Topic 1: Complexities of Setting Compendial Specifications for Excipient Composition and Impurities - Organic Impurities

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The Complexity of Setting Compendial Specifications for Excipient Composition and Impurities[a]

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ABSTRACT

Setting specifications for excipients is complex due to the vast array of materials that are utilized in drug product formulation and is becoming increasingly more complicated with the need to update excipient monographs through the introduction of modern analytical techniques. These techniques provide additional information about the makeup of the excipients and a further understanding of the complexity of the materials utilized in the formulations of drug products. The variety of sources, manufacturing methods, and functionality of excipients must be considered when setting specifications. Strict adherence to guidelines intended for active ingredients when setting specifications for excipients is not always possible, advantageous, or necessary to ensure public safety. It is important to recognize the potential impact of excipients on product formulations and understand that any changes to the excipient specifications could have unintended consequences on effectiveness of drug products or impact the availability of materials needed to manufacture products. The February 2017 FDA–USP Workshop on the *Critical Importance of Excipients in Product Development—Why Excipients are Important Now and In the Future* highlighted the importance of advancing the science of excipient selection and regulatory evaluation that impact generic drug development (*1*). The workshop sought

- Challenges for setting specifications:
  - Complexity of the materials
  - Variety of sources (synthetic, animal, and plant)
  - Variety of manufacturing processes
  - Functionality
  - No general chapters in USP-NF on how to specify excipient composition, including control of impurities

- The *Stimuli* shared:
  - the views of Excipient Expert Committees on the complexity of excipient composition;
  - **definitions** for simple excipient, complex excipient, excipient composition, and excipient impurity;
  - examples of challenges in setting specifications for different components and impurities in excipients;
  - examples of the current principles and approaches in setting specifications for excipient components (case studies and a decision tree).

Purpose of the *Stimuli* article

***Stimuli* Article is**	***Stimuli* Article is not**
One of the tools/platforms: • For sharing views of the Excipient Expert Committees on the complexity of excipient composition and challenges in setting specifications for different components and impurities in excipients • For sharing collective knowledge (principles and approaches for setting specifications) accumulated over the years • For engaging stakeholders in solving complex issues such as excipient composition and impurities by providing constructive comments	A comprehensive and final guidance for setting specification for excipient composition and impurities

Thank You

Overview of guiding principles and approaches for setting specifications for excipient composition and impurities

J Richard Creekmore

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The standard of trust

Session description and objectives

- Why
  - The USP at the request of the FDA embarked on a program to modernize the pharmacopeial testing of excipients due to an increase in the number of instances of adulteration. Many tests were wet chemistry or non-specific or not reliable in their quantitation. With the modernization of the compendial methods for excipients came related challenges in understanding the new information and creating new monographs without jeopardizing the current products using these excipients.
- How
  - Explain the need for use of modern analytical techniques for setting of compendial standards for excipients.
  - Explain how APIs and excipients differ with respect to setting compendial specifications.
  - Describe the Principles and Approaches for setting compendial specifications for excipient composition and impurities

Introduction

Excipients are critical to quality of medicine

- Adulteration of APIs and excipients is a growing problem brought to light by recent events.
- While APIs have captured most of the attention, the potential for adulteration of excipients has been recognized by the FDA and USP.
- A number of excipients have compendial tests that are outdated (e.g., wet chemistry, pass/fail, visual endpoint, simple proxy tests).
- Applying modern analytical techniques leads to increased knowledge about excipients. The challenge is to understand the new information and what this information means.
- Developing compendial standards while helping to ensure quality, but not jeopardizing current drug products patients depend on is a key challenge.

Need for excipient monograph modernization

Risks in the excipients supply chain

- Increase in adulterated excipients, especially imports.
  - Inability to detect adulterated excipients may lead to distrust of vendors, regulatory authorities and pharmacopeias.
- Competition between suppliers is keen which leads to a small number of vendors tempted to use shortcuts to increase profitability from small margins.
- FDA recognized need in 2007 for stricter limits for DEG and EG in Glycerin. Propylene Glycol and sugar polyols were added in 2009 for DEG and EG limits. USP responded with GC methodology for testing.
- In 2010 FDA formed Monograph Modernization Task Group (MMTG) and asked USP to update 19 high priority excipient monographs.
- Key tests that needed improvement were *generally* related to *Identification* and *Assay*.
- Some terms related to APIs may not be appropriate for excipients due to differences between excipients and APIs which can lead to confusion. One example: Impurities

Principles and approaches: definitions of each

We know we want change, but what's our guidance to be successful?

