Building a Global Framework for Assessing Inactive Ingredients in Generic Drug Applications

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Disclaimer

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Overview

- Background
- Polling fellow Cluster participants
- Case Studies and Considerations
- Discussion

Background

Inactive Ingredient Evaluation

- Assures the safety of inactive ingredients within drug products.
- Evaluation occurs during review of:
  - Inactive Ingredient Controlled Correspondences (CCs)
  - Abbreviated New Drug Applications (ANDAs)
- Evaluation in all populations the drug is indicated for (i.e., adult and pediatric).
- Maximum daily exposure (MDE) for inactive ingredients calculated utilizing the maximum daily dose (MDD) from the reference listed drug (RLD) label.
- MDE for proposed inactive ingredient compared to amounts for the same inactive ingredient in approved NDAs or ANDAs.
- Applicants may submit clinical or toxicological data to use as justification for a proposed inactive ingredient MDE in an ANDA submission.

Inactive Ingredient Evaluation Continued

- What are the practices for other regulatory jurisdictions?
- Are there commonalities or areas for alignment?

Polling Fellow Cluster Members

Generic Drug Cluster

- Comprised of membership from:
  - US FDA
  - Health Canada
  - European Medicines Agency (EMA)
  - Ministry of Health (Israel)
  - Medicines and Healthcare products Regulatory Agency (UK)
  - Swissmedic (Switzerland)
  - Therapeutic Goods Administration (Australia)
- Provides a forum to foster scientific alignment between generic drug regulatory agencies.

Polling

- Sought to understand inactive ingredient evaluation practices of fellow regulatory jurisdictions within the Cluster.
- Seven questions sent to Cluster members for their responses.

Question 1: Does your Agency assess the safety of inactive ingredients in a generic formulation? If yes, how do you perform safety assessment?

Agency A	Assess the safety of inactive ingredients the same way as the reference product.
Agency B	Evaluates inactive ingredients especially for pediatric patients.
Agency C	Only assess new inactive ingredients or inactive ingredients used in the pediatric population. Clinical data are available to inform on other risks. Assessment is based on provided data for new inactive ingredients or compliance to published thresholds for the pediatric population.
Agency D	Reviews novel inactive ingredients. Novel including inactive ingredients used for the first time, at a greater daily exposure than what is normally administered, or new route of administration. Utilizes literature and available databases. May review supporting safety data (nonclinical/or clinical) for justification.
Agency E	Evaluation for inactive ingredients that are novel, given via novel route, the human dose is increased, or the administered strength (for a non-oral product) is increased. Sponsor provided information and data currently held by Agency.
Agency F	The quality assessor always considers the safety of the excipients and if any uncertainties (e.g. new, or unusual excipients) the non clinic assessor is consulted. We check monographs, food legislation, reliable published data.
US FDA	We assess all inactive ingredients within a generic formulation.. If amounts exceed what is accepted for the Agency or the inactive ingredient is found to be novel (not in approved product or an in approved product for the same route of administration); the applicant may submit literature, clinical data, toxicological data, etc. for review by our Office of Safety and Clinical Evaluation.

Key Takeaway

Each regulatory jurisdiction evaluates the safety of inactive ingredients for a test product, but approach varies.

What type of data does your Agency rely on during your assessment of safety?
Do you maintain a database or list of inactive ingredients which are unacceptable in your jurisdiction?

Agency A	Rely on databases maintained by other jurisdictions.
Agency B	Does not maintain a database for inactive ingredients and accepted levels. Inactive ingredients are considered on a case-by-case basis. Nothing is banned. Complete formulations of all drug products are recorded within a database.
Agency C	Does not maintain a database. Does not maintain a database for excipients that the Agency would consider unacceptable in your jurisdiction but may be allowed in other countries.
Agency D	Consultation would be sent to clinical division. Rely on its database and that of another Agency.
Agency E	Nonclinical studies, published literature, and safety reviews from other Agencies are used. Do not maintain a database of accepted levels for inactive ingredients for prescription drug products.
Agency F	The quality assessors assess the safety of the excipients based on already approved drug products containing the excipients, the amounts in relation to the route of administration, dosage regimen, duration and exposure in relation to age of the patient. Maintains database. There is no specific list of unacceptable excipients allowed in other jurisdictions.
US FDA	We maintain the publicly available Inactive Ingredient Database which contains accepted levels for inactive ingredients per unit of an approved drug product and per maximum daily intake for that drug product. Our Code of Federal Regulations contains inactive ingredients that have general safety concerns.

Key Takeaway

A few regulatory jurisdictions maintain databases for acceptable levels of inactive ingredients or have a list of inactive ingredients which are banned.

