AAHP Summit:
Implementing HPUS Guidelines for FDA Compliance

September 23, 2020

American Association of Homeopathic Pharmacists

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The AAHP Summit: Implementing HPUS Guidelines for FDA Compliance featured:

- **Francis Godwin, MBA,** director, FDA Office of Manufacturing Quality, Office of Compliance;
- **Emily N. Babik, Ph.D.,** vice president, Research & Development, Hyland's Inc., a division of Standard Homeopathic Co.; and
- **Adam W. Grobin, Ph.D.,** independent consultant.

The following slides are a small sampling of the breadth of information provided to attendees. More information is available.

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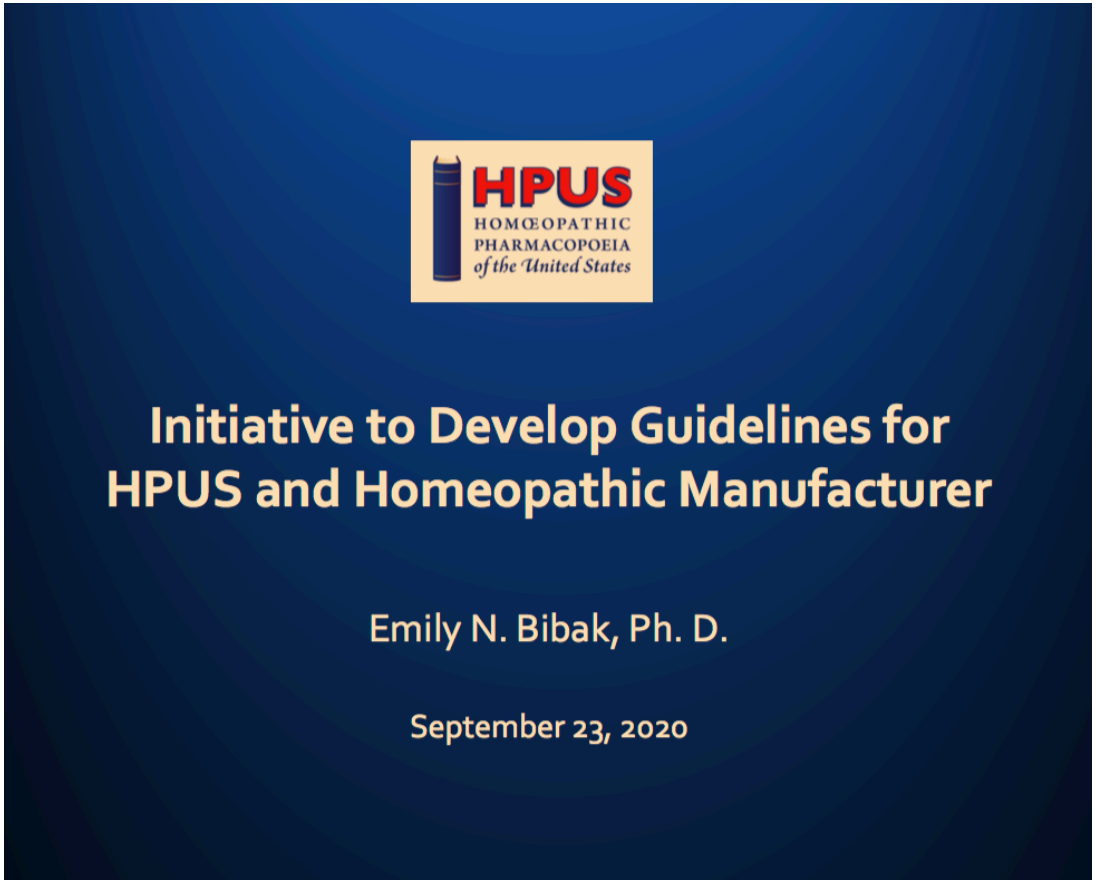
Dr. Bibak

... opened with a brief introduction to the five areas for which the HPUS is developing Guidelines to assist manufacturers and marketers comply with current Good Manufacturing Practice requirements in the Code of Federal Regulations.