- Principles
  - Fundamental assumptions or rules
- Approaches
  - This is the "how to" part

Principles

	Principle
1	Compliance with USP General Notices, General Chapters, and policies
2	USP-NF excipients permitted for use in FDA regulated drugs are considered safe and fit for intended use
3	Specific lots of excipients that meet the antecedent (old) *USP-NF* specifications will meet the revised (new) specifications
4	Tests/specifications designed to evaluate excipient composition, detect potential adulteration, or prevent mix-ups and substitutions
5	Samples obtained reflect the marketplace where possible
6	Good analytical practices, <1225> Validation of Compendial Procedures, <1226> Verification of Compendial Procedure
7	For simple excipients, 0.1% is a threshold for unknown impurities
8	For complex excipients, the best source on composition and impurities is the excipient manufacturer(s)

Approaches

Order does not reflect priority

	Approaches
1	Excipient performance will not be evaluated for setting specification for composition and impurities
2	Inviting stakeholder engagement
3	Conducting extensive literature search and expert/stakeholder/government liaison consultation
4	Holistic
5	Consistent
6	Statistically driven
7	Replacing titration/pass-fail/non-quantitative tests and tests with safety issues where possible with specific techniques
8	Understanding of differences between antecedent and revised specifications
9	Explaining differences between results for antecedent and revised analytical tests.
10	Orthogonal tests
11	Collaboration with other Pharmacopeias

“Impurities”: How do APIs and excipients differ?

- APIs are generally single, well-characterized substances (biologics are more complex).
- Generally, excipients are more complex and have other components as part of the excipient. What are these other compounds and what is their role in the functioning of the excipient?
- Many excipients have been in use for decades and have a long history of safety. The challenge is to determine what the complexity looks like and knowing many of the excipients have been manufactured and used for decades.
- How does the USP organize the description of excipients? How does the USP describe/differentiate the “impurities” in APIs and excipients?

Terminology for “impurities”: API vs Excipients

APIs <1086> (simplified view)	Excipients PF 44(3) Stim Article
Ordinary Impurities	Nominal component
Related Substances	Minor component
Concomitant component	Concomitant component
Others that are listed in <1086> Impurities in Official Articles	Added substances in official substances
	Excipient impurities
	Others listed in <1086> Impurities in Official Articles

List is not intended to be comprehensive; used for comparison only

Classes of excipients from the *Stimuli* article PF44(3)

We have a lot of excipients; how do we make the list manageable?

- Classifying excipients is helpful in prioritizing which excipients would benefit from method modernization and how to think of them in general terms. Each excipient has its own unique set of challenges. Based on the Principles & Approaches, some excipients may have additional sources to consider that were not previously considered.

