

What's new in the Inactive Ingredient Database (IID)?

SBIA 2020: Advancing Innovative Science in Generic Drug Development Workshop
Session 2: Excipient and Formulation Considerations

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Big changes are underway in the IID



- New data standards
- Added transparency
- New excipient levels based on exposure
- New tool for excipient qualification



Learning Objectives

- We will review recent IID enhancements to:
 - Define current IID terms and data
 - Discuss changes that were implemented in 2019 and 2020
 - Explain how to read the new Quarterly IID Change Log
 - Clarify how excipient Maximum Daily Exposure (MDE) is determined and displayed in the IID

Introduction to the IID

Online, searchable list of excipients in FDA-approved drug products

Available IID resources:

- IID FAQ
- Draft IID Guidance
- Record of changes by quarter (Change Log)



Questions & Answers Regarding Enhancements to the Inactive Ingredient Database (IID)

1. How will the IID change?

Several changes are planned in 2019 as we phase in enhancements to meet our GDUFA II commitments (see page 17 of the GDUFA II Commitment Letter). In Phase I, the terminology for routes of administration (ROA) and dosage forms (DF) will be standardized for consistency. The current version of the IID does not have

Using the Inactive Ingredient Database Guidance for Industry

Quarter	Inactive Ingredient	Route of Administration	Dosage Form	Maximum Potency per unit dose	Maximum Daily Exposure	Status
Q2 2020	ALPHA-TOCOPHEROL	ORAL	TABLET, FILM COATED	82.00 mg		MDE Replacement
Q3 2020	ALPHA-TOCOPHEROL	ORAL	TABLET, FILM COATED		246 mg	MDE Replacement
Q2 2020	5-METHOXY-2-(4-STYRYL-3-SULFOPHENYL)-2-H-BENZOTRIAZOLE	TOPICAL	SOAP	0.75 %w/w		Correction
Q3 2020	2-(4-STYRYL-3-SULFOPHENYL)-5-METHOXYBENZOTRIAZOLE	TOPICAL	SOAP	0.75 %w/w		Correction
Q2 2020	ACACIA	ORAL	CAPSULE, EXTENDED RELEASE	25.50 mg		MDE Replacement
Q3 2020	ACACIA	ORAL	CAPSULE, EXTENDED RELEASE		51 mg	MDE Replacement

For purposes only, limited within 90 days of day of the draft. Submit written comments to the Center for Drug Evaluation, 5630 Rockledge Drive, Bethesda, MD 20895-4529. 240-402-9133.

IID Basics

IID contains only excipients in NDAs and ANDAs.



SRS preferred terms

Maximum Potency per unit dose

New item: Maximum Daily Exposure (MDE)

Inactive Ingredient	Route	Dosage Form	CAS Number	UNII	Maximum Potency per unit dose	Maximum Daily Exposure (MDE)	Record Updated
.ALPHA.-TOCOPHEROL	ORAL	CAPSULE	1406184	H4N855PNZ1	5mg		
.ALPHA.-TOCOPHEROL	ORAL	SOLUTION	1406184	H4N855PNZ1	1.05mg/1ml		
.ALPHA.-TOCOPHEROL	ORAL	TABLET	1406184	H4N855PNZ1	42.5mg		
.ALPHA.-TOCOPHEROL	ORAL	TABLET, CHEWABLE	1406184	H4N855PNZ1	0.1mg		
.ALPHA.-TOCOPHEROL	ORAL	TABLET, EXTENDED RELEASE	1406184	H4N855PNZ1	1.34mg		
.ALPHA.-TOCOPHEROL	ORAL	TABLET, FILM COATED	1406184	H4N855PNZ1		246mg	Y
.ALPHA.-TOCOPHEROL ACETATE	ORAL	CAPSULE	7695912	9E8X80D2L0	2mg		
.ALPHA.-TOCOPHEROL ACETATE	ORAL	TABLET	7695912	9E8X80D2L0	0.5mg		
.ALPHA.-TOCOPHEROL, DL-	ORAL	CAPSULE	10191410	7QWA1RIO01	1mg		
.ALPHA.-TOCOPHEROL, DL-	ORAL	SUSPENSION	10191410	7QWA1RIO01	0.01mg/1ml		
.ALPHA.-TOCOPHEROL, DL-	ORAL	TABLET	10191410	7QWA1RIO01	0.9mg		
.ALPHA.-TOCOPHEROL, DL-	ORAL	TABLET, CHEWABLE	10191410	7QWA1RIO01	0.02mg		

Displays one record per unique Excipient-RoA-DF combination

CAS and UNII

Flag for new records

SRS is FDA's Substance Registration System
 CAS is the Chemical Abstracts Service Registry Number
 UNII is a unique code assigned by SRS

Ongoing IID Changes

New Data Standards



SPL is FDA's Structured Product Labeling system.
IID uses SPL terminology for routes of administration and dosage forms.

