

# **Morphine Milligram Equivalents (MMEs)**

Current Applications and Knowledge Gaps, Research Opportunities, and Future  
Directions

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## What is an MME?

- Definition: The amount of milligrams of morphine an opioid dose is equal to when prescribed. Calculating MME accounts for differences in opioid drug type and strength.<sup>a</sup>

*MMEs are increasingly being used to indicate abuse and overdose potential and to set thresholds for prescribing and dispensing of opioid analgesics.*

## Purpose

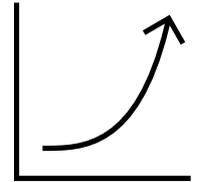
- To bring stakeholders together to discuss the scientific basis of morphine milligram equivalents (MMEs), which are widely used as metrics in multiple areas throughout the healthcare system

## Goals

- Describe the science underlying MMEs
- Describe uncertainties and complexities in calculating/applying MMEs as:
  - **Opioid Conversion Factors**
  - **Risk predictors for overdose/nonmedical use/opioid use disorder**
- Discuss a research agenda to fill knowledge gaps to refine and improve the use of MMEs across applications

# Scientific Workshop

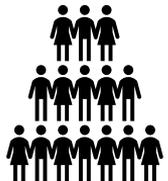
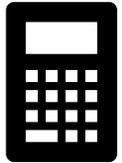
- Patients and Public Health
  - The expanded and varied uses of MMEs and the impact on patients reinforce the need to understand and build the science of MMEs
- Focus is on describing and enhancing the science
  - Discussion of specific regulatory actions, policies, and applications of MMEs is not the focus of this meeting
  - Our goal is to facilitate a productive discussion to better understand and advance the science



# Opioid Conversion Factors



- Based on small clinical studies in limited populations
  - Clinical Practice: Originally intended to assist clinicians in determining initial dose when converting an individual patient's opioid therapy
- Resources (e.g., tables, online calculators) contain different conversion factors
- Patient and drug characteristics
  - Ex. Opioid tolerance, pharmacogenetics
  - Ex. Partial agonists (buprenorphine), novel drugs (tapentadol)



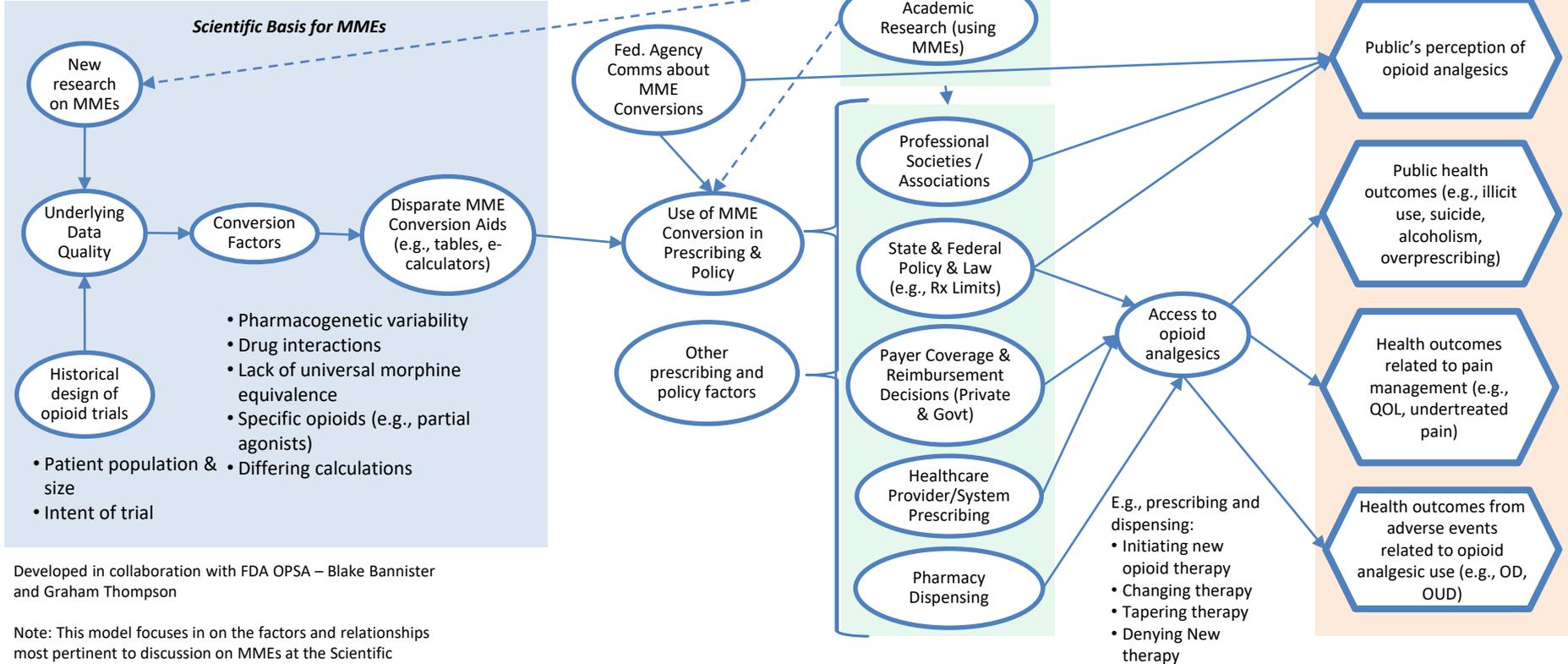
# MMEs and Risk

- Epidemiologic studies show convincing association between increasing daily dose of opioid analgesics and increasing risk of ***overdose***
  - Studies have generally used daily MME threshold categories to assess risk (e.g., > 50 MME/day, > 90 MME/day)<sup>1</sup> but stated no clear threshold
- Studies have also examined the association between daily dose and adverse outcomes (e.g., opioid use disorder/addiction, misuse/abuse), but causality is unclear