Do you evaluate the MDE of each inactive ingredient based on the MDD of the drug product? If not, what is your approach? How do you assess MDDs and if not specified in the RLD label do you rely on a standard weight or BSA?

Agency A	Qualitative and quantitative composition of generic product should comply with the composition of the reference product and any deviation should be justified.
Agency B	The MDD in the label for the drug product is considered or worst-case scenario (e.g., youngest child for which the drug is indicated). For eye drops the volume of the drop and the conjunctival sac are considered. There are challenges with topical ointments and cream, however 100 % absorption of inactive ingredient is considered initially to determined if any potential problems arise. No standard weight is used.
Agency C	For adults a general weight of 50 kg. Refer to WHO charts for pediatric population.
Agency D	Maximum daily exposure is considered for inactive ingredients. If the amount is greater than what is normally delivered , the safety should be supported and reviewed. The MDD would be based on a product monograph, A standard weight of 50 kg is utilized. The clinical assessor evaluates safety data studies or data in literature to determine the permitted daily exposure in humans. A weight of 50 kg is used for an adult.
Agency E	If non-clinical safety assessment is considered necessary MDD is evaluated based on label and if based on weight estimation is made by using information from for example WHO on age, weight and length. When dosing is by BSA (mg/m2) conversion to mg/kg to calculate MDD is done by dividing BSA dose by a mass constant (km). Special care is taken for products with a pediatric indication.
Agency F	Intake of an inactive ingredient is calculated with respect to MDD in label. If no MDD is identified, maximum clinical doses are identified from clinical trials. Where local assessment is required, it is based on strength rather dose. A 50 kg weight is assumed where mg doses are specified in the label (to yield highest expected amount) and 70 kg is used where doses are mg/kg or mg/m^2 (for a typical adult).
US FDA	MDE of a drug product based on MDD of the drug product as specified in the RLD label. For drug products that do not specify an MDD or the MDD is unclear we may consult the Office of Safety and Clinical Evaluation. A weight of 60 kg is used if not specified in the drug product label. For drug products administered based on body surface area (mg/m^2) a standardized average body surface area is used. Body weights for children are taken from 95th percentile for boys CDC growth charts unless.

Key Takeaway

- For most regulatory jurisdictions MDD is determined from the RLD label.
- If a weight is not specified in the RLD for dosing dependent on weight, some jurisdictions utilize 50 or 70 kg for adults.

Do you differentiate between different grades for an inactive ingredient for a solid oral dosage form or do you leverage data from various grades of the same inactive ingredient?

Agency A	At times may differentiate between various grades when it is deemed relevant.
Agency B	Grade is not usually stated in product information. Grade is usually recorded in regulatory information.
Agency C	No unless there is a reason to do so (e.g., particle size).
Agency D	When considering if an inactive ingredient is novel, different grades are not generally considered unless there is literature that states otherwise.
Agency E	Considered only in safety assessment where impurities are recognized to contribute to toxicity of an inactive ingredient.
Agency F	This may be done on a case-by-case basis.
US FDA	Considers different grades of inactive ingredients. Justifications can be made by leveraging data for various grades present in the same inactive ingredient group.

Key Takeaway

Most regulatory jurisdictions evaluate difference in grades for inactive ingredients on a case-by-case basis.

Do you consider the context of use for the drug product in which the inactive ingredient is present (i.e., population, duration of use, or route of administration)?

Agency A	Considered in specific cases (e.g., use of alcohol in formulation indicated for pediatric population).
Agency B	Case-by-case basis considering risk versus benefit.
Agency C	Only assess new inactive ingredients or inactive ingredients used in the pediatric population. Clinical data are available to inform on other risks. Assessment is based on provided data for new inactive ingredients or compliance to published thresholds for the pediatric population.
Agency D	• Will consider if the data submitted is sufficient to characterize safe use in the intended population, and according to the duration of use and route of administration of the drug (and inactive excipients). Particularly for pediatric formulations, the clinical division will additionally assess excipients as per what is presented in ICH guideline E11 (Clinical Investigations of medicinal products in the pediatric population). Duration of use: Yes, it is considered.
Agency E	Considered as needed. Acceptable levels can vary or be justified from duration, indication, etc. For excipients exhibiting low toxicity, acceptable levels will generally show widespread applicability and continue to be acceptable in more sensitive groups
Agency F	The context of use is considered with respect to patient population and route of exposure and in some cases also rate of administration. Pediatric population is always considered. Duration of treatment can also be considered in some cases.
US FDA	We consider context of use when evaluating inactive ingredients. We evaluate all inactive ingredients in pediatric or renally impaired population. Duration of use is also considered in drug products indicated for the pediatric population. We also justify inactive ingredient amounts based on the same route of administration as exposure may vary greatly..

Key Takeaway

Most regulatory jurisdictions considered context of use on a case-by-case basis.