Inactive Ingredient	Route	Dosage Form	CAS Number	UNII	Maximum Potency per unit dose	Maximum Daily Exposure (MDE)	Record Updated
ALPHA-TOCOPHEROL	ORAL	CAPSULE	1408184	H4N855PNZ1	5mg		
ALPHA-TOCOPHEROL	ORAL	SOLUTION	1408184	H4N855PNZ1	1.05mg/1ml		
ALPHA-TOCOPHEROL	ORAL	TABLET	1408184	H4N855PNZ1	42.5mg		
ALPHA-TOCOPHEROL	ORAL	TABLET, CHEWABLE	1408184	H4N855PNZ1	0.1mg		
ALPHA-TOCOPHEROL	ORAL	TABLET, EXTENDED RELEASE	1408184	H4N855PNZ1	1.34mg		
ALPHA-TOCOPHEROL	ORAL	TABLET, FILM COATED	1408184	H4N855PNZ1		246mg	Y
ALPHA-TOCOPHEROL ACETATE	ORAL	CAPSULE	7695912	9E8X80D2L0	2mg		
ALPHA-TOCOPHEROL ACETATE	ORAL	TABLET	7695912	9E8X80D2L0	0.5mg		
ALPHA-TOCOPHEROL, DL-	ORAL	CAPSULE	10191410	7QWA1RIO01	1mg		
ALPHA-TOCOPHEROL, DL-	ORAL	SUSPENSION	10191410	7QWA1RIO01	0.01mg/1ml		
ALPHA-TOCOPHEROL, DL-	ORAL	TABLET	10191410	7QWA1RIO01	0.9mg		
ALPHA-TOCOPHEROL, DL-	ORAL	TABLET, CHEWABLE	10191410	7QWA1RIO01	0.02mg		

SPL terms for Route and
Dosage Form
as of July 2019

A comprehensive list of mapped terms can be found on the IID webpage. Select the link for [Most Recent Changes to the IID Database](#).

Ongoing IID Changes



Quarterly Inactive Ingredient Database (IID) Change Log
Notice of changes to the IID since the previous quarterly IID publication.

Quarterly Inactive Ingredient Database (IID) Change Log

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- IID Quarter 3 – July 2020 Corrections/Replacements and Deletions (PDF - 157 KB)
- IID Quarter 2 – April 2020 Corrections/Replacements and Deletions (PDF - 57 KB)
- IID Quarter 1 – January 2020 Corrections/Replacements and Deletions (PDF - 52 KB)
- IID Quarter 4 – October 2019 Corrections/Replacements and Deletions (PDF - 123 KB)

Understanding the Change Log

Welcome to the Quarterly IID Change Log. FDA publishes the IID on a quarterly basis. The Quarterly IID Change Log displays changes made since the previous quarterly IID publication.

Change Log made available as of October 2019

Updated from static to searchable and interactive Change Log as of June 2020

Q1 2020 Change Log						171 Corrections
Corrected Records						
Quarter	Inactive Ingredient	Route of Administration	Dosage Form	Maximum Potency per Unit Dose	Maximum Daily Exposure	Status
Q4 2019	ALCOHOL	TOPICAL	GEL	95.04 %w/w		
Q1 2020	ALCOHOL	TOPICAL	GEL	64.38 %w/w		
Q4 2019	AMMONIA SOLUTION	ORAL	CAPSULE	0.03 mg		
Q1 2020	AMMONIA SOLUTION	ORAL	CAPSULE	0.02 mg/mg		
Q4 2019	AMMONIA SOLUTION	ORAL	CAPSULE, EXTENDED RELEASE	0.01 mg/mg		
Q1 2020	AMMONIA SOLUTION	ORAL	CAPSULE, EXTENDED RELEASE	NA		
Q4 2019	BUTYLATED HYDROXYANISOLE	ORAL	TABLET, ORALLY DISINTEGRATING	0.66 mg		
Q1 2020	BUTYLATED HYDROXYANISOLE	ORAL	TABLET, ORALLY DISINTEGRATING	0.42 mg		
Q4 2019	BUTYLATED HYDROXYTOLUENE	ORAL	TABLET, ORALLY DISINTEGRATING	0.30 mg		
Q1 2020	BUTYLATED HYDROXYTOLUENE	ORAL	TABLET, ORALLY DISINTEGRATING	0.21 mg		
Q4 2019	CARBOMER 1382	TOPICAL	GEL, NETERED	0.90 %w/w		
Q1 2020	CARBOMER COPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)	TOPICAL	GEL, NETERED	0.90 %w/w		
Q4 2019	CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)	TOPICAL	GEL	3.50 %w/w		
Q1 2020	CARBOMER HOMOPOLYMER TYPE C (ALLYL PENTAERYTHRITOL CROSSLINKED)	TOPICAL	GEL	0.88 %w/v		
Q4 2019	CARBOXYPOLYETHYLENE	ORAL	TABLET, EXTENDED RELEASE	195.00 mg		
Q1 2020	CARBOMER HOMOPOLYMER	ORAL	TABLET, EXTENDED RELEASE	195.00 mg		
Q4 2019	CARBOXYPOLYETHYLENE	RECTAL	ENEMA	NA		

