance of this type exists for the manufacturer of allopathic drug products, but the direct application of that is not always possible or practical given the nature of homeopathic treatments.
- Establishing guidelines recognizing the unique challenges associated with homeopathic products would advance the assurance of product quality and safety.

HPUS Projects

Category	Purpose
Active Pharmaceutical Ingredients (API)	Guideline to establish the requirements for receiving, testing and storing the Active Pharmaceutical Ingredients used for manufacturing homeopathic products.
Product Release	Guideline to establish the required testing for Homeopathic Finished Products.
Validation of Dilution Process for Preparation of Hahnemannian Liquids	Guideline to describe the requirements for validation of Dilution Process used in manufacturing liquid homeopathic products.
Validation of Dilution Process for Powders	Guideline to describe the requirements for validation of Dilution Process used in manufacturing powdered homeopathic products.
Dosage Form Manufacture – Discrete Solid Oral Dosage Forms	Guideline to define the Blend Uniformity (BU) and Content Uniformity (CU) procedure and requirements during the manufacturing of homeopathic drug products.

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Active Pharmaceutical Ingredients

Charters	Overview	Deliverable
API	• Detailed guideline for APIs such as starting materials, active drug substances, intermediate and high dilutions in powder or liquid form. • To ensure the material received is in compliance with the recipient's expectations and applicable regulatory requirements.	White paper and guideline encompass the topics listed under 21 CFR 211 Subpart E-Control of Components and Drug Product Containers and Closures.

Product Release

Charters	Overview	Deliverable
Product Release	• Guideline for appropriate laboratory testing of satisfactory conformance to final specifications for drug products, with consideration to starting material diminishing during many attenuation steps, resulting in very low concentration of the analyte in homeopathic products.	White paper and guideline encompass the tests to be universally considered (description, identity, assay, impurities, and microbiological quality).

Product Release

- Based on HPUS, assays should be mandatory whenever there are safety issues, or when the API is a single, well-defined chemical entity.
- When the API is a complex substance and an assay only serves a supplementary qualitative purpose, then the assay should only be an optional step for which the manufacturer must determine the need.
- Establish a procedure for industry and FDA to describe the requirements for objective measurement of quality of the final product at release based on scientific justification, including the analyte concentration, LOD (limit of detection) and LOQ (limit of quantitation) of the analytical methods and instruments.

Validation of Dilution Process for Liquids

Charters	Overview	Deliverable
Validation of Dilution Process for Preparation of Hahnemannian Liquids	• Guideline describing the requirements to assess adequacy of mixing and diluting in each attenuation process steps through measurement of an analyte/marker (e.g., drug substance, starting material) for liquids intermediates in homeopathic manufacturing. • The guideline will also focus on utilization of grouping of target solutes sharing similar physical and chemical characteristics to minimize the number of validations that might ultimately be necessary. • Initially accomplished by reviewing literature for similar approaches within the greater pharmaceutical industry. The guideline will be applicable for the homeopathic manufacturing process utilizing a wide range of equipment used for the Hahnemannian dilution process.	White paper and guideline that defines Hahnemannian liquid attenuation process procedure steps, variables and controls necessary to establish a Hahnemannian attenuation manufacturing process within a state of control.

Validation of Dilution Process for Liquids

- Homeopathic products are successively attenuated (diluted) many times until the final concentration for the finished product.
- Validation of the attenuation processes is required to assess adequacy of mixing and dilution in the attenuation steps for products in liquid form.
- Guideline to establish variables and in-process control for intermediate products and describe requirements for validation of Hahnemannian liquid dilution processes.
- Guideline also to address applicable analytical testing procedures required to monitor and control the liquid dilution processes.
- Limitation of analytical tools for quantitative analysis at very low concentrations (testing of the target solute based on its detection limit).
- The sampling and/or sample analysis may be adjusted to a statistically appropriate and representative level.

