Standardized Approaches for Determining Maximum Daily Dose (MDD)

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Overview

- Background
  - Definitions, Impact, Challenges
- CDER Internal MDD Alignment Efforts
  - Importance of Alignment, Key Alignment Elements
- Feedback for Industry
- Summary

What is MDD?

MDD is …

- Numeric value (amount/day) calculated based on API amount reasonably administered in a day to most patients per drug labeling
- Suitable standard applicable to most patients indicated by drug labeling
- Multidisciplinary standard used during technical review of new and generic drugs
- Not intended to impact dosing in clinical practice

API = Active Pharmaceutical Ingredient

Why is MDD Important?

MDD is critical …

- During safety and quality review of new and generic drugs:
  - To determine impurity control in drug substances and drug products
  - To set acceptable limits for *N*-nitrosamine impurities
  - To establish AET for extractables and leachables studies/reviews
  - To establish excipient MDE posted on FDA's IID
- To ensure regulatory consistency across similar drugs

AET = analytical evaluation threshold
MDE = maximum daily exposure
IID = Inactive Ingredient Database

What are the Challenges?

MDD is a numeric value (e.g., mg/day), drug labeling often does not list MDD as amount/day – *variables* in drug labeling create calculation uncertainties:

Examples of Variables Listed in Dosage & Administration Section of Drug Labeling
• Highest recommended dose is 0.05 mg/*kg*/day
• Recommended to apply a *pea-size* of gel to each of the five areas of the face daily
• Recommended to apply *one drop* in the *affected eye(s)* twice a day
• Highest recommended dose is 300 mg/m^2/day

What are the Challenges?

Complex dosing scenarios in drug labeling add further uncertainties to MDD calculation:

Examples of Information from Dosage & Administration Section of Drug Labeling
• *Multiple indications* with different dosing regimens
• Different dosing regimens for specific *patient subpopulations* for the same indication
• *Individualized titration-based dosing* (e.g., titration based on patient response, tolerability, or achievement of specific pharmacological endpoints) or a *dosing range*
• Combination of any variables and/or complexities

Why Standardize MDD?

- Regulatory consistency across similarly situated drugs
  - E.g., acceptance criteria for N-nitrosamine impurities
- Consistent and efficient review of new and generic drugs
- Consistent and clear communication between FDA and industry
  - Helpful for drug development and application approval

Standardization streamlines drug review by reducing the complexities of MDD determination.

MDD Alignment across CDER

Key Elements of MDD Alignment:

- Current progress
  - Standardized Approaches and Principles
- Continued work
  - Single MDD Concept
  - Active Knowledge Management
  - Quality Control

Standardized Approaches & Principles

Standardization of Clinical Parameters

Clinical Parameters	Standardization
Adult Body Weight (BW)	60 kg BW (unless the patient population falls significantly out of this scope)
Adult Body Surface Area (BSA)	1.62 m^2 BSA (unless the patient population falls significantly out of this scope)
Dosing every "X" hours	MDD determined based on 24 hours (generally no adjustment for waking hours) E.g., for a drug taken every four hours, MDD is determined considering six doses within 24 hours

Standardized Approaches & Principles

Standardization of Clinical Principles for Common Scenarios

Common Scenario	Standardization
Labeling listing multiple indications	In general, MDD is based on highest dose across labeled indications (some exceptions apply)
Labeling listing adjusted dosing for concomitant use of Cytochrome P450 (CYP) enzyme inducers	MDD based on dose representative for most labeled patients → CYP450 inducer adjusted doses generally not used as MDD
Over-the-counter (OTC) and prescription (Rx) drugs	MDD for OTC products is based on the Rx labeling, if the drug is available as OTC *and* Rx product

Standardized Approaches & Principles

Consistent Calculation Methods

Special Case Therapeutics	Standardization
Topical Ophthalmic Drugs	MDD based on API (e.g., %) per dose unit (e.g., drop) multiplied by maximum dose units per day; product specific drop size and density used to convert daily number of drops to amount API/day
Injectable Drugs with Specified Infusion Rates and Adjustments	MDD based on sum of maximum amount of bolus dose and maintenance dose using a specified duration for the maintenance phase
Inhaled and injectable anesthetics	MDD generally based on maximum infusion rate per labeling and 10-hour surgery for duration

Single MDD Concept

Ensures ANDAs are evaluated using same standards applied during RLD review

- Goal to determine MDD at original NDA approval
  - Subsequently, same MDD used throughout drug lifecycle (includes RLD, RS, ANDAs)
- MDD updates for RLD propagated to subsequent ANDAs

RLD = Reference Listed Drug
RS = Reference Standard
ANDA = Abbreviated New Drug Application

Knowledge Management

Ensures same MDDs applied for TEs across disciplines and applications

- Process for reviewers to efficiently and reliably identify MDD
- Preserves institutional knowledge

TE = Therapeutic Equivalent

Quality Control

Need for quality control of MDDs documented and used subsequently during regulatory review

- Resources for review staff when questions arise
- Resolution of discrepancies and MDD verification
- MDD determination/identification for NDAs approved prior to alignment efforts

TE = Therapeutic Equivalent

How Industry can Obtain Feedback

- Generic applicants can submit a CC for confirmation of MDD for regulatory assessment and drug development
- Particularly useful for drugs with complex dosing instructions or route of administration, e.g.,
  - Dosing to effect (e.g., blood pressure control)
  - Complex routes of administration (e.g., topical drug applied as a thin film to affected areas)

CC = Controlled Correspondence
Resource: Guidance for Industry: CC Related to Generic Drug Development (March 2024)

Summary

- Standardization makes determination of seemingly challenging MDDs less complex → streamlines review
- MDD is a reasonable standard applied during regulatory assessment
- MDD is *not* intended to impact dosing in clinical practice

- Continued FDA-internal efforts developing knowledge management in support of MDD alignment
- Future FDA-internal efforts seek further alignment for “complex” MDDs
  - E.g., *complex dosing scenarios* warranting expert clinical judgement
- Feedback for industry available via Controlled Correspondences


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