Regulatory Utility of MMF for Development of Long-Acting Injectable Drug Products

2024 Workshop: Considerations and Potential Regulatory Applications for a Model Master File

Day 1, Session 3: MMF Applications for Long-Acting Injectable Drug Products

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May 2, 2024

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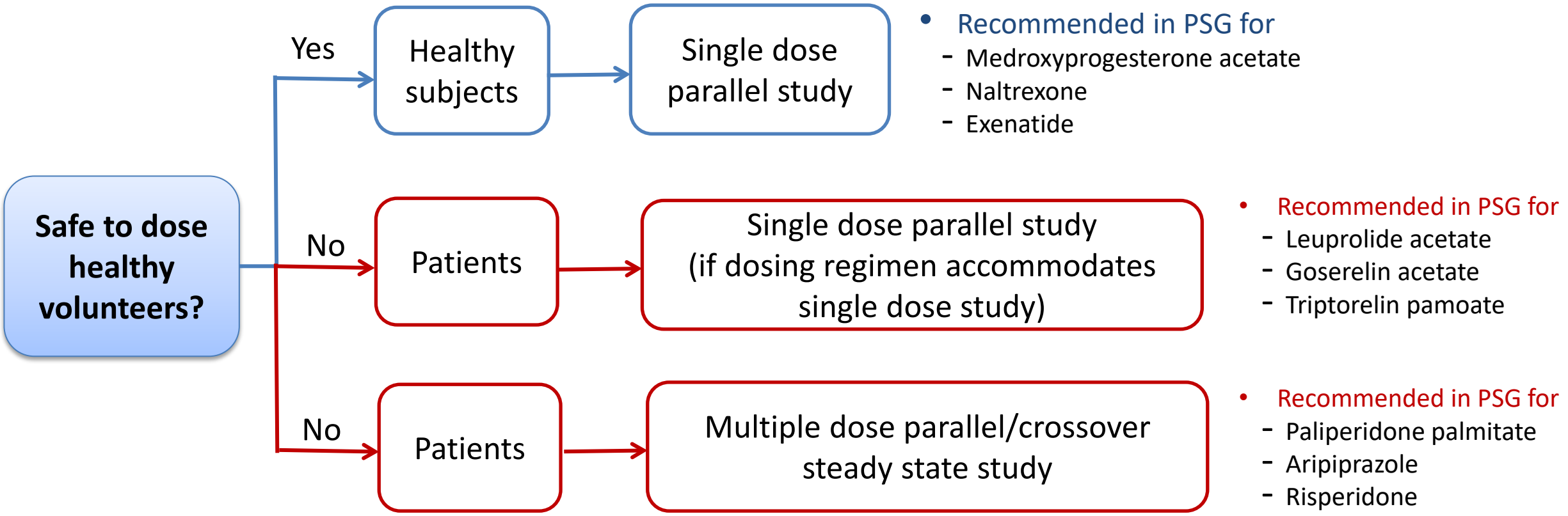
FDA Recommended PK BE Studies for LAI Products



- Recommended in PSG for
  - Medroxyprogesterone acetate
  - Naltrexone
  - Exenatide

- Recommended in PSG for
  - Leuprolide acetate
  - Goserelin acetate
  - Triptorelin pamoate

- Recommended in PSG for
  - Paliperidone palmitate
  - Aripiprazole
  - Risperidone

Partial AUC is recommended in single dose study for certain LAI products based on considerations on clinical relevance/formulation characteristics

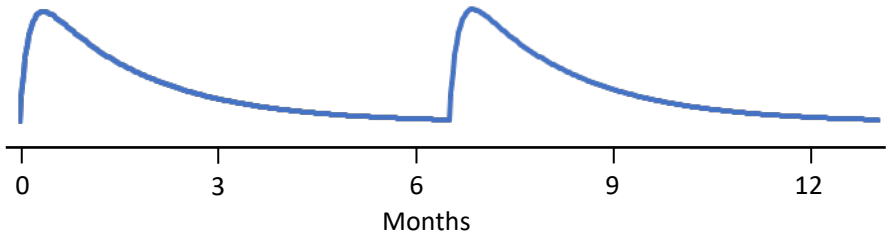
PK: pharmacokinetics
BE: bioequivalence
LAI: long-acting injectable
PSG: product-specific guidance

Slide courtesy of Yuqing Gong, Ph.D.: *Considerations and Challenges of Pharmacokinetics Bioequivalence Studies for LAIs and the Application of Model-Integrated Evidence (MIE) Approaches, GBHI 2024, Apr. 16, 2024*