- Special attention given to pediatric population.

How do you assess safety of flavoring agents and colorants?

Agency A	Flavoring agents and colorants should comply with internationally accepted purity criteria in food use.
Agency B	Flavorings must comply with food legislation. There is no regulatory requirement to label natural ingredients in medicines). Colors –the same colors as used in foods can be used in medicines.
Agency C	Consider the national food regulations for flavoring agents and colorants and take published thresholds into consideration.
Agency D	Coloring agents must be in accordance with Food and Drug Regulations, The full list of components should be provided including the qualitative & quantitative formulation. Interactions between the excipients and/or the API would be assessed (e.g., degradation products). Compatibility studies would be considered. Otherwise, no other special considerations.
Agency E	If it is a new flavor or coloring agent, assessment will be through submitted nonclinical data, or acceptability by reference to approval for use in food. Special consideration will be given to sub-excipients depending on dose (rather than mere presence).
Agency F	Flavoring agents should comply with food legislation and where applicable the exposure of any excipient with known safety concerns are evaluated. There are special considerations for components with known safety concerns, specific considerations for youngest age groups.
US FDA	The established use for color additives can be found in Title 21 Code of Federal Regulations Sections 70 through 82. In general, we evaluate flavors as a whole by utilizing amounts present in other approved products for the same context of use. However, if the flavor is determined to be novel, then the individual components of the flavor are taken into consideration. All inactive ingredients such as benzyl alcohol or propylene glycol may need further justification for use in the flavor if it is contained in a drug product indicated for the pediatric population.

Key Takeaway

- Some regulatory jurisdictions state that flavorings and coloring agents must comply with criteria in their jurisdiction for food. Others have separate regulations for coloring agents.
- Subcomponents may be given special consideration if there are known safety concerns.

Do you maintain a list of inactive ingredients that may need a warning statement in the label (e.g., tartrazine)?

Agency A	Does not maintain such a list.
Agency B	Follows national guidance.
Agency C	Yes. “Pharmaceutical excipients of particular interest”.
Agency D	There is no list. However, as part of the label review, we consider the following non-medicinal ingredients for safety reasons and internal consultation are done to determine if a warning statement is recommended for the label: Aspartame, benzyl alcohol, lactose, sucrose, latex, peanut oil, sepitrap 80 (polysorbate 80 and magnesium aluminometasilicate)
Agency E	Yes, if certain ingredients are present they are required to be declared on a medicine’s label. This includes sulfates and benzoates. This list also contains certain restrictions and labelling requirements (e.g., tartrazine).
Agency F	Yes, there is a list. In addition, there are databases or specially compiled lists that include excipients that may need a warning statement in the label.
US FDA	A list of inactive ingredients needing warning statements in the label are contained in Title 21 Code of Federal Regulations Section 201 (e.g., metabisulfite and tartrazine).

Key Takeaway

Some jurisdictions do not maintain a list of inactive ingredients that may need a warning statement. Others consult internal guidelines or regulations.

Case Studies and Considerations

Case Study I:

Evaluation all Inactive Ingredients in Drug Products

- ANDA submitted for “Drug A” Delayed-release Capsules
- Consult sent to Office of Safety and Clinical Evaluation for evaluation of proposed level for ***talc***.
  - Proposed level was higher than maximum approved level.
- Talc is generally recognized as safe (GRAS) as a food additive.
- Conversely talc is not absorbed in the GI tract which may worsen GI adverse events associated with therapy for this drug product.
- Adequate information could not be identified to justify lifelong use at the proposed levels in adults and children.
- Amount of talc was determined to be unacceptable.

Case Study II:

Evaluating Different Grades of Inactive Ingredients

- ANDA submitted for Nystatin and Triamcinolone Acetonide Cream, 100,000 units/g; 0.1%
  - Treatment of cutaneous candidiasis.
- Consult sent to Office of Safety and Clinical Evaluation for evaluation of a proposed level for inactive ingredient “X”.
  - Proposed level was higher than maximum approved level.
- Proposed amount of “X” significantly exceeded currently approved amounts for topical products.
- “X” is a penetration enhancer for topical products, whereas lower weight “Xs” are minimally absorbed through the skin.
- Concern for increase absorption of APIs, namely triamcinolone in children.
- The amount of “X” was found unacceptable and could not be justified.

Considerations

- Evaluation of all inactive ingredients in a drug product could prove useful, especially for vulnerable subpopulations.

- Evaluation based on grades may adequately define the safety profile of inactive ingredients.

Summary

- Commonalities exist between regulatory agencies in the Cluster regarding evaluation of inactive ingredients for drug products.
- Further exploration of these areas is needed to determine if we can alleviate burden on industry for justifying proposed inactive ingredient amounts while ensuring safety.

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