Considerations When Submitting Proposed Excipient Levels in Inactive Ingredient (IIG) Controlled Correspondences

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DISCLAIMER

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Learning Objective

- To encourage focused correspondence per the dosing guidelines provided in the reference listed drug labeling.
  - To explain how Maximum Daily Exposure (MDE) levels are evaluated according to the respective Maximum Daily Dose (MDD) when based on the requested patients' age and/or weight.

Introduction

Evaluating proposed MDE excipient levels often presents a nuanced challenge.

- Comprehensive assessments of MDDs are based on patient age, body surface area, and weight.

Introduction cont.

- IIG CC inquiries for proposed MDE levels should align with:
  - the reference listed drug labeling dosing instructions across patient populations, *and*
  - the recommended three-evaluation limit in the Controlled Correspondence Related to Generic Drug Development Guidance for Industry (March 2024) (CC Guidance).

Introduction cont.

CC Guidance: **Section IV. C. Additional Recommendations on the Content of Specific Types of Controlled Correspondence Inquiries**

1. Requests Related to Inactive Ingredients

The Agency often receives requests for information pertaining to whether particular inactive ingredients present at higher levels than the maximums listed in the Agency's Inactive Ingredient Database (IID) are permissible in a generic drug.[33] FDA recommends that a requestor submit for evaluation no more than three inactive ingredients and no more than three proposed levels for a drug product in any given controlled correspondence. For example, in any given controlled correspondence:

- A requestor can submit (1) a request that proposes three inactive ingredients with one level each, or (2) a request that proposes one inactive ingredient with three levels.
- If the drug product is indicated for the adult and pediatric populations, a requestor can submit (1) a request that proposes one inactive ingredient with one level for three different dosing ranges (based on body weight or age range specified in the RLD labeling), or (2) a request that proposes three inactive ingredients with one level for one dosage range.

Case studies

The following slides contain example case studies.

Example Case Study #1

Prospective applicant Z inquired about three proposed MDE levels in the pediatric population with a body weight of **1 kg to less than 7 kg.**

The applicant's proposed MDE levels were based on an MDD of 6 units.

**prospective applicant will be referred as 'applicant' here forth*

Example Case Study #1 cont.

Per the reference listed drug labeling, the MDD varies according to 04 different weight ranges:

1. ***1 kg < 3 kg bodyweight***: 2 units per day.
2. ***3 kg < 5 kg bodyweight***: 4 units per day.
3. ***5 kg < 7 kg bodyweight***: 6 units per day.
4. ***7 kg bodyweight and above***: 8 units per day.

Example Case Study #1

Office of Bioequivalence Evaluation

Evaluations of MDE levels were conducted according to *the MDD used by the applicant* which corresponds to pediatrics weighing **5 kg < 7 kg.**

Example Case Study #1

Response to Requestor

- As stated in the reference listed drug labeling, there are four distinct MDDs based on various weights across the patient population.
- Acceptability of MDE levels was evaluated using *the MDD you considered (6 units) which* corresponds to pediatrics weighing 5 kg < 7 kg.
- Evaluation of MDE levels as requested i.e. **1 kg to less than 7 kg body weight** would
  - require evaluations for each distinct weight range, and
  - exceed the evaluation limit of three as recommended in the CC Guidance.
- For evaluations in other weight ranges, please submit a CC inquiry for the respective patient population based on the corresponding MDD per the RLD label.

Note: acceptability of excipient levels for all patient populations will be evaluated during scientific assessment of the ANDA

Example Case Study #2

Applicant A proposed an MDE level for each of three different excipients "*in pediatric patients, i.e., infants and children up to 3 years of age or 13 kg of body weight.*"

The applicant proposed MDE levels based on a patient weighing 13 kg.

Example Case Study #2 cont.

Per the reference listed drug labeling, dosing is mg/kg, i.e. the MDD varies as it is calculated according to the patient's weight.

Example Case Study #2 cont.

Office of Bioequivalence Evaluation

Proposed MDE levels were evaluated specifically for pediatric patients weighing 13 kg, *i.e. the weight used by the applicant*.

Example Case Study #2 cont.

Response to Requestor

- As stated in the reference listed drug labeling, the MDD varies according to weight.
- Acceptability of MDE levels were evaluated considering the weight you used which is *only* for pediatrics weighing 13 kg.
- Evaluations were not conducted considering the weight for the youngest patients (infants).

Example Case Study #2 cont.

Response to Requestor

- Evaluation of MDE levels as requested **i.e. infants and children up to 3 years of age or 13 kg of body weight**, would
  - include patients as young as infants *and* patients up to 3 years old,
  - exceed the evaluation limit of three as recommended in the CC Guidance.
- For evaluations of MDE levels in any other patient population (i.e. weighing < 13 kg), please submit a CC inquiry for the respective patient population considering the respective MDD.

Note: acceptability of excipient levels in all patient populations for which the product is indicated will be evaluated during scientific assessment of the ANDA

Example Case Study #3

Applicant Y inquired about three proposed MDE levels specifically for pediatrics aged 6 months to < 7 years.

The applicant proposed MDE levels considering an MDD of 222 mg.