Quarter	Inactive Ingredient	Route of Administration	Dosage Form	Maximum Potency per unit dose	Maximum Daily Exposure	Status
Q2 2020	ALPHA-TOCOPHEROL	ORAL	TABLET, FILM COATED	82.00 mg		NDE Replacement
Q3 2020	ALPHA-TOCOPHEROL	ORAL	TABLET, FILM COATED		248 mg	NDE Replacement
Q2 2020	5-METHOXY-2-(4-STYRYL-3-SULFOPHENOL)-2-H-BENZOTRIAZOLE	TOPICAL	SOAP	0.75 %w/w		Correction
Q3 2020	2-(4-STYRYL-3-SULFOPHENOL)-6-METHOXYBENZOTRIAZOLE	TOPICAL	SOAP	0.75 %w/w		Correction
Q2 2020	ACACIA	ORAL	CAPSULE, EXTENDED RELEASE	25.50 mg		NDE Replacement
Q3 2020	ACACIA	ORAL	CAPSULE, EXTENDED RELEASE		51 mg	NDE Replacement

How to Read the Quarterly Change Log

Record = Excipient Name + Route + Dosage Form

Inactive Ingredient	Route	Dosage Form
BETADEX	ORAL	TABLET

Three types of changes to a record

- Deletions
- Corrections
- MDE Replacements

Quarterly Change Log Terms

Deleted Record

- Record was removed in this IID quarter

Quarter is identified

Record Status

Searching: Change and Deletion by Inactive Ingredient Name Beginning with View All

Show 10 rows CSV Excel Filter: 152

Quarter	Inactive Ingredient	Route of Administration	Dosage Form	Maximum Potency per unit dose	Maximum Daily Exposure	Status
Q2 2020	HYDROCHLORIC ACID	INTRAVENOUS	INJECTION, SOLUTION	1525.00 ml		Deletion

Quarterly Change Log Terms

Corrected Record

- Record was corrected and replaced with a lower potency in this quarter
- Excipient name was corrected

Previous and current quarters are identified

Lower potency

Record Status

Quarter	Inactive Ingredient	Route of Administration	Dosage Form	Maximum Potency per unit dose	Maximum Daily Exposure	Status
Q2 2020	BENZYL ALCOHOL	RECTAL	GEL	3.10 %w/v		Correction
Q3 2020		RECTAL	GEL	1.55 %w/v		Correction

Corrected name

Quarter	Inactive Ingredient	Route of Administration	Dosage Form	Maximum Potency per unit dose	Maximum Daily Exposure	Status
Q2 2020	SODIUM STARCH GLYCOLATE TYPE A POTATO	ORAL	TABLET, COATED	73.00 mg		Correction
Q3 2020	SODIUM STARCH GLYCOLATE TYPE A	ORAL	TABLET, COATED	73.00 mg		Correction

Challenge Question

What happens if the record is replaced with a higher potency?

It is flagged as “new” in the IID.

Records corrected with lower potencies appear in the Change Log.

Records replaced with higher potencies appear with a “Y” flag on the primary IID page.

Quarterly Change Log Terms

MDE Replacement

- Record displaying maximum potency was replaced with a record displaying MDE.