Validation of Dilution Process for Powders

Charters	Overview	Deliverable
Validation of Dilution Process for Preparation of Hahnemannian Powders	• Guideline describing the requirements to assess adequacy of mixing and diluting in each attenuation process step through measurement of an analyte/marker (e.g., drug substance, starting material) for powder intermediates in homeopathic manufacturing. • To focus on utilization of grouping or classification of target analyte sharing similar physical and chemical characteristics to minimize the number of validations that might ultimately be necessary. • This should be initially accomplished by reviewing literature for similar approaches within the greater pharmaceutical industry, with an emphasis on review of powder flow literature.	White paper and guideline that defines powder dilution process procedure steps, variables and controls necessary to establish an attenuation manufacturing process within a state of control.

Validation of Dilution Process for Powders

- Homeopathic products are successively attenuated (diluted) many times. Validation of the dilution processes (trituration) is required to assess adequacy of mixing and dilution in the attenuation steps.
- To establish variables and in-process control for intermediate products and describe requirements for validation of powder dilution process (trituration) at a homeopathic manufacturer.
- Guideline to also address applicable analytical testing procedures required to monitor and control the dilutions.
- Limitations in analytical tools for quantitative analysis at very low concentrations (testing of the target solute based on its detection limit).
- The sampling and/or sample analysis adjusted to a statistically appropriate and representative level.

Dosage Form Manufacture – Solid Oral Form

Charters	Overview	Deliverable
Dosage Form Manufacture – Discrete Solid Oral Dosage Forms	• Guideline describing the requirements to assess adequacy of mixing by monitoring the uniformity of active/starting material to appropriate levels in powder blends (BU) and to ensure uniform content of the finished dosage units for solid oral drug products in homeopathic manufacturing. • The bulk hold study and effect of BU when powders are held for periods of time between manufacturing steps. • Guideline to be applicable for homeopathic manufacturing process control utilizing a wide range of equipment used.	White paper and guideline that clearly defines procedures for Blend Uniformity (BU) and Content Uniformity (CU) requirements during manufacturing homeopathic products.

Dosage Form Manufacture – Solid Oral Form

- A guideline to describe the requirements of demonstrating the adequacy of in-process powder mixing in homeopathic solid oral products.
- In homeopathic products the starting material diminishes through many attenuation steps.
- The final product is formulated with extremely low concentration, therefore statistically rigorous sampling and analysis is required to assess the uniformity of the homeopathically-prepared powder blends and the uniformity of content of the finished dosage units based on product safety and risk-assessment.
- Limitations in analytical tools for quantitative analysis at low concentrations, the testing will be limited to intermediates where the analyte can be quantitated.
- The manufacturing process controls and testing requirements in this guideline will be in-line with the guideline for “validation of dilution process for powders”.

Active Pharmaceutical Ingredients

- The manufacturing of homeopathic drug products involves the repeated attenuation with vigorous succussion of active ingredients.
- Receiving, testing and storing a homeopathic intermediate products, the tincture, or the starting material is an important part of overall cGMP practice.
- At this stage, the prevention of mix-ups and control of foreign materials or objectionable micro-organisms needs to be performed to ensure the APIs meet the requirements.
- The first and lowest cost opportunity to turn away non-conforming material is during receipt.

Active Pharmaceutical Ingredients

- FDA's cGMP (21CFR parts 210 and 211) provides a foundation for the requisite quality steps during the entire production phase, including the requirements of 21 CFR 211, Subpart E for all incoming components.
- All processes used for preparing homeopathic drug products must comply with applicable federal regulatory requirements.
- Manufacturers are encouraged to reference 21 CFR parts 210 and 211, as well as FDA guidance documents on Process Validation and Cleaning Process Validation.
- Manufacturers should consult FDA's Q7 Good Manufacturing Practice Guidance for APIs regarding cGMP applicability to APIs. The most recent versions of all CFR, USP and FDA guidance documents must be used.

