

Safety Review of Flavors in Generic Drug Products

SBIA 2021: Advancing Generic Drug Development: Translating Science to Approval
Day 1, Session 2: Considerations in Assessing Generic Drug Products of Oral Dosage Forms

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Learning Objectives

- Define and Describe Flavors in Drug Products
 - Identify regulatory framework
- Describe CDER Pharm/Tox Safety Assessment of Flavors and its Challenges
 - Learn about principles, approaches, and steps taken to navigate complexities
- Review Case Studies

Pharm/Tox Review of Generic Drugs



- OGD Pharm/Tox conducts a comparative safety assessment on consult-basis
 - Do differences between RLD and generic drug impact the safety of the formulation?
 - Is safety profile of generic drug the same as that of the RLD?
 - Risk-benefit assessment considering the specific context of use of the drug product
 - Principles and approaches used are similar to those used by OND Pharm/Tox
- OGD Pharm/Tox is consulted on approximately 10% of ANDAs filed yearly
 - Roughly 25% of these consults are for excipient-related issues (including flavors)
 - Excipients are typically assessed from both Nonclinical and Clinical perspectives
 - Context of use is key, including risk assessment in vulnerable patient populations (e.g., neonates, pregnant women, patients with renal failure)

RLD = Reference Listed Drug
ANDA = Abbreviated New Drug Application
OND = Office of New Drugs

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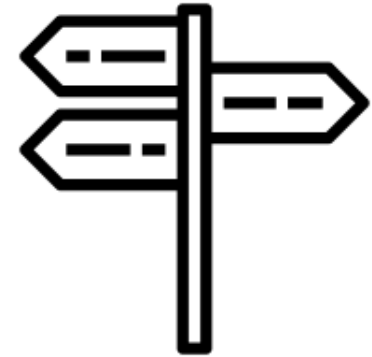
Flavors in Drug Products – Definition



Flavor additives are *excipients* and are reviewed as such

- Ingredients intentionally added to therapeutic and diagnostic products
 - Flavor additives increase palatability of oral formulation (e.g., pediatric formulations, gums, lozenges, orally disintegrating tablets)
- Excipients should not exert therapeutic effects at the intended dosage
- Excipient safety should be demonstrated before marketing of pharmaceuticals

Flavors in Drug Products – Regulatory Framework



21 CFR regulations set standard for flavor additives

- 21 CFR 201.3 defines excipients in drugs
- 21 CFR 314.94(a)(9) defines requirements for excipient safety in generics

“FDA Guidances for Industry” help apply the regulatory framework to our reviews

- *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*; final guidance, May 2005
- *Using the Inactive Ingredient Database*; draft guidance, July 2019
- *Good ANDA Submission Practices*; draft guidance, January 2018
- *Drug Master Files (DMF)*; draft guidance, October 2019

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Flavor Safety Assessment - Principles



- Risk-benefit assessment considering the specific context of use of the drug product
 - Dose, duration of use, patient population, and route of administration
- In *new drugs*, flavor additives are qualified during product development
- In *generics*, flavor safety often relies on prior findings of clinical safety



Flavor Safety Assessment - Principles



Applying prior findings of clinical safety during review

- Reference to IID
 - FDA-approved products containing higher levels of proposed flavor (or individual flavor components)
 - No further justification needed if proposed level is lower than previously approved levels
 - Context of use matters
- Review of published human and nonclinical safety data to justify flavor safety
- All information should support that the generic has a similar safety profile as RLD
- Pre-submission guidance on formulation can be requested via controlled correspondence

Flavor Safety Assessment - Approaches



Safety assessment of a flavor additive *as a whole*

or

Safety assessment of the *individual components* of a flavor additive



- Review approach determined by the following
 - Nature of submitted data (clinical/nonclinical data or safety justification)
 - Prior findings of safety available for the exact proposed flavor additive
- Regardless of approach, same review principles apply, i.e., risk-benefit assessment under specific context of use

Flavor Safety Assessment – Challenges



Challenges in a nutshell...

- Flavor additives are often complex mixtures
- Composition of flavor additives are proprietary
- Identifying FDA-approved amounts of flavor additives (or components) can be challenging
- Criteria used to flag safety issues

...and steps taken to navigate complexities



Flavor Safety Assessment - Challenges



Flavor Additives are Complex Mixtures that consist of numerous compounds

- Example of Composition of 'Pineapple Flavor'

A Pineapple Flavor Composition*	
Allyl hexanoate	Vanillin
Allyl heptanoate	Maltol
Allyl cyclohexanepropionate	Furaneol
Ethyl-3-methylthiopropionate	Ethyl hexanoate
Methyl-3-methylthiopropionate	Ethyl heptanoate
Ethyl butyrate	γ -Valerolactone
Isoamyl acetate	γ -Hexalactone
Isoamyl butyrate	γ -Heptalactone
Ethyl acetate	Acetic acid
Sweet orange oil	Methional
Lemon oil	Pineapple base
Citral	Ethanol
γ -Undecalactone	Propylene glycol
γ -Nonalactone	