APIs

Dr. Bibak continued with an overview of the areas upon which the first guideline document will focus in addressing Active Pharmaceutical Ingredients.

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.

Issues of Concern

As a part of her presentation, Dr. Bibak noted the usual steps in qualifying a vendor to supply an API for a homeopathic drug product. She went on to enumerate a number of issues which can often arise during this qualification process pointing out ones which can seriously impact homeopathic drug products, and why.

Dr. Bibak's talk covered many other steps and issues which are being addressed in the development of the Guidelines.

Active Pharmaceutical Ingredients

Vendor Qualification

Steps:

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

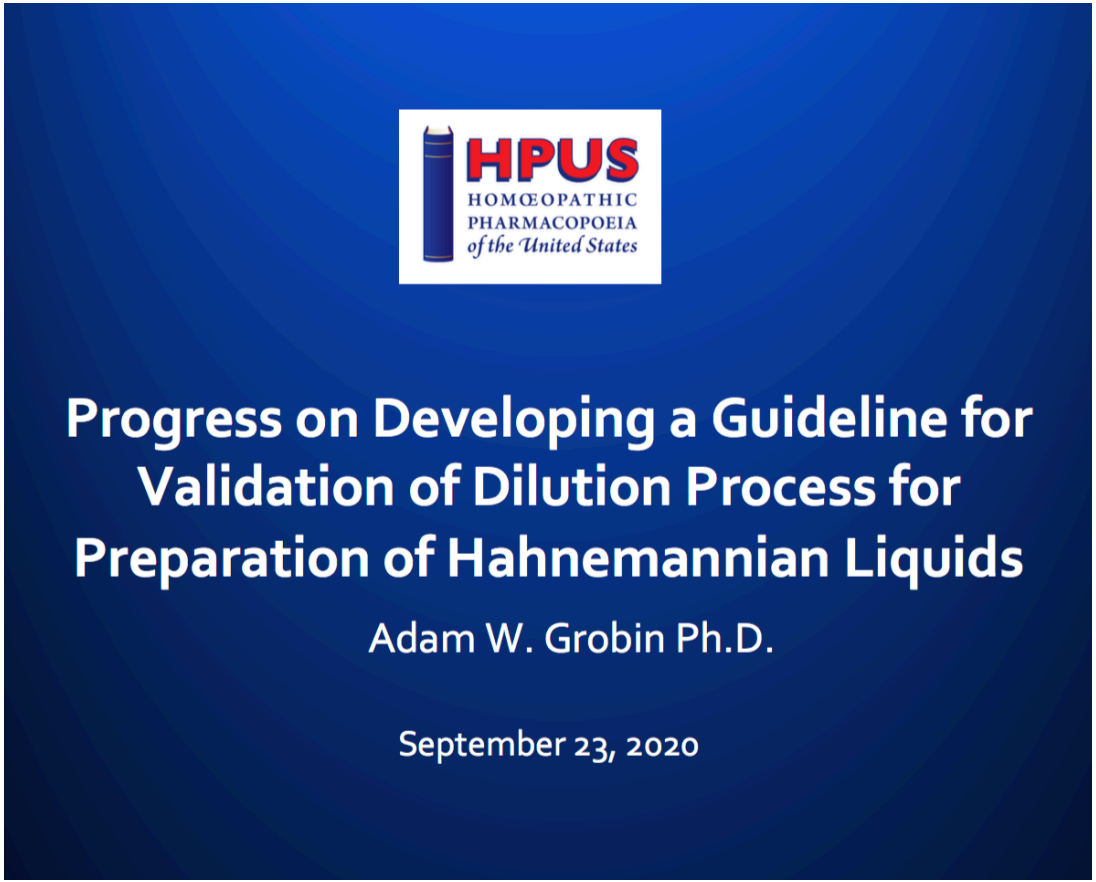
Issues:

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

Dr. Grobin

… provided details on the areas which have been a focus in his development of one of the five Guideline documents.

