How to Leverage the Inactive Ingredient Database and Justify Excipient Safety in ANDAs

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Disclaimer

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Overview: Part 1

- IID introduction & use
- Limitations of IID
- IID mailbox and contact information

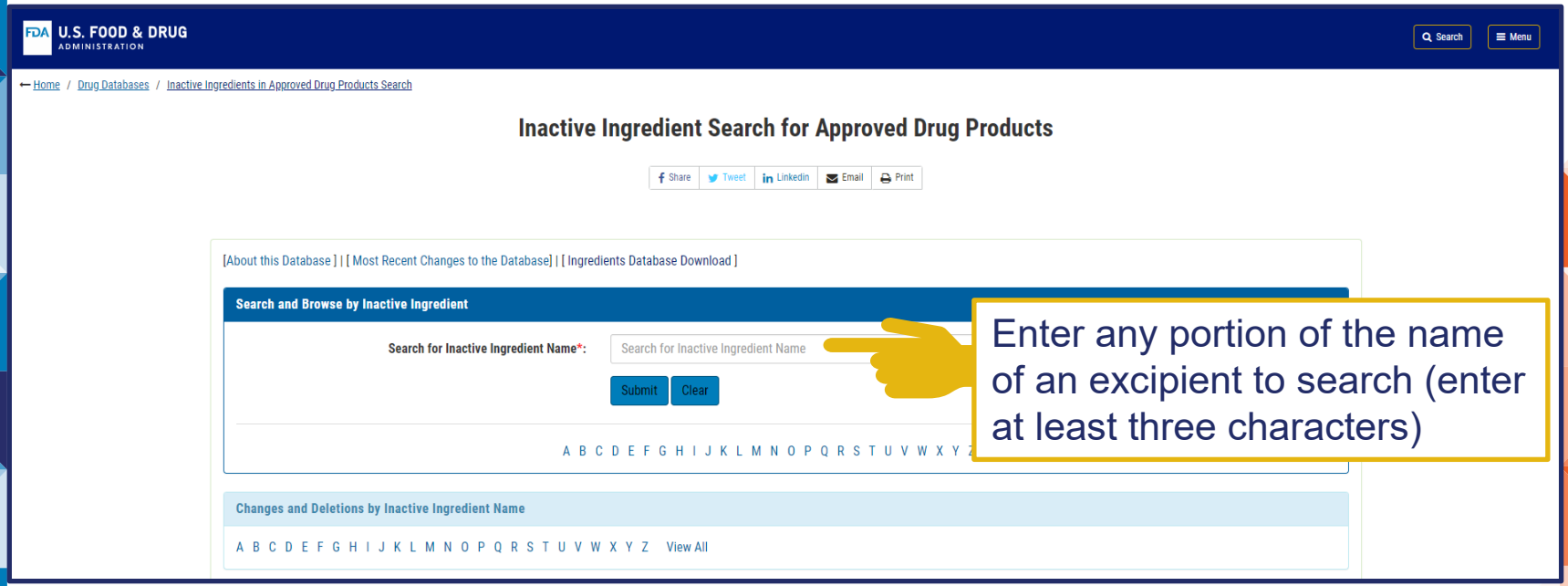
What is the IID & How to Use It

- IID provides information on excipients present in FDA-approved drug products.*
- IID includes excipients in approved Abbreviated New Drug Applications (ANDAs) and New Drug Applications (NDAs). Excipients in approved Biologics License Applications (BLAs) or Over the Counter (OTC) Monograph products are not included in the IID.*
- If an excipient is used in approved drug products for a particular route of administration, the excipient generally is not considered new and may warrant less extensive review the next time it is included in a new drug product.*
- Can be accessed at:

Inactive Ingredient Search for Approved Drug Products

*Using the Inactive Ingredient Database Guidance for Industry | FDA

How to Use the IID



[Inactive Ingredient Search for Approved Drug Products (fda.gov)]

[fda.gov/cdersbia]

How to Use the IID (cont.)

Inactive Ingredient	Route	Dosage Form	CAS Number	UNII	Maximum Potency per unit dose	Maximum Daily Exposure (MDE)	Record Updated
ACACIA	ORAL	CAPSULE, EXTENDED RELEASE	9000015	5C5403N26O		64mg	Y
ACACIA	ORAL	LOZENGE	9000015	5C5403N26O		108mg	
ACACIA	ORAL	POWDER	9000015	5C5403N26O	800mg		

Displays one row per unique Inactive Ingredient – Route of Administration – Dosage Form combination

CAS = Chemical Service Abstracts Registry Number
UNII = Unique Ingredient Identifier assigned by FDA's Global Substance Registration System (GSRS)

Flag for new records

Limitations of the IID*

- The IID does not currently provide information regarding the different exposure models (e.g., maximum daily intake based on the dosing recommendations indicated in the labeling, safety in pediatric populations, acute versus chronic use) that may be needed during such a technical review.
- The inclusion of an excipient at a level described in the IID does not necessarily satisfy the requirements in FDA regulations with respect to maximum allowable limits for specific categories of products.