Flavor Safety Assessment - Challenges



Flavor Additives are Complex Mixtures

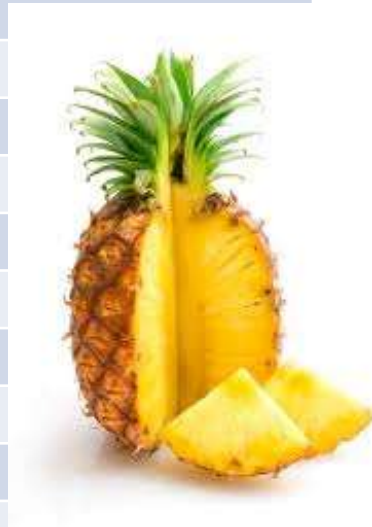
- Flavors consists of numerous compounds...
 - Cumbersome when assessing individual components of flavor agent
 - Pharm/Tox applies safety threshold based on context of use to enhance review efficiency
- ... and no two flavors are alike
 - same name (i.e., pineapple flavor) but different composition (quantitative and qualitative)
 - FDA guidances outline information needed to assess safety of flavor additives

Flavor Safety Assessment - Challenges



Complex Mixture – Pineapple Flavor *versus* Pineapple Flavor

A Pineapple Flavor Composition*	
Allyl hexanoate	Vanillin
Allyl heptanoate	Maltol
Allyl cyclohexanepropionate	Furaneol
Ethyl-3-methylthiopropionate	Ethyl hexanoate
Methyl-3-methylthiopropionate	Ethyl heptanoate
Ethyl butyrate	γ -Valerolactone
Isoamyl acetate	γ -Hexalactone
Isoamyl butyrate	γ -Heptalactone
Ethyl acetate	Acetic acid
Sweet orange oil	Methional
Lemon oil	Pineapple base
Citral	Ethanol
γ -Undecalactone	Propylene glycol
γ -Nonalactone	



Also a Pineapple Flavor Composition**	
Vanillin	
Maltol	
Benzyl alcohol	
Linalool	
Isoamyl butyrate	
Ethyl acetate	
Ethyl butyrate	
Ethyl hexanoate	
Ethyl heptanoate	
Methylthiomethyl octanoate	
Methylthiomethyl heptanoate	
Propylene glycol	



*Composition obtained from G. Zhu and G Yu (2000) A pineapple flavor imitation by the note method;
Food and Science Technology, ahead of print, DOI: <http://dx.doi.org/10.1590/fst.26019>

**Composition obtained from European Patent Application 0007673 (1979)
Flavoring compositions and foodstuffs containing methylthiomethyl ester;
<https://data.epo.org/publication-server/document?iDocId=16839&iFormat=0>

Flavor Safety Assessment – Challenges



**TOP
SECRET**

Proprietary Composition of Flavor Additives

- Commonly made by third party companies
- Quantitative breakdown/composition often not readily available for review
 - Not always submitted up front, may need to be requested during the safety review
 - If present, information may be submitted to FDA under a DMF
- Applicants are not always privy to proprietary information under a DMF
 - Unknown to applicants, flavor additives may contain components that are not safe for the intended patient population
 - Changes in a flavor composition may not be known to the applicant
 - Caution required when communicating with applicants to not reveal proprietary information

→ FDA guidances outline information needed to assess safety of flavor additives

Flavor Safety Assessment – Challenges



Criteria used to flag safety issues

- Sometimes flavor manufacturers provide statements of safety, which are then included in the ANDA or NDA
 - These statements often do not include supportive safety data
 - Without full composition and context specific justification, safety review can be challenging
- Pharm/Tox safety considers context of use and MDE to flavor or flavor components, similarly to how other excipients are evaluated
 - The amount of flavor as a percent of the total formulation (w/w or w/v) is not sufficient to forego a *safety* assessment
 - Depending on context of use, a GRAS statement is not sufficient to forego a *safety* assessment

NDA: New Drug Application
MDE: Maximum Daily Exposure
GRAS: Generally Regarded as Safe

Flavor Safety Assessment – Challenges



FDA-Approved flavors (or components) can be challenging to identify

- Inconsistent reporting of flavor names in FDA-databases (including those populated by flavor manufacturers)
- Comparing generic flavor names is not possible because compositions differ greatly
- Quantitative breakdown of approved flavor additives not listed in FDA-databases

→ OGD Pharm/Tox catalogues details of our prior flavor safety reviews to facilitate data mining for similar review issues




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Case Study 1

Background

- Generic diagnostic product used via oral route in adult and pediatric (> birth) patients
- Proposed use of 'lemon' flavor additive 
 - Unknown to the generic applicant, main component of the flavor is propylene glycol
 - RLD also contains lemon flavor, but of different composition without propylene glycol
- No safety justification submitted
- Safety assessment conducted from Nonclinical and Clinical perspectives

Case Study 1

Safety assessment of individual component 'propylene glycol'

- Non-genotoxic
- No-effect levels from published systemic and developmental nonclinical studies determined large safety margins for the proposed clinical exposure
- Population-specific considerations
 - Metabolized via ADH to lactic acid and subsequently glucose (Krebs cycle): Children (especially neonates) have immature ADH activity
 - Risk for propylene glycol toxicity due to accumulation
 - Hyperosmolarity, metabolic acidosis, hemolysis, renal failure, CNS depression, cardiovascular decompensation

Case Study 1

Safety assessment of individual component 'propylene glycol' contd.