Example Case Study #3 cont.

Per the reference listed drug labeling, there are two recommended maximum daily doses for children 6 months to < 7 years old.

1) 111 mg for children 6 months to 12 months old, and
2) 222 mg for children 13 months to < 7 years old.

Example Case Study #3 cont.

Office of Bioequivalence Evaluation

Evaluations were conducted *considering the MDD used by the applicant* (222 mg) which corresponds to children 13 months to < 7 years old.

Example Case Study #3 cont.

Response to Requestor

- As stated in the reference listed drug labeling, there are two recommended maximum doses for children 6 months to < 7 years old.
- Acceptability of MDE levels were evaluated using *the MDD you considered (222 mg)* which corresponds for children 13 months to < 7 years old.
- Evaluations were not conducted for patient 6 months to 12 months old which corresponds to a different MDD.

Example Case Study #3 cont.

Response to Requestor

- Evaluations of MDE levels as requested**, 6 months to < 7 years old,** would
  - exceed the evaluation limit of three as recommended in the CC Guidance.
- For evaluations of MDE levels in patient 6 months to 12 months old, please submit a CC inquiry for the respective patient population considering the respective MDD.

Note: acceptability of excipient levels in all patient populations for which the product is indicated will be evaluated during scientific assessment of the ANDA

Example Case Study #4

Applicant D stated its intent to develop a drug product *for a specific indication* and inquired about MDE levels in pediatrics patients 5 months old.

The proposed MDE levels were based on an MDD corresponding to a different indication and using a weight for patients that are 10 years old.

Example Case Study #4 cont.

- Per the reference listed drug labeling, this product has two strengths each with a distinct indication tied to a specific patient (pt) population.
- Dosing for both strengths is weight (wt.) – based and have different MDDs:
  - The lower strength has multiple wt.-based daily doses for pt.'s 5 months old to 5 years old.
  - The higher strength also has multiple wt.- based daily doses, but for pt.'s 5 months old to 10 years old.

Example Case Study #4 cont.

Office of Bioequivalence Evaluation

- MDE levels were recalculated using the proposed per-unit amounts and the MDD **for the lower strength** in patients **5 months old** based on the indication and age-range *that the applicant mentioned in its query*.

Example Case Study #4 cont.

Response to Requestor

- As stated in the reference listed drug labeling, there are two strengths, each with a distinct indication for specific patient populations.
- The reference labeling also lists different MDDs based on various patient weights for the respective strengths.
- Although you stated your intent to develop the lower strength in pediatrics patients 5 months old, your proposed MDE levels were based on
  - an MDD for the higher strength, and
  - a weight for patients that are 10 *years* old.

Example Case Study #4 cont.

Response to Requestor

- MDE levels were evaluated using the proposed per-unit amounts considering the weight of patients *5 months old* and the corresponding MDD for the lower strength.

Note: acceptability of excipient levels in all patient populations for which the product is indicated will be evaluated during scientific assessment of the ANDA

Example Case Study #5

Applicant A inquired about proposed MDE levels for an excipient in 3 different strengths, 5 mg, 20 mg, and 40 mg, specifically for the following pediatric population:

- 3 months to less than 6 months.
- 6 months to less than 8 months.
- 8 months to less than 10 months.

Per the reference listed drug labeling, the MDD *is strength dependent*, ***and*** is based on both age and various body weights

- 1 unit of 5 mg for patients 3 months to less than 6 months weighing > 5 kg.
- 1 unit of 20 mg for patients 6 months to less than 8 months weighing > 10 kg.
- 2 units of 40 mg for patients 8 months to less than 10 months weighing > 15 kg.

Example Case Study #5 cont.

Office of Bioequivalence Evaluation

- Evaluations were conducted on the proposed MDE levels as submitted.
- Levels were accurately calculated **by the prospective applicant** according to the age, body weight, and respective dosage strengths.

Example Case Study #5 cont.

Response to Requestor

- Per the reference listed drug labeling, you calculated your proposed MDE levels in accordance with the dosing instructions for the respective drug product strengths.
- Based on OGD evaluation, your proposed MDE levels **do not exceed** the limit for the same inactive ingredient in previously FDA-approved drug products for the same route of administration and context of use.

Key Takeaways

- If a specified patient population is queried, and the drug product MDD varies based on age or weight,
  - Please calculate the MDD according to the weight or age that corresponds to the queried patient population.
  - The proposed MDE levels will be evaluated for the specified patient population *according to the corresponding weight or age*.
  - Evaluation of the proposed MDE level will be based on the MDD used by the applicant.
  - MDE levels will be re-calculated if calculations are not aligned with the recommended MDD per the reference listed drug labeling.
- The number of MDE level evaluations will not exceed 3.

Challenge Question

The MDD calculated by the applicant based on patients with varying weights should:

A. Cover the entire patient population.

B. Be calculated for any weight.

C. Be specific to a weight or weight range that corresponds to an MDE evaluation limit of 3.

Closing Thought

When you calculate proposed MDE levels according to the reference listed drug labeling, this will help us answer your query and ***support your generic drug development****.*

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Questions?

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