*Using the Inactive Ingredient Database Guidance for Industry | FDA

IID Mailbox and Contact Information

Contact Information

- Questions and concerns about IID entries, send to IIDUpdate@fda.hhs.gov
- Nomenclature corrections, questions about excipient names, and UNII requests, send to FDA-SRS@fda.hhs.gov
- Application-specific questions related to the use of excipients in generic products under development should be submitted through the Controlled Correspondence pathway (https://www.fda.gov/media/164111/download)

Questions to the IID Mailbox

Ask us! We want to hear from you!

- ✓ Questions about changes in the IID listings and error reporting
- ✓ Requests for clarification of units or excipient names
- ✓ Questions should not be application-specific

We won't be able to provide an answer to…

- × Questions that may disclose proprietary information, e.g.,
  - × What NDA/ANDA a specific record belongs to
  - × Reference listed drug formulation
- × Acceptability of proposed excipient levels

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Overview: Part 2

- Introduction
- Safety Justifications: When, Why, What
- Case Studies
  - Using the IID and addressing safety gaps
  - Excipient bridging argument as a safety justification
- Summary

Introduction

- Excipients are inactive ingredients intentionally added to drug products that are not intended to exert therapeutic effects at the intended dosage
- Excipients can differ quantitively and qualitatively between generics and their reference listed drug (RLD)*

  *exceptions are products for parenteral, ophthalmic, or otic use
- Generic drug applicants must:
  - Identify and characterize differences in excipients compared to RLD
  - Provide information to demonstrate that these differences do not affect the safety and efficacy of the proposed drug product

Safety Review of Excipients

- Approaches for assessing safety of excipients:
  - Evidence of safe use in humans including levels in FDA-approved drug products with similar context of use (i.e., dose, route, duration of use, and patient population)
    - IID is a tool to determine prior use of excipient at specified level for a particular route of administration
  - Relevant toxicological information (i.e., genotoxicity, general toxicity, reproductive/developmental toxicity, carcinogenicity, etc.) to support the safety of the excipient at the proposed level, considering the context of use of the proposed drug product

Safety Justifications: When, Why, What

- A common misconception: the proposed maximum daily exposure (MDE) level is justified just because it does not exceed the IID listing for the proposed route
  - Actually, an excipient in the IID has a specific context of use that might not match your proposed use in an ANDA
  - An excipient may exacerbate a disease state and/or alter the safety profile if used long term, or if used in a pediatric population
    - Excipient safety for chronic use may be addressed by assessing chronic/subchronic toxicity and carcinogenicity
    - Excipient safety for pediatric use may be addressed by assessing developmental/reproductive toxicity

Safety Justifications: When, Why, What

- An applicant may wish to use an excipient that is found in the IID, but at a higher MDE than the IID listing.
  - Prior evidence of safe use is considered as part of the weight of evidence, but additional justification is needed
  - "Dose makes the poison": margins of exposure are considered
    - Relevant repeated dose toxicity information that characterizes any safety signal and target organs of toxicity
    - Justification should address whether prior use of excipient and available toxicity information support that the safety of the generic is the same when compared to that of the RLD

Safety Justifications: When, Why, What

- An applicant may attempt to leverage information for a polymer using related grades on the IID.
  - Large polymers that differ from other characterized excipients only in molecular weight (MW), chain length, viscosity, etc., may **BRIDGE SAFETY** with similar polymeric excipients
  - Bridging considerations will evaluate safety of different grades:
    - ❖ What are the specific differences between proposed grade and grade used in previously approved products (physicochemical properties, function, and manufacturing process)?
    - ❖ Can the toxicological profile be extrapolated to this grade based on what is known about other grades?