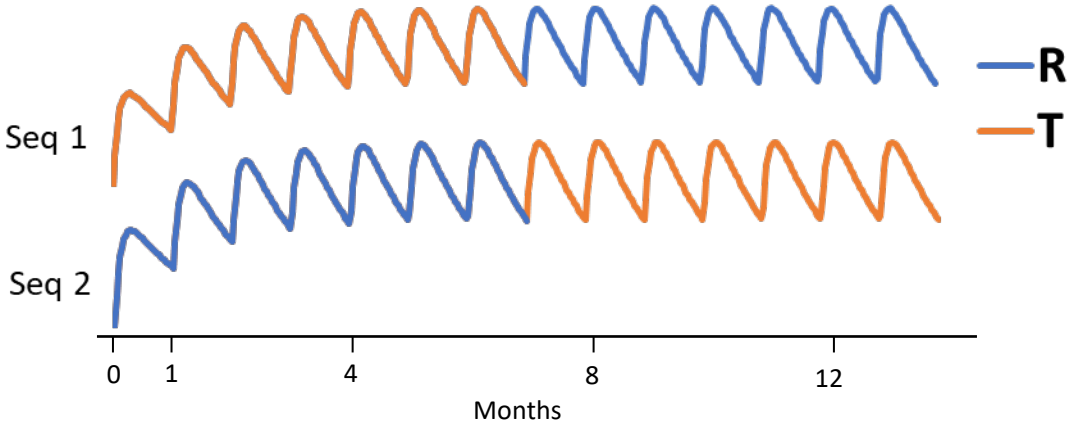
Challenges in BE Studies for Generic LAIs

- For most LAIs, there are no approved generics to date.
- Due to the long-acting nature of LAIs, in vivo BE studies can last for several months or even years.
  - Long study duration
  - High variability/large sample size
    - Parallel study design, multiple clinical centers, demographics, etc.
  - Recruiting difficulty
    - BE studies often need to be conducted in patients for safety concerns
  - High dropout

LAI: long half-life, long washout



Single-dose crossover BE study – not practical



Steady state crossover BE study – long study duration

Slide courtesy of Yuqing Gong, Ph.D.: *Considerations and Challenges of Pharmacokinetics Bioequivalence Studies for LAIs and the Application of Model-Integrated Evidence (MIE) Approaches, GBHI 2024, Apr. 16, 2024*

Opportunities for MIE in Generic LAI Development

- Two different strategies for alternative BE approaches supported by model-integrated evidence (MIE)
  - Conduct the PK BE studies, but enhance their efficiency (e.g., alternative design strategies) through population PK (popPK) modeling
  - BE based of in vitro characteristics/studies in lieu of conducting PK BE studies mediated through mechanistic modeling such as physiologically based PK (PBPK) modeling
- Generate pivotal evidence through MIE for BE decision via:
  - a prespecified model-based analysis of an in vivo BE study
  - a virtual bioequivalence (VBE) study
- We see a clear demand: increased use of modeling approaches in pre-ANDA meeting requests and ANDA submissions

Slide adapted from Yuqing Gong, Ph.D. and Miyoung Yoon, Ph.D.

Opportunities for MIE in Generic LAI Development – popPK

- Enhance the efficiency of PK BE studies
  - Alternative BE study designs with …
    - Shorter study duration
      - In silico continuation to simulate steady-state from non-steady state conditions
      - Carryover adjustment to account for no washout in patient studies
      - Switch-over and repeated designs
      - Alternative BE metrics associated with narrowed BE limits
    - Smaller sample size
      - Incorporation of reference scaling
      - Carryover adjustment to allow crossover design over parallel
      - Optimal study design strategies

Opportunities for MIE in Generic LAI Development – Mechanistic Modeling

- Mechanistic models can integrate key formulation attributes and physiology
  - Integrate key formulation attributes and physiology to predict PK
  - Define safe space between test and reference drug products
  - Guide selection of clinically relevant/in vivo predictive in vitro studies
  - Mechanistic in vitro-in vivo correlation (IVIVC) by incorporating in vitro release or dissolution data in PBPK models

Regulatory Considerations for Using MIE

- Meeting regulatory standards to generate BE evidence
  - Sensitive to detect formulation difference with confidence
  - Reasonable passing rate for BE products
- Sufficient model verification and validation for the intended regulatory use
  - Capable to discern formulation difference with type 1 error control
  - Characterization of uncertainty and impact on BE determination
- Modeling analysis plan prior to seeing study results
  - Communication with the agency via Controlled Correspondence, Pre-ANDA interactions, or through NEW MIE Industry Meeting Pilot Program