Active Pharmaceutical Ingredients

- Quality Management
- Personnel
- Buildings and Facilities
- Process Equipment
- Documentation and Records
- Material Management
- Production and In-process Controls
- Packaging and Identification Labelling of APIs and Intermediates
- Storage and Distribution
- Laboratory Control
- Validation
- Change Control
- Rejection and Re-use of Material

ICH harmonisation for better health

Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

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Active Pharmaceutical Ingredients

Raw Materials from
Chemical, Mineral, Botanical, and Zoological Origin

Active Pharmaceutical Ingredients

Raw Material of Chemical Origin

- Includes inorganic or organic chemical products, complex substances of mineral origin.
- The identity, quality and purity of the raw materials of chemical origin used in the manufacture of homeopathic drugs impacts product purity, quality, and safety.
- To ensure raw materials of chemical origin meet established specifications, there are guidelines for the certification:

  Identity and quality testing, retest period and storage of raw materials

Active Pharmaceutical Ingredients

Raw Material of Chemical Origin

- Vendor qualification
- Raw material specification
- Written certification (Certificate of Analysis, Certificate of Manufacture, Certificate of Conformity)
- QC testing
  - Identity test
  - Purity test
- Expiration and retest period
- Storage

Active Pharmaceutical Ingredients

Vendor Qualification

Vendors supplying material to homeopathic manufacturers must be qualified. The homeopathic manufacturer should determine the means of qualification using a risk-based approach (internal procedure/SOP).

- Key issue: supplier vs distributor.
- Knowledge about suppliers, their systems, how they qualify their own suppliers.
- Ongoing review of systems, audits, and inspections.
- Assess the suitability and competence of the other party to carry out the activity or provide the material using a defined supply chain (e.g., audits, material evaluations, qualification).

Active Pharmaceutical Ingredients

Vendor Qualification

Steps:

- Vendor self assessment audit
- On-site audit
- Quality agreement
- Re-audit schedules

Issues:

- Transparency/traceability
- Lack of full knowledge of suppliers/GMPs/GDPs
- Detection concerns

Active Pharmaceutical Ingredients

Raw Material Specification

- Each material to be incorporated in a drug product needs a raw material specification; apply specification if provided by HPUS.
- Based on a facility's experience, it may be appropriate to have requirements above and beyond the HPUS requirements or to have more restrictive acceptance ranges (should be prospectively included in any purchase agreements).
- A specification is the combination of a material's properties (test parameters), the acceptance range for the parameter, and the test methodology.

Active Pharmaceutical Ingredients

Raw Material Specification

One approach to managing the receipt of incoming materials at a site is to establish a receiving specification that includes (or incorporates by reference):

- A list of approved vendors (qualified vendors) for that material.
- Documents to be received with the shipment (e.g., Vendor's Certificate of Analysis (CoA), Safety Data Sheet (SDS), Packing List.)
- Visual checks — may include material-specific information, as well as reference to an SOP for visual inspection of incoming material.
- Storage requirements.
- Sampling requirements (could include the need for aseptic sampling to sterile containers for microbiological testing, as well as quantity requirements for any samples taken such as number of samples, amount per sample, and labeling instructions).
- Reserve sample information (could include the need for aseptic sampling to sterile containers, other container closure information, quantity requirements, and labeling instructions).

Active Pharmaceutical Ingredients

Written Certification

- Each raw material received must minimally meet the specifications established in the HPUS.
- For sites with established vendor certification programs, possibly product release using the vendor supplied CoA and acceptable identity test results.
- For materials received from vendors not or not yet qualified, full specification testing may be required.
- Test results must be reviewed for conformance to the HPUS before the material is released.

Active Pharmaceutical Ingredients

Identity Testing

- Sampling Procedures: The sampling plan and methods for sampling chemical substances should be in writing and should be based on statistically sound sampling practices. Manufacturers are encouraged to reference 21 CFR 211.84 Testing and approval or rejection of components, drug product containers, and closures.
- Statistically sound sampling plans should be established with reference to an acceptable quality level (AQL). Such sampling plans can be established following procedures described in ANSI Standard Z1.4, ISO Std. 2859, and Mil. Std 105E.
- To comply with 21 CFR 211.84 (d) (1), at least one test shall be conducted to verify the identity of each component of a drug product (using specific identity tests).
- The specificity of the identity test is crucial to ensure the material is correctly identified.