- GRAS listed with 21 CFR reference
 - Substances added to food that are generally recognized, among qualified experts, as safe under the conditions of their intended use
- Search of FDA-databases:
 - At the MDD, propylene glycol intake *did not* exceed FDA-approved levels in adults
 - At the MDD, propylene glycol intake *exceeded* FDA-approved levels in *neonates*

MDD = Maximum Daily Dose

Case Study 1

Conclusion and Recommendation

- Nonclinical data not suitable to inform safe exposure in neonates
 - No prior clinical findings of safety for the proposed levels in neonates
- Data gap and, therefore, safety of the proposed flavor not qualified

... Your proposed flavor contains components that pose an unacceptable safety concern in young infants and neonates for whom your product is labeled. Therefore, we recommend that you reformulate to remove the proposed flavor additive...



Case Study 2

Background

- Generic diagnostic product used via oral *and* rectal route of administration
- Proposed use of ‘cherry’ flavor additive
 - RLD also contains cherry flavor, but of different composition
 - Proposed cherry flavor not present in FDA-approved products
 - Therefore, an assessment of individual components (i.e., 25 components), rather than the flavor as a whole was needed
- No safety justification submitted
- Safety assessment conducted from nonclinical perspective (adult patients only)



Case Study 2

Context driven safety assessment

- Because the product is a diagnostic, the duration of use is acute
 - Allowable exposures (genotoxicity and general toxicity) established based on acute use of the drug product
 - MDE to each of the individual components calculated at the respective MDD
 - Oral and rectal MDDs differed, therefore, conservatively assessed safety of higher MDE
 - Applying safety threshold for acute duration of use decreased number of components needing a safety assessment
- Oral and rectal route → assessment of systemic *and* mucosal safety

Case Study 2

Safety assessment of five individual components exceeding threshold

- Systemic safety
 - No-effect levels from published nonclinical systemic studies determined sufficient safety margins for the proposed clinical exposure
 - MDEs to components *did not* exceed FDA-approved levels in oral products
- Mucosal safety
 - Published data for mucosal safety were not identified
 - Only three components present in FDA-approved products for the rectal route

Case Study 2

Conclusion and Recommendation

- Systemic safety of flavor was successfully qualified
 - No nonclinical data to support mucosal safety
 - No prior clinical findings to support mucosal safety of two components
- Data gap identified and, therefore, safety of the proposed flavor was not qualified

... Your proposed flavor contains components for which local safety could not be justified based on published information or FDA-approved products with similar context of use. Therefore, provide a justification to address local (rectal mucosa) safety of your proposed flavor ...



Challenge Question #1

Flavors do not need to be justified for safety in drug products, since they are used in foods.

A. True

B. False

Challenge Question #2



To support the safety of a flavor in a proposed generic product, an applicant can

- A. Reference FDA-approved products with similar context of use containing the flavor
- B. Submit published clinical and nonclinical information for this flavor
- C. Submit published clinical and nonclinical information for the individual components of this flavor (if composition is known to applicant)
- D. All of the above



Summary and Conclusion

- Flavors are excipients and are reviewed by OGD Pharm/Tox like other excipients
 - CFR regulations set standard for flavors; FDA guidances recommend how requirements can be met
 - Comparative safety review to the RLD
 - Safety review of flavors is a risk-benefit evaluation considering context of use
 - Depending on the context of use, flavor safety is reviewed by nonclinical and clinical discipline
- Safety review of flavors poses many challenges
- OGD Pharm/Tox actively takes steps to navigate complexities with flavor reviews
 - Contributed to FDA guidance describing the information needed for comprehensive review
 - Ongoing OGD internal cataloguing to leverage prior review efforts
 - Collaborate with CDER colleagues to harmonize review approaches used for flavors

Resources

- Final Guidance for Industry “*Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*” (May 2005)
<https://www.fda.gov/media/72260/download>
- Draft Guidance for Industry “*Using the Inactive Ingredient Database*” (July 2019)
<https://www.fda.gov/media/128687/download>
- Draft Guidance for Industry “*Good ANDA Submission Practices*” (January 2018)
<https://www.fda.gov/media/110689/download>
- Draft Guidance for Industry “*Drug Master Files*” (October 2019)
<https://www.fda.gov/media/131861/download>

Thanks Goes To...

- YOU, for your attention
- OGD Pharm/Tox Supervisors, Sruthi King and Robert Dorsam
- OGD/DPTR