Slide adapted from Miyoung Yoon, Ph.D.: Model-Integrated Evidence for Bioequivalence Assessment of Long-Acting Injectables From a Generic Drug Perspective, *CRCG LAI MIE Workshop, Nov. 30, 2021*

MMF Use Cases in popPK

- Establish alternative study designs and evaluation from conventional approaches that can applied across a long range of products
  - **Shorter duration** in vivo PK studies
  - Reduced sample size and treatment cycle-compatible in vivo PK studies

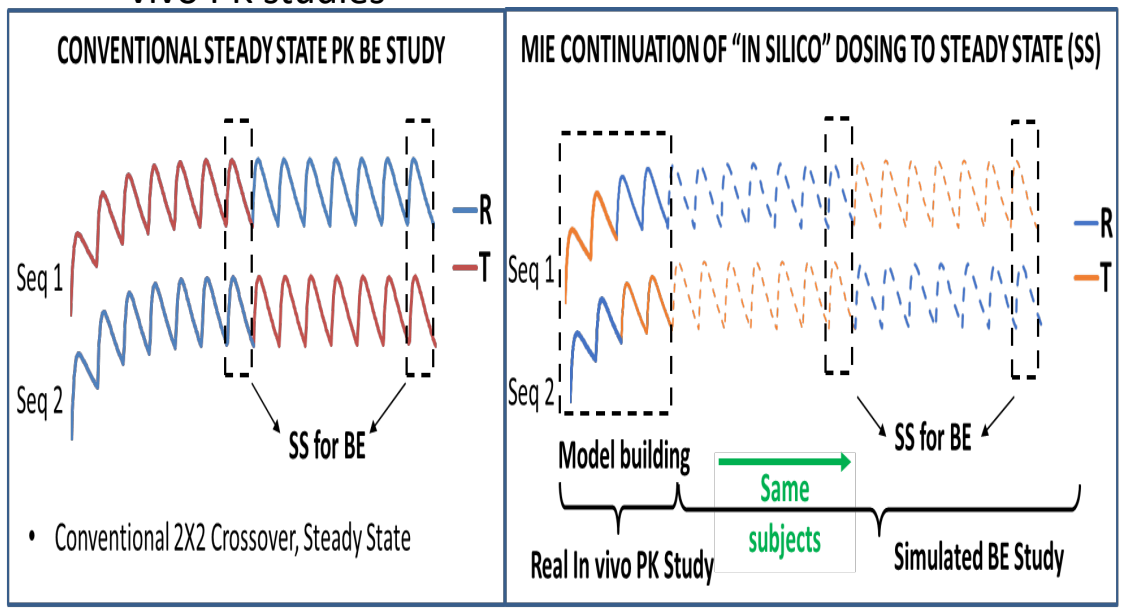
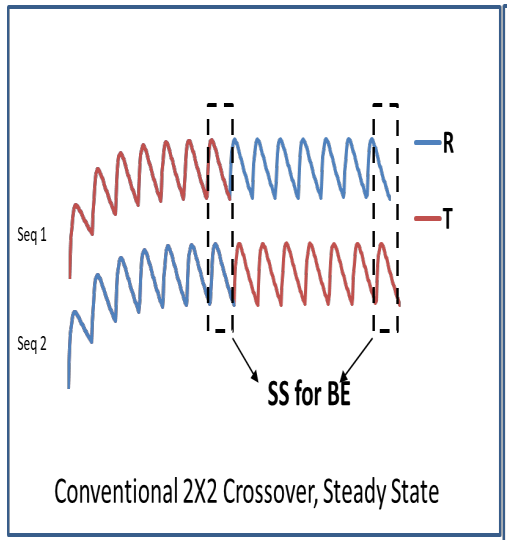


Illustration of In silico Dosing MIE for LAI products

  - **Reduced sample size** and shorter duration in vivo PK studies
  - MIE framework for LAIs by Uppsala University (GDUFA research*) can be applied

