Calculating Maximum Daily Dose for Orally Administered Drug Products

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Day 1, Session 2: Excipient and Formulation Considerations

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Learning Objectives

- What is maximum daily dose (MDD) and why it is important
- How to determine MDD
  - Straightforward examples
  - Complicated examples
- Special considerations when determining MDD

Maximum Daily Dose

- The MDD is the highest dose that a patient may be administered in one day (i.e., 24 hours).
- The correct MDD is important to:
  - accurately determine the maximum daily exposure (MDE) of each excipient in a drug product; and
  - ensure the excipient MDEs are within levels previously accepted by FDA or otherwise justified.
- Generally, the MDD is determined from the *Dosage and Administration (D&A)* section of the reference listed drug (RLD) or reference standard (RS) labeling.

Considerations when Determining MDD

- In general, when a drug product is available in multiple strengths, the MDE for excipients in the lower strengths should be based on the MDD using lower strengths when such dosing regimens are realistic in clinical practice.

- When determining the MDD based on body surface area (BSA) or body weight (BW), unless the RLD or RS labeling specifies otherwise, the MDD is calculated assuming*:
  - BSA of 1.62 m^2
  - BW of 60 kg

**Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers* (July 2005; https://www.fda.gov/media/72309/download)

Simple Examples…

Example 1: Straightforward MDD Determination

- CELEBREX® (celecoxib) capsules, 50 mg, 100 mg, 200 mg and 400 mg (NDA 020998)
  - Per the *D&A* section of the labeling, there are 5 indications:
    - Osteoarthritis – *200 mg per day* (200 mg MDD)
    - Rheumatoid Arthritis – *100 mg to 200 mg twice daily* (400 mg MDD)
    - Juvenile Rheumatoid Arthritis – *For patients ≥10 kg to ≤25 kg…50 mg twice daily. For patients >25 kg…100 mg twice daily* (200 mg MDD).
    - Ankylosing Spondylitis – *The dosage is 200 mg daily…If no effect is observed after 6 weeks…400 mg daily…*(400 mg MDD).
    - Management of Acute Pain and Treatment of Primary Dysmenorrhea – *The dosage is 400 mg initially, followed by an additional 200 mg dose if needed on the first day* (400 mg + 200 mg = **600 mg MDD**).
- Based on the dosing for all indications, the MDD is 600 mg.

Example 2: Labeling Specifies MDD for Each Strength

- LYRICA® CR (pregabalin) extended-release tablets, 82.5 mg, 165 mg and 330 mg (NDA 209501)
  - Per the *D&A* section of the labeling, there are 2 indications:
    - Neuropathic Pain Associated with Diabetic Peripheral Neuropathy – *The maximum recommended dose of LYRICA CR is 330 mg once daily*.
    - Postherpetic Neuralgia – *Patients who do not experience sufficient pain relief following 2 to 4 weeks of treatment with 330 mg once daily and who are able to tolerate LYRICA CR, may be treated with up to 660 mg once daily…The maximum recommended dose of LYRICA CR is 660 mg once daily.*
  - To achieve an MDD of 660 mg, the MDD *could* be based on eight 82.5 mg tablets.
  - HOWEVER, the RLD labeling specifies the number of tablets to use when switching from LYRICA to LYRICA CR.

Example 2: Labeling Specifies MDD for Each Strength (cont.)

LYRICA Total Daily Dose (dosed 2 or 3 times daily)	LYRICA CR Dose (dosed once a day)
75 mg/daily	82.5 mg/day
150 mg/daily	165 mg/day
225 mg/daily	247.5 mg/day[a]
300 mg/daily	330 mg/day
450 mg/daily	495 mg/day[b]
600 mg/daily	660 mg/day[c]

a. 247.5 mg = 3 x 82.5 mg tablets taken once a day.
b. 495 mg = 3 x 165 mg tablets taken once a day.
c. 660 mg = 2 x 330 mg tablets taken once a day.

- The maximum number of tablets of each strength to be used for MDE calculations is 3 x 82.5 mg, 3 x 165 mg and 2 x 330 mg, consistent with the RLD labeling.

➢ Drug labeling's limits on the number of units impacts the MDE for excipients in different strengths.

Example 3: Labeling Specifies BSA

- TARGRETIN® (bexarotene) Capsules, 75 mg (NDA 021055)

Initial Dose Level (300 mg/m²/day)		Number of 75 mg TARGRETIN Capsules
Body Surface Area (m²)	Total Daily Dose (mg/day)	
0.88 – 1.12	300	4
1.13 – 1.37	375	5
1.38 – 1.62	450	6
1.63 – 1.87	525	7
1.88 – 2.12	600	8
2.13 – 2.37	675	9
2.38 – 2.62	750	10

Example 3: Labeling Specifies BSA (cont.)

- Also per the D&A section of the labeling, *Dose Modification Guidelines: …If there is no tumor response after eight weeks of treatment and if the initial dose of 300 mg/m^2/day is well tolerated, the dose may be escalated to 400 mg/m^2/day with careful monitoring.*

- MDD is 1000 mg or 14 capsules
  - (400 mg/m^2/day x 2.62 m^2) / 75 mg = 13.97 (~14 whole capsules)

➢ Although a BSA of 1.62 m^2 is generally used, some reference labeling specifies a different BSA to determine MDD.

Challenge Question #1

When determining MDD based on body surface area or body weight, the MDD is always calculated using 1.62 m^2 for body surface area or 60 kg for body weight.