Active Pharmaceutical Ingredients

Purity Testing

- Testing to assure conformance with purity requirements as outlined in the specific HPUS monograph, USP, EP or other official compendia.
- If other testing methodologies are used, they need to be validated and conform to established laboratory controls for GMP.

Active Pharmaceutical Ingredients

Residual Solvents

- All residual solvents should be removed to the extent possible to meet product specifications, good manufacturing practices, or other quality-based requirements.
- Reference FDA's Guidance for Industry: Residual Solvents in Drug Products Marketed in the United States (November 2009) and ICH Q3C Maintenance Procedures for the Guidance for Industry Q3C Impurities: Residual Solvents (July 2017).

Active Pharmaceutical Ingredients

Elemental Impurities

- Elemental impurities may arise from several sources (e.g., residual catalysts added intentionally in synthesis, may be present as impurities, through interactions with processing equipment or container/closure systems).
- Reference FDA's Guidance for Industry: "Elemental Impurities in Drug Products", August 2018 (Pharmaceutical Quality/CMC) and USP General Chapters <232> and <233>.
- Recommendations on applying a risk-based approach to control elemental impurities in drug substances, excipients, or drug product and permitted daily exposure (PDE).

Active Pharmaceutical Ingredients

Elemental Impurities

- In general, it is only necessary to test for metals introduced from known and potential sources of elemental impurities (as identified through a risk assessment).
- Manufacturers may choose to test the drug product; a cumulative method may be used to calculate the elemental impurities levels in the drug product from the levels in the ingredients used to produce the drug product.

Active Pharmaceutical Ingredients

Expiration and Retest Period

- If no expiration date is provided, the material should be retested prior to any use, using the most appropriate methods for conformance to HPUS or the homeopathic manufacturer's established specifications.
- Consider the materials properties, packaging, handling, storage, and history of use when retesting is required.
- For example, immutable properties such as elemental impurity content need not be repeated unless the actual container closure systems were not considered as a possible source of elemental impurities.

Active Pharmaceutical Ingredients

Expiration and Retest Period

- Consider situations where the retest data is good, but there has been change from initial.
- For materials routinely used, but no expiration date is provided, establish a long-term stability program for the purpose of assigning an expiration date.
- When appropriate, literature review of that specific chemical's or chemical family's stability may be acceptable to determine an appropriate "use by" or expiration date.

Active Pharmaceutical Ingredients

Raw Material of Botanical Origin:

- Many homeopathic medicinal products are derived from materials of botanical origin, whole plants or specific plant parts such as roots or flowers.
- Marker compounds (such as alkaloids) may be used for characterization (one of many substances that make up the totality of the medicine).
- The identity, quality and purity of the botanical substances used in the manufacture of homeopathic drugs impacts product purity, quality, and safety.
- Guidelines for the collection, cultivation, harvesting, storage conditions, identity and quality testing of these raw materials.

Active Pharmaceutical Ingredients

Raw Material of Botanical Origin:

- Good Cultivation Practices (for cultivated plants)
- Good Collection Practices (for wild-crafted plants)
- Good Harvesting Practices
- Storage/Shipment
- Botanical Verification of Collected Plant Materials
- Sampling/Testing

Active Pharmaceutical Ingredients

Botanical Verification of Collected Plant Materials

- Because the drug substance's active constituents may not be unequivocally identified, the technical challenges for quality control are to determine a botanical drug's identity and ensure its consistency of strength.

Active Pharmaceutical Ingredients

Sampling/Testing

- The specificity of the identity test is crucial to ensuring the material is correctly identified.
- The alkaloids in the plants may vary depending on harvesting time, locations, soil, etc.
- Some test specified in HPUS (such as TLC) may not always be specific enough for identification purpose.