<sup>1</sup> Bohnert et al. Med Care 2016; 54(5):435-441

# Expanding Scope of Influence

## MME Influence Diagram



Developed in collaboration with FDA OPSA – Blake Bannister and Graham Thompson

Note: This model focuses in on the factors and relationships most pertinent to discussion on MMEs at the Scientific Workshop. It does not capture every factor or relationship associated with MMEs.

# Conclusion

- **Given the expanded and varied uses of MMEs, understanding and building upon the science of MMEs is needed to refine and improve the scientific basis for MME applications**
  - Scientific Workshop goals are to understand and seek to improve the scientific basis of MMEs
  - Inform a future research agenda

# Meeting Materials

- Available Online
  - Meeting agenda
  - Speaker bios and disclosures
  - Panel discussion questions

# Agenda: Day 1



- **Impact of Science on Real Life Experiences:** Penney Cowan
- **Overview of Current Applications and Uses of MMEs:** Corinne Woods
- **Calculating Conversations in Opioid Conversions:** Mary Lynn McPherson
- **Individual Patient & Medication Factors that Invalidate Morphine Milligram Equivalents:** Jeffrey Fudin
- **Opioid Prescribing and the Opioid Safety Initiative in the Veterans Health Administration:** Friedhelm Sandbrink, Thomas Emmendorfer, Fran Cunningham
- **Clarifying Questions**

Lunch

- **Overview of the Opioid NDC and MME Analytical File Compiled by CDC:** Kun Zhang
- **MHRA-UK work in development of MME tables:** Justin Pittaway-Hay
- **Improving information for opioids prescribers on the safest possible effective dose of morphine or equivalent: a UK perspective:** Maria Luisa Molinari
- **Clarifying Questions**
- **Public Comment Session**

# Agenda: Day 2

- **Welcome and Recap of Day 1:** Grace Chai
- **Opioid Conversion Information in Approved Labeling:** Mary Therese O'Donnell
- **Nonclinical Pharmacology and Toxicology Considerations Regarding Opioid Comparisons and Risk Assessments (Basic Opioid Pharmacology 101):** Dan Mellon and Donna Volpe
- **MME calculations and Abuse liability considerations:** Chad Reissig
- **Clarifying Questions**
- **Relative potency of oral and intravenous oxymorphone compared to other  $\mu$  opioid agonists in humans:** Shanna Babalonis
- **Opioid Potency: Pharmacological and Nonpharmacological Factors:** Sandra Comer
- **Inches, Centimeters, and Yards: Overlooked Definition Choices Inhibit Interpretation of Morphine Equivalence:** Nabarun Dasgupta
- **Clarifying Questions**

## Lunch

- **Panel Discussions** (FDA Co-Moderators: Judy Staffa and Jennifer Nadel)

# Panel Discussion Questions



- 1) Discuss any potential knowledge gaps in the science underlying MMEs across various applications.
  - a. Drug Considerations
  - b. Patient-Level
    - i. analgesia/opioid rotation/conversion
    - ii. risk predictor
    - iii. other
  - c. Population-Level/Public Health
    - i. risk predictor
    - ii. research
    - iii. other
- 2) Discuss types of studies and designs that may be helpful to address knowledge gaps in the science across various applications.
- 3) Discuss additional factors that should be considered to inform/supplement the use of MMEs, at a patient-level and/or population-level across the various applications.

# Panel Discussion Questions (cont'd)



- 4) Given the availability and variability of multiple MME conversion tables, analytical files, online calculators, references, and tools, discuss the benefits and limitations of a common MME reference table(s) (gold-standard) vs. multiple reference tables.
  - a. Discuss if a gold-standard reference table(s) is necessary
  - b. Discuss for what purpose(s) is it possible/feasible
- 5) Discuss calculation of MMEs (MME per day, etc.).
  - a. What are the challenges and knowledge gaps in the calculation of MMEs for patient care decisions?
  - b. Discuss whether different MME conversion factors or algorithm definitions are needed for certain patient populations (e.g., opioid-naïve patients, patients with current opioid use), for use at the patient-level or aggregate/population level.
- 6) What are other gaps in the science that haven't been discussed; where and how can research enhance/refine/develop knowledge about MMEs to support the varying applications and uses?
  - a. How should novel opioids and/or analgesics be considered in this paradigm?
- 7) Based on previous discussions, prioritize the research to fill the identified gaps.