A. True
B. False

However…

Determining the MDD is not always straightforward

Example 4: MDD Adjusted due to Converting to a Different Dosage Form

- LAMICTAL® XR™ (lamotrigine) extended-release tablets, 25 mg, 50 mg, 100 mg, 200 mg, 250 mg and 300 mg (NDA 022115)

Regimen for LAMICTAL XR in Patients Aged 13 and Older

	In Patients TAKING Valproate	In Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone or Valproate	In Patients TAKING Carbamazepine, Phenytoin, Phenobarbital or Primidone and NOT TAKING Valproate
Weeks 1 and 2	25 mg every other day	25 mg every day	50 mg every day
Weeks 3 and 4	25 mg every day	50 mg every day	100 mg every day
Week 5	50 mg every day	100 mg every day	200 mg every day
Week 6	100 mg every day	150 mg every day	300 mg every day
Week 7	150 mg every day	200 mg every day	400 mg every day
Maintenance Range (week 8 and onward)	200 to 250 mg every day	300 to 400 mg every day	400 to 600 mg every day

Example 4: MDD Adjusted due to Converting to a Different Dosage Form (cont.)

- Also per the D&A section of LAMICTAL XR labeling, *The initial dose of LAMICTAL XR should match the total daily dose of immediate-release lamotrigine.*

- Therefore, per the D&A section of LAMICTAL® (lamotrigine) tablets (NDA 020241) labeling:

Regimen for LAMICTAL in Patients Older than 12 Years with Epilepsy

	In Patients TAKING Valproate	In Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone or Valproate	In Patients TAKING Carbamazepine, Phenytoin, Phenobarbital or Primidone and NOT TAKING Valproate
Usual maintenance dose	100 to 200 mg/day with valproate alone; 100 to 400 mg/day with valproate and other drugs that induce glucuronidation (in 1 or 2 divided doses)	225 to 375 mg/day (in 2 divided doses)	300 to 500 mg/day (in 2 divided doses)

Example 4: MDD Adjusted due to Converting to a Different Dosage Form (cont.)

- HOWEVER, the *D&A* section of LAMICTAL® labeling states *In patients receiving multidrug regimens employing carbamazepine, phenytoin, phenobarbital, or primidone without valproate, maintenance doses of adjunctive LAMICTAL as high as 700 mg/day have been used.*

- It is important to look at all *D&A* aspects to determine if the MDD may be affected when converting to a different dosage form [e.g., converting from immediate release (IR) to extended release (ER)].
- A controlled correspondence (CC) may be submitted to obtain clarity in such ambiguous situations.

Example 5: MDD is Ambiguous

- PHOSLYRA® (calcium acetate oral solution), 667 mg/5 mL (NDA 022581)
  - Per the *D&A* section of the labeling, *The recommended initial dose of PHOSLYRA for the adult dialysis patient is 10 mL with each meal...Titrate the dose every 2 to 3 weeks...Most patients require 15-20 mL with each meal.*
  - The D&A section does not specify how many meals per day. How many meals per day would this patient population generally eat?
  - Is the MDD based on 20 mL with three meals/day even though this is for most patients and three meals/day is a typical scenario?

➢ If one is concerned about the 'remaining' patient population and acceptability of MDEs is uncertain, a CC may be submitted.

Example 6: MDD is Ambiguous

- AMICAR® (aminocaproic acid) Tablets, 500 mg and 1000 mg (NDA 015197)
  - Per the *D&A* section of the labeling:
    - *For the treatment of acute bleeding syndromes due to elevated fibrinolytic activity, it is suggested that…(5 g)...be administered during the first hour of treatment, followed by a continuing rate of…(1 g)…per hour. This method of treatment would ORDINARILY be continued for about 8 hours until the bleeding situation has been controlled.*
  - What if dosing is required beyond eight hours?

➢ When the duration of treatment is unclear, a CC may be submitted to request clarification.

Example 7: Is the MDD Realistic in Clinical Practice?

- ORFADIN® (nitisinone) capsules, 2 mg, 5 mg, 10 mg and 20 mg (NDA 021232)
  - Per the D&A section of the labeling, *A maximum total daily dosage of 2 mg/kg may be needed based on the evaluation of all biochemical parameters.*
- The MDD is 120 mg assuming a BW of 60 kg (2 mg/kg x 60 kg). For the 2 mg capsules, this would be 60 capsules per day.
- This is NOT realistic in clinical practice.

➢ When clinical practicality is uncertain, a CC may be submitted to request guidance.

Special Considerations

- If determining the MDD is complicated, ambiguous or if the maximum number of units could be limited by clinical practicality, a CC may be submitted to request confirmation or clarification of the MDD*.

- Some excipients have safety concerns in special populations, such as pediatric or renally impaired patients. In these instances, the MDD in the specific patient population is considered to appropriately evaluate the MDE of the excipients with safety concerns.

*See *Draft Guidance for Industry: Controlled Correspondence Related to Generic Drug Development* (November 2017; https://www.fda.gov/media/109232/download)

Challenge Question #2

Which of the following is true when determining the MDD of a drug product:

A. It is important to determine the correct MDD so that one may accurately evaluate the MDE of each excipient in a drug product.
B. The MDD is generally determined from information in the *Dosage and Administration* section of the referenced drug labeling.
C. The MDD may be impacted by converting to a different dosage form.
D. All of the above.

Conclusions

- The correct MDD is important to accurately determine the MDE of each excipient in a drug product.
- It is important to look at all *D&A* aspects to determine the correct MDD (e.g., if the MDD is impacted by converting to a different dosage form).
- The maximum number of units administered in one day could be limited by clinical practicality.
- A CC may be submitted to get clarification of an MDD or a proposed excipient MDE.

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Questions


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