This will be a Guideline that close to 100% of the industy will be able to make use of as it will addrees the most common manufacturing process used throughout the industry.



Manageable Validation Steps

The majority of HPUS substances are botanical in origin; these widely vary in their constituents and properties. This creates a need to simplify process validation into a manageable approach. The HPCUS has identified two which can have an immediate widespread impact on successful validation efforts throughout the homeopathic industry.

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

Why Class Groupings?

Appropriate and effective validation can be accomplished across many monographed substances due to inherent similarities. These comparable properties can be the basis for simplification.

Justification for the Grouping Approach

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

What to Test?

Technological limits, in conjunction with lowered risks due to the repeated dilution process make test beyond certain attenuations meaningless in assuring safety for consumers.

Dr. Grobin covered many additional and useful facets in his presentation, laying the groundwork for a fuller comprehension of the scope of the planned Guideline.

Justification for the Testing Approach

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

Summit Conclusion

Mr. Godwin of FDA gave the closing presentation and offered a look at the Agency's concerns regarding current Good Manufacturing Practices. He emphasized these apply to all drug products, and spoke of trends and concerns from recent inspections of homeopathic drug facilities.

Mr. Godwin also provided attendees with a heads-up regarding new USP requirements that apply to all manufacturers who make homeopathic drug products that have a liquid phase at some point in the manufacturing process.

Homeopathy's FDA Slice

The number of homeopathic manufacturers seems like a same percentage of FDA's overview responsibility. But, Mr. Godwin noted, the wide range of current Good Manufacturing Practices issues that have been cited is concerning to the Agency; there seems to be little change in the compliance level of the industry as a whole.

List of Citations within Warning Letters with Homeopathic Drugs by FY*

Charge	2017	2018	2019	2020	Grand..
211.84(d)(1) and (2) - Components tested for identity and conformity with specifications.	3	4		2	9
211.100(a) - Validated production and process controls.	3	1	2	2	8
211.22(a) - Responsibilities of quality unit.	1		5		6
211.22(a) and (d) - Responsibilities of quality unit; written procedures.		3	1	2	6
211.192 - Investigations of discrepancies and OOS results.	1		4		5
211.113(b) - Control of microbiological contamination (sterile).		1	2	1	4
211.180(e) - No annual review of records.	1		2		3
211.67(a) - Equipment cleaning and maintenance.			2	1	3
211.165(a) - Failure to test finished products.		1		1	2
211.42(c)(10) - Separate areas to prevent contamination during aseptic processes.			2		2
211.188 - Incomplete batch production and control records.			2		2
211.165(e) - Validation of test methods.			1	1	2
211.110(a) - Adequate and validated procedures for batch uniformity.	2				2
211.84(d)(2) - Components tested for conformity with specifications.	1				1
211.22(a) and (c) - Responsibilities of quality unit.		1			1
211.67(b) - Written procedures for equipment cleaning and maintenance.		1			1
211.82(a) - Examination of untested component labelling.		1			1
211.165(a) and (b) - Failure to test finished products, including for microorganisms.		1			1
211.166(a) - Inadequate stability testing.		1			1
211.100(a) and (b) - Establish and follow procedures for production process control.			1		1
211.165(b) - Failure to test finished products for microorganisms.			1		1
211.22 - Responsibilities of quality unit.			1		1
211.22(c) - Responsibilities of quality unit.			1		1
211.56(a) - Sanitary conditions of building with no vermin.			1		1
211.63 - Equipment design, location, and maintenance.			1		1
211.84(d)(1), (2), and (3) - Components, containers, closures tested for identity and confo..			1		1
211.160(b) - Lack of established lab controls.				1	1
211.28(a) - Lack of appropriate clothing.				1	1
211.42(c)(10)(iv) and (v) - Environmental monitoring for aseptic processes and cleaning/di..				1	1
211.84(d)(1) - Components tested for identity.				1	1
Grand Total	12	15	30	14	71

What Must Industry Learn?

There are key areas of concern that will likely be the focus of inspections and enforcement efforts. It is not only FDA that wants homeopathic products to be safe and effective; our customers also expect those attributes in what they purchase.