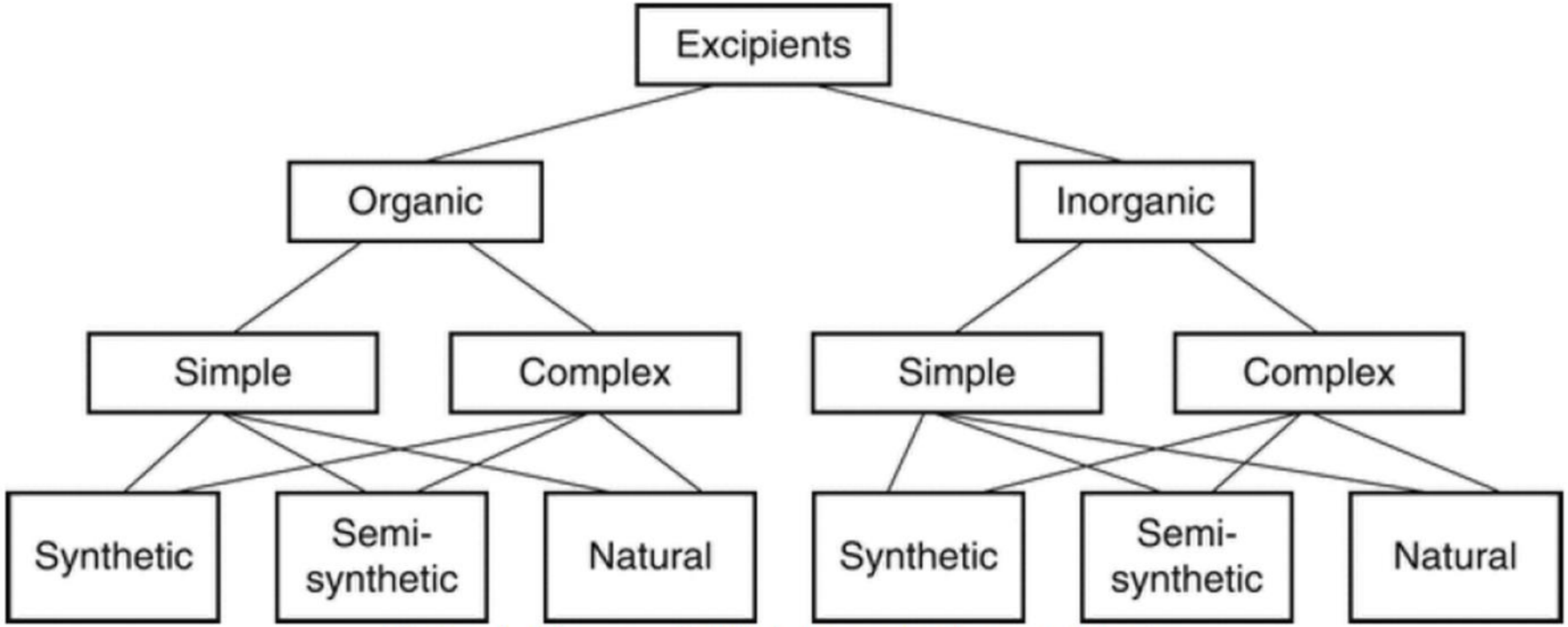

Figure 1. Classes of substances used as excipients.

Case Study 1: Anise Oil & Star Anise Oil

Test/Article	Anise Oil	Anise Oil	Star Anise Oil
USP/NF Edition	USP34-NF29	USP43-NF39 1S	USP43-NF39
Sol in 90% alcohol	1 in 3 parts	1 in 3 parts	1 in 3 parts
Specific Gravity	0.978-0.988	Not Specified	Not Specified
Congealing Temp	NLT 15°	Not Specified	Not Specified
Angular Rotation	-2° - +1°	Not Specified	Not Specified
Refractive Index (20°)	1.553-1.560	1.553–1.560	1.553-1.556
Heavy Metals	NMT 0.004%	Not Specified	Not Specified
Limit of Phenols	No blue or brown color develops with addition of 1 drop Ferric Chloride TS	No blue or brown color develops with addition of 1 drop Ferric Chloride TS	Not Specified
Assay: *trans*-Anethol (GC)	N/A	87%-94%	86%-93%
Impurities: Safrole (GC)	N/A	NMT 0.01%	NMT 0.01%
Impurities: Foeniculin (GC)	N/A	NMT 0.01%	NLT 0.10%
Impurities: Pseudoisoeugenyl 2-methylbutyrate (GC)	N/A	NLT 0.30%	NMT 0.01%
ID	N/A	GC Based	GC Based

Non-specific

Specific
Differentiates 2 similar excipients; eliminates similar toxic material

Case Study 1: Anise Oil & Star Anise Oil

Examples shown; may not include all possible Principles & Approaches

- Principles
  - Adulteration, mix-ups(4): Tests distinguish between at least 3 different botanical sources of anise and detect the presence of toxic Japanese Star Anise
  - Marketplace samples(5): Sampling based on new knowledge to differentiate excipients
- Approaches
  - Literature/expert consultation(3,11): Consulted with EP and other experts along with literature→very similar to EP tests
  - Holistic(4): Complete rethinking of how to set specifications
  - Pass/fail etc.(7): Elimination of tests that were non-specific where possible and tests that are based on characterizing highly variable thermodynamic phenomena
  - Specific(7): New tests use modern techniques capable of distinguishing between 3 similar substances
  - Orthogonality(10): Includes orthogonal tests that are specific and reduce amount of testing