You are Searching: *Change and Deletion by Inactive Ingredient Name Beginning with* **View All**

Show 30 rows CSV Excel

Quarter	Inactive Ingredient	Route of Administration	Dosage Form	Maximum Potency per unit dose	Maximum Exposure	Status
Q2 2020	.ALPHA.-TOCOPHEROL	ORAL	TABLET, FILM COATED	82.00 mg		MDE Replacement
Q3 2020	.ALPHA.-TOCOPHEROL	ORAL	TABLET, FILM COATED		246 mg	MDE Replacement

Showing 1 to 2 of 2 entries (filtered from 895 total entries)

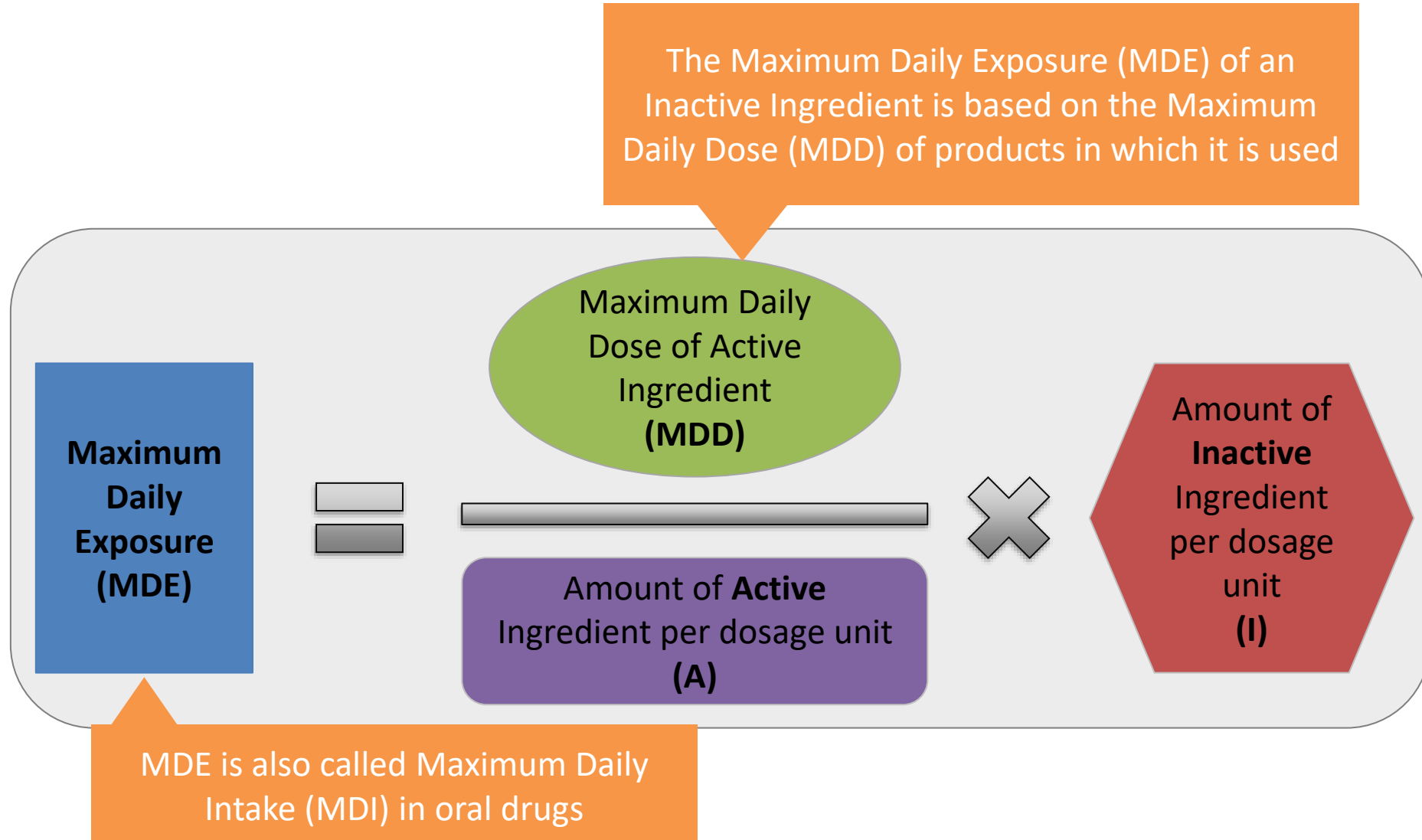
Previous 1 Next

MDE replaces unit dose potency

Maximum Potency = highest excipient amount in one unit

Maximum Daily Exposure = highest excipient amount in a daily dose

Excipient Maximum Daily Exposure



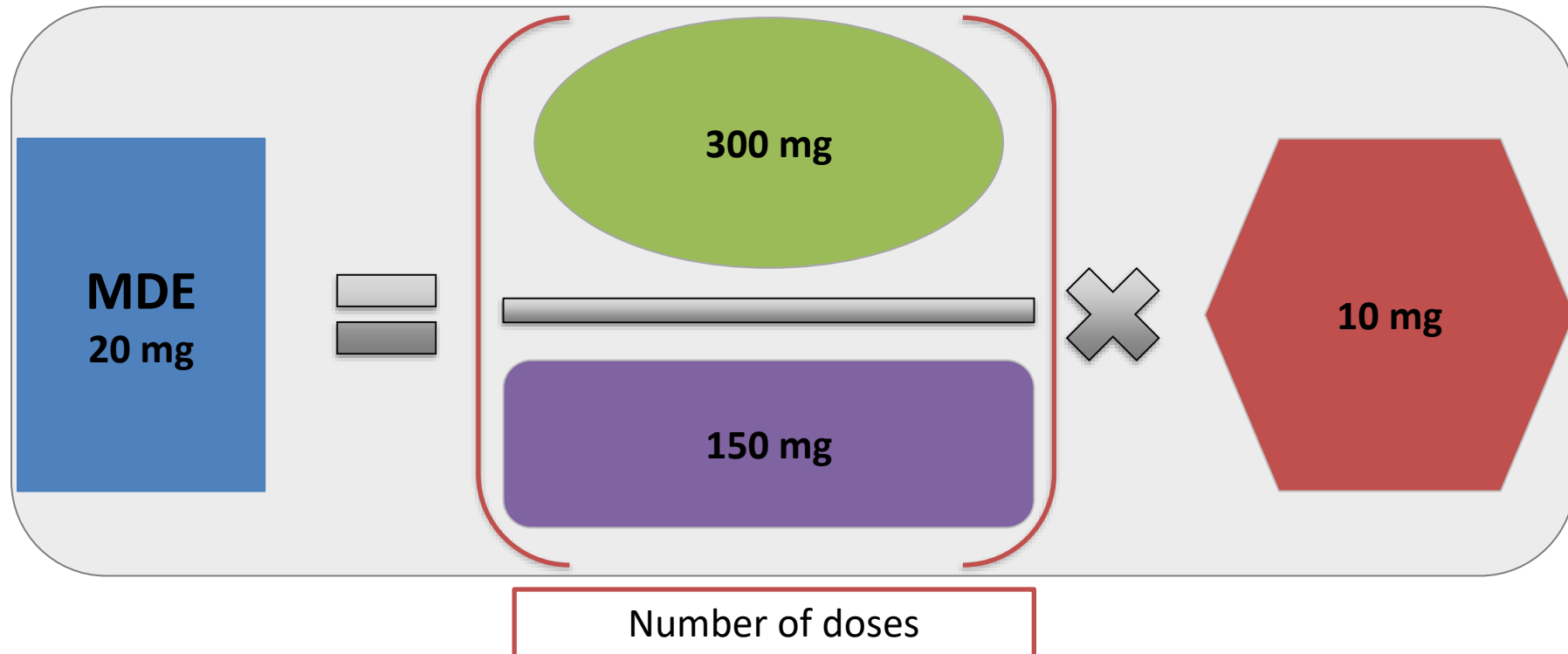
Sample MDE Calculation

Oral tablet X has MDD **300 mg/day**

Tablet strength is **150 mg (A)**

Each tablet contains **10 mg** of excipient A (I)

MDE of excipient A = **20 mg**



Using MDE in ANDAs

Transition from Maximum Potency to MDE

MDE values can be used to justify the amount of excipient a patient will receive when given the highest daily dosing regimen.

- MDE will replace maximum potency.
- MDE values will be added gradually to the IID.
- MDE values are expected to increase as data is obtained.
- MDE will typically be displayed in mg (mg/day).

Summary

- IID adopted new data standards in July 2019
- IID began reporting quarterly changes in Oct. 2019
- Quarterly Change Log identifies
 - Deletions
 - Corrections
 - MDE replacements
- New IID entries and higher potencies are flagged with “Y” in the IID
- IID began reporting MDE in July 2020
- More MDEs will appear in the IID as data is gathered



Contact Information

- Questions and concerns about IID entries, send to IIDUpdate@fda.hhs.gov
- Nomenclature corrections and questions about excipient names, send to fda-srs@fda.hhs.gov
- Questions about excipients used in development of generic products should be submitted through Controlled Correspondence. Refer to <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM411478.pdf>

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Thank you SBIA



Q&A