Mr. Godwin noted that the HPCUS project's focus areas are positive steps in the right direction for the industry.

Takeaways for Homeopathic Manufacturers

FDA

As with all CGMP case evaluations, product and patient risk are considered, with several recent key takeaways:

- Contractor and Supplier oversight
- Ensuring proper dilutions is paramount
  - Particularly for toxic ingredients
- Oversight of raw material is critical
  - Especially important with emerging concerns regarding ethanol

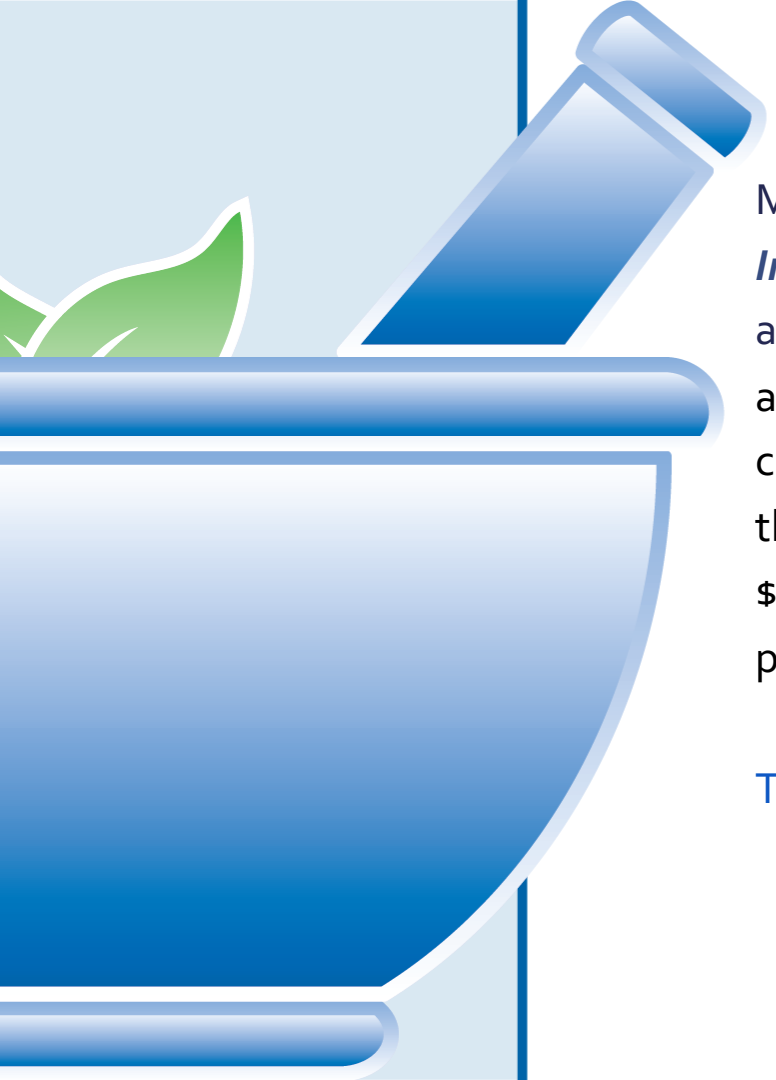
What's Next for AAHP?

As each guideline document is drafted, HPUS will ask AAHP to reach out to members, non-members and regulatory personnel for input and feedback. Your participation will help ensure each guideline is complete, accurate and feasible for implementation.

Be sure to be aware of the process and steps from the beginning (the 2020 AAHP Summit) to make certain you do not miss an essential element or intention.

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

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



More details and information from ***The AAHP Summit: Implementing HPUS Guidelines for FDA Compliance*** are available. A complete video recording of the Summit, along with copies of the three PowerPoint slide decks, can be purchased from the AAHP for $249; the set of three slide decks can be purchased alone for $99. (AAHP members get a $50 discount for either purchase).

To buy now, visit: **theaahp.org/summit2020**

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