Case Study 2: Butylated Hydroxytoluene

Test/NF Edition		USP34-NF29	USP37-NF32	USP43-NF38
Assay	Method	Not specified	Not specified	HPLC
	Limits	Not specified	Not specified	99.0%–101.5%
Organic Impurity	Method	TLC	TLC	HPLC
	Individual impurity	Any spot from the test solution is not more intense than the corresponding reference spot; NMT 0.5%	Any spot is not more intense than the spot from the *Standard solution* - NMT 0.5%	NMT 0.1%
	Total impurities	Not specified	Not specified	NMT 0.7%
Residue on Ignition	Limits	NMT 0.002%	NMT 0.002%	NMT 0.002%
Congealing Temperature	Specification	NLT 69.2°, corresponding to NLT 99.0% of $C_{15}H_{24}O$	NLT 69.2°, corresponding to NLT 99.0% of $C_{15}H_{24}O$	Not specified
Identification A	Method	Infrared Spectroscopy <197K>	Infrared Spectroscopy <197K>	Infrared Spectroscopy <197K>
	Specification	Matches	Matches	Matches
Identification B	Method	Not specified	Not specified	HPLC
	Acceptance criteria	Not specified	Not specified	Retention time matches standard
Heavy Metals	Limits	NMT 0.001%	NMT 0.001%	Not specified

Case Study 2: Butylated Hydroxytoluene

Examples shown; may not include all possible Principles & Approaches

- Principles
  - Adulteration/mix-ups(4): Removed non-specific tests such as congealing temperature which are based on thermodynamic phenomena with known/unknown interferences
  - Analytical practices(6): Recognition of impurity profile with specifications reflecting this knowledge. Addition of assay.
- Approaches
  - Modern/specific(7): New tests that have higher specificity
  - Orthogonality(10): Better tests that give more specific results that reduce the number of tests needed. Increased efficiency.
  - Holistic(4): Monograph contains less tests that give more information than the previous monographs but easier to run. Improved results but fit for purpose.

Case Study 3: Maleic Acid

Test/NF Edition		USP34/NF29	USP42-NF37 1S	USP43-NF38
Assay	Method	Not Specified	Titration	HPLC
	Limits	Not Specified	99.0-101.0% anhydrous basis	98.5-101.5% anhydrous basis
Organic Impurity	Method	TLC	TLC	HPLC
	Fumaric Acid	NMT 1.5%	NMT 1.5%	NMT 1.0%
	Malic Acid	Not Specified	Not specified	NMT 0.5%
Identification A	Method	pH	pH	pH
	pH of 5% solution	LT 2	LT 2	LT 2
Identification B	Method	TLC	TLC	HPLC
	Specification	Corresponds in color, size, and R_F value to standard	Corresponds in color, size, and R_F value to standard	Retention time matches standard
Identification C	Method	Resorcinol	IR	Not Specified
	Specification	Violet-pink color	Matches	Not Specified

Case Study 3: Maleic Acid

Examples shown; may not include all possible Principles & Approaches

- Principles
  - Literature/expert consultation(3): Initial results for development required consultation with the literature and various experts to understand results and give direction on revising monograph
  - Marketplace(5): Samples from various sources obtained to understand initial results and set specifications
- Approaches
  - Statistically driven(6): Specifications are set using USP statistical procedures especially considering new information about organic impurities
  - Modern/specific(7): Tests are specific and use updated techniques to increase efficiency
  - Understanding differences(8,9): Better understanding of the excipient's Organic Impurities. Impurities always present; just not detected with antecedent methodology
  - Orthogonality(10): Fewer tests that give more information about the excipient than the previous 2 versions shown.

Conclusions

- Need for modernization became apparent as there was an increase in adulterated excipients as reported by FDA.
- APIs are generally well characterized substances while excipients range from simple to complex, organic to inorganic, natural to synthetic.
- PF 44(3) *Stimuli* article explained challenges faced with modernization of procedures in excipient monographs.
- *Stimuli* article proposed simplified classification system for organizing excipients and to prioritize the modernization process.
- *Stimuli* article proposed new terminology to differentiate excipients from APIs as some excipients may have other components that are the nominal component but may aid in the excipient's functionality. Challenges associated with differentiating relevant terms and gaining acceptance.
- *Stimuli* article outlined Principles and Approaches of setting specifications for excipient composition and impurities.

References

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Thank You