Active Pharmaceutical Ingredients

Aconitum Napellus

- Aconite is a commonly used homeopathic medicine
- Nine subspecies
- HPUS (test method and specifications)

  Starting Material:

  - Macroscopic identification

  Tincture:

  - Characteristics (color, odor, taste)
  - Identification (Test 3: TLC)
  - Alcohol Content
  - Dry Residue
  - Assay (Titration for total alkaloids)

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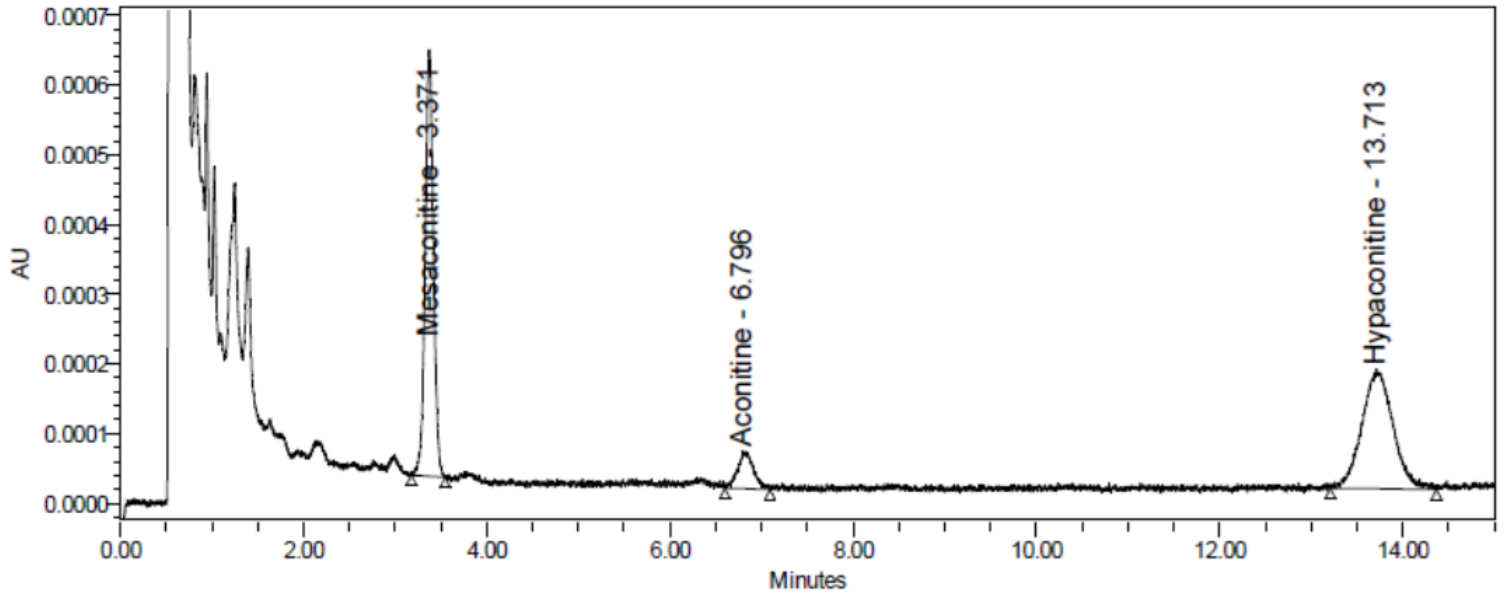
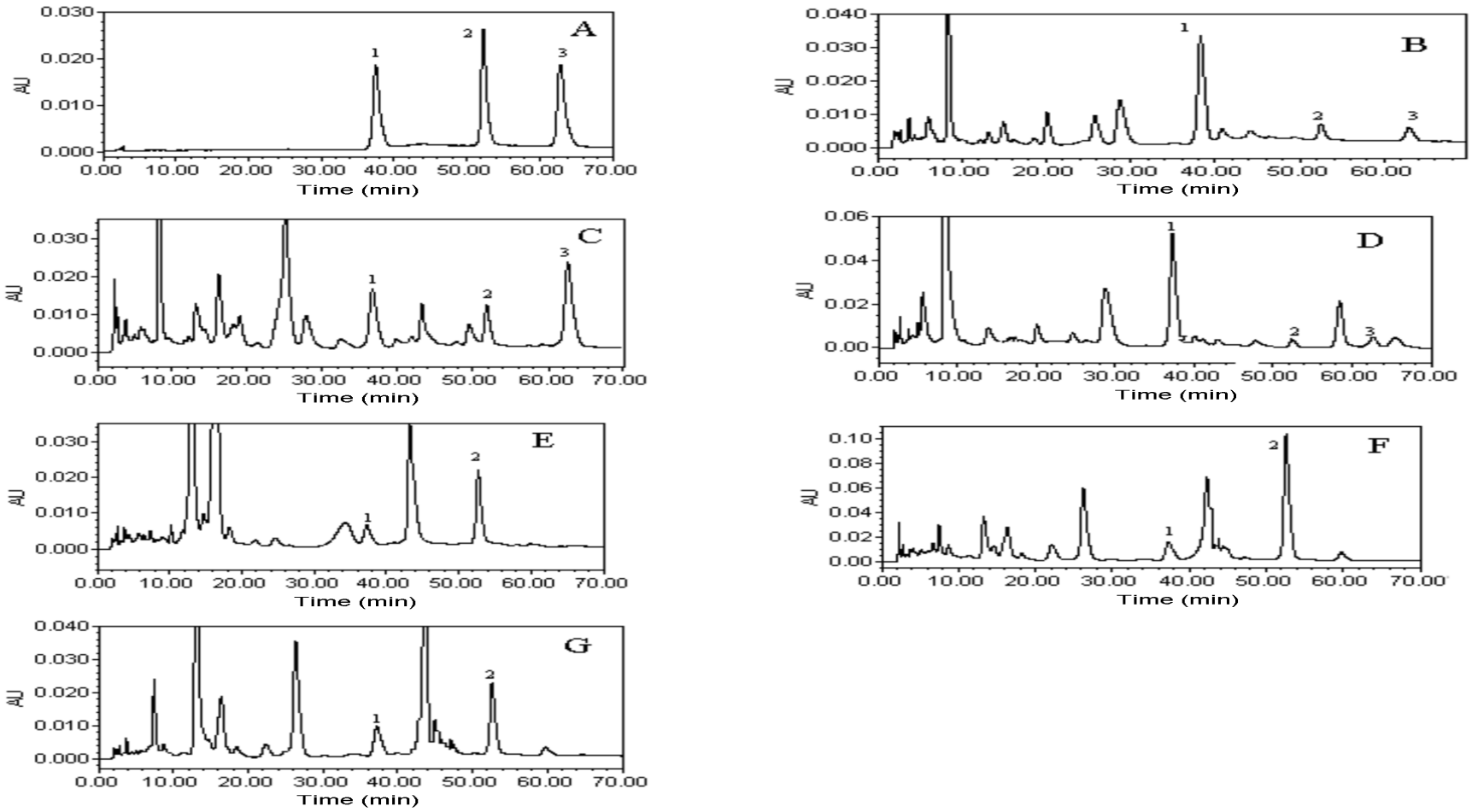
HPLC Chromatogram of Aconitum Napellus

Three alkaloids: Mesaconitine, Aconitine and Hypaconitine



	Peak Name	RT	Area	% Area	Height	USP Plate#	USP Res	USP s/n	USP Tf
1	Mesaconitine	3.371	3857	45.24	612	6674		83.13	1.04
2	Aconitine	6.796	648	7.60	54	7865	14.52	6.36	1.10
3	Hypaconitine	13.713	4020	47.16	170	7351	14.62	22.43	0.95

HPLC Chromatogram of Aconitum



HPLC chromatogram of (A) standard mixture, (B) A. *Kusnezoffii Reichb*., (C) *A. carmichaeli* Debx., (D) *A. taipeicum* Hand-Mazz., (E) *A. pendulum* Bush., (F) *A. szechenyianum* Gay harvested in October, and (G) *A. szechenyianum* Gay harvested in June. Mesaconitine,1; Aconitine, 2; and Hypaconitine, 3.

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Conclusion

Category	Purpose
Active Pharmaceutical Ingredients (API)	Guideline to establish the requirements for receiving, testing and storing the Active Pharmaceutical Ingredients used for manufacturing homeopathic products.
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QUESTIONS