Safety Justifications: When, Why, What

- An applicant should provide justification if a flavoring agent is not found in the IID.
  - Safety of individual ingredients should be qualified with respect to genotoxicity and general toxicity, considering the context of use of the proposed drug product
    - ❖ Quantitative breakdown of mixture of inactive ingredients with CAS numbers and applicable CFR citations

    OR

    - ❖ Statement of right to reference the drug master file (DMF) of the flavor from the flavor manufacturer to allow for composition and safety assessment

Safety Data Gaps

- If OGD identifies a data gap during safety review of excipients:
  - Non-clinical information may be requested if it addresses the data gap
  - If a gap in safety data remains that warrants additional clinical studies or needs an extensive battery of safety studies, then applicant will be advised to either reformulate or pursue a 505(b)(2) application

Case Study #1

- Product: Oral product, chronic use for pediatric and adult populations, MDE for excipient is 200 mg/day for pediatrics and adults

Route	Dosage	Daily Exposure (MDE)
ORAL	CAPSULI	
ORAL	CONCEN	
ORAL	LIQUID	
ORAL	SOLUTIO	640mg #1
ORAL	SUSPENS	40mg
ORAL	SUSPENS	100mg #2
ORAL	SYRUP	80mg #3

	IID	Context of Use	
	MDE	Duration of use	Patient population
1	640 mg	Acute use	Adult
2	100 mg	Chronic use	Adult
3	80 mg	Similar context use	Adult 80 mg/day Pediatric 40 mg/day

- 1st review cycle:
  - Applicant proposed MDE 640 mg, but does not address safety in pediatrics for a chronic duration of use
  - FDA's recommendation: Deficiency; reduce levels of the excipient; justify the safety gaps, which are: 1) duration of use, and 2) patient populations

Case Study #1 – continued

- Applicant submitted a Controlled Correspondence

  Q: Are acceptable MDEs 80 mg, 100 mg, or 150 mg for both adults and pediatrics?

	IID	Context of Use	
	MDE	Duration of use	Patient population
1	640 mg	Acute use	Adult
2	100 mg	Chronic use	Adult
3	80 mg	Similar context use	Adult 80 mg Pediatric 40 mg

- *#3 covers patient population, but… does not cover the MDE in pediatric patients*
- *FDA input: if you pursue 80 mg, provide justification to support pediatric safety*

- 2nd review cycle: ANDA proposed MDE 80 mg with justification
  - Developmental toxicity study from the literature was submitted
  - Upon review, developmental study provides sufficient margin of safety
  - The formulation was then determined to be adequate for use in the proposed patient populations. Acceptable

Case Study #2

- Product: Oral solution, chronic use in adults; polymer grade 2000 at MDE of 250 mg (RLD uses polymer grade 1000)

Inactive Ingredient	Route	Dosage Form	CAS Number	UNII	Maximum Potency per unit dose	Maximum Daily Exposure (MDE)
Polymer grade 200	ORAL	SOLUTION	691397134	LQA7B6G8JG		1800mg
Polymer grade 200	ORAL	GRANULE, FOR SOLUTION	691397134	LQA7B6G8JG		624mg
Polymer grade 500	ORAL	TABLET	691397134	TUF2IVW3M2		495mg
Polymer grade 1000	ORAL	SUSPENSION	691397134	1S66E28KXA	0.09mg/1ml	
Polymer grade 3000	ORAL	POWDER, FOR SOLUTION	691397134	IS93EQR73R	1000mg/5ml	

- 1st review cycle:

Similar grades have been exposed to patients chronically

  - Justification: Information on polymer grade 2000 (molecular weight, chain length, viscosity, etc.) and impurity specification
  - Safety gap: same family/different grade excipient

Case Study #2 – continued

- How did FDA evaluate the excipient?
  - Confirmed similarities between proposed grade and grades with known safety information
  - Conducted literature review related to same family of polymer
- Toxicology data
  - Considered general toxicity information by the oral route of a related polymer
  - Correlated degree of absorption from oral exposure to MW of polymer
  - Considered similarity in impurity profiles of excipients
- Weight of evidence approach: Similar grades have been exposed to patients chronically, and toxicology data show low safety concern at the proposed level. Acceptable

Summary

- The IID can be leveraged as justification if an excipient was previously used in a similar context of use (i.e., dose, route, duration of use, and patient population)
- Pharm/Tox assesses excipient safety when there are potential gaps in information:
  - Differences in dose, duration of use, patient population, route of administration
  - Key question: Does this difference result in a different safety profile from the RLD?

Call to Action

- Applicants should provide information that characterizes their excipient and supports its safety for the proposed context of use
  - Quality submissions and gaining advice via Controlled Correspondences are ways to facilitate review and reduce review cycles

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Resources

- Inactive Ingredient Search for Approved Drug Products
- Quarterly Inactive Ingredient Database (IID) Change Log | FDA
- Using the Inactive Ingredient Database Guidance for Industry | FDA
- ANDA submission-Refuse-to-Receive standards: Questions and Answers Guidance for Industry,Q25-26
- Guidance for Industry Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients
- Guidance for Industry Good ANDA Submission Practices, section B3 inactive ingredients

Let the Q&A Panel begin!