*FDA Research Contrac#75F40119C10018



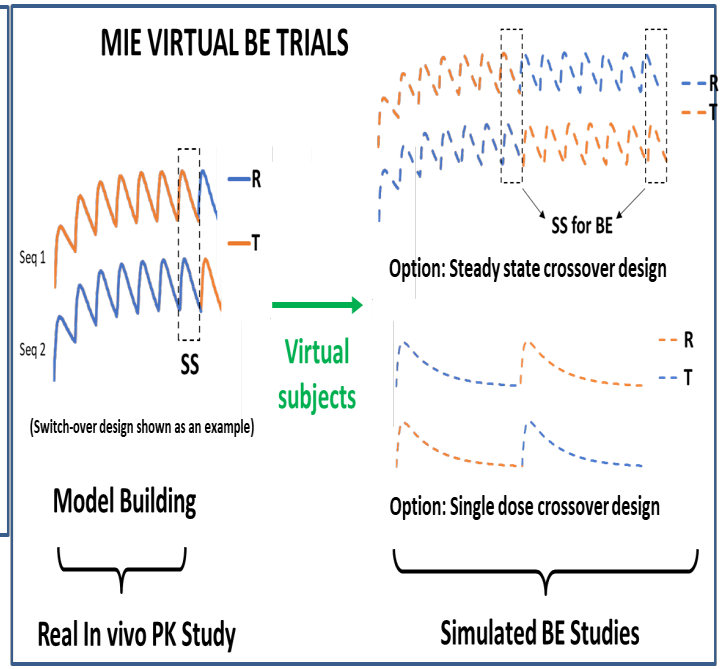


Illustration of Virtual BE MIE for LAI products

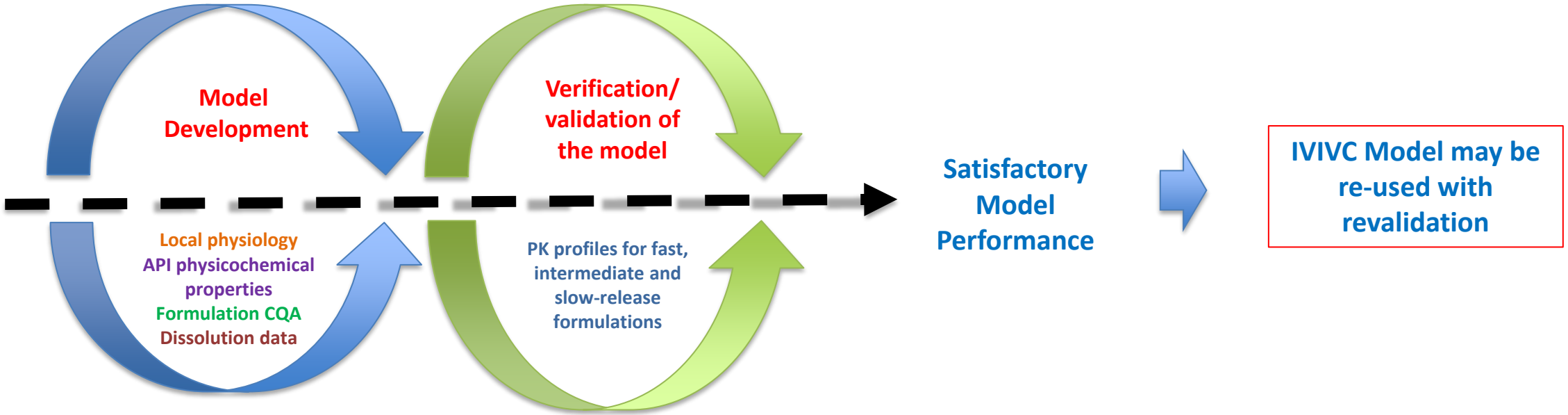
Slide adapted from Miyoung Yoon, Ph.D.: Model-Integrated Evidence for Bioequivalence Assessment of Long-Acting Injectables From a Generic Drug Perspective, *CRCG LAI MIE Workshop, Nov. 30, 2021*

MMF Use Case: Mechanistic IVIVC for LAI

Major CQA in an LAI suspension is “particle size”

Use conventional Level-A IVIVC established by the NDA applicant

Here comes the opportunity for mechanistic IVIVC model as MMF use case…



Final Thoughts – Benefits of LAI MMF

- Establish alternative methodologies for establishing systemic PK BE to the typical single-dose parallel or multiple-dose steady state crossover studies
- Establish mechanistic modeling platforms to support BE approaches without conduct of the systemic PK BE study
- MMFs would provide implementation details including verification and validation such that approach can be applied across a wide range of drug products …
  - Saving industry time in redeveloping and submitting these methods
  - Increasing industry confidence that deviations from the PSG may be permissible particularly in alternative in vivo PK study designs
  - Benefiting regulators in reducing assessment these methods across applications (e.g., ANDAs)

Acknowledgments

OGD/ORS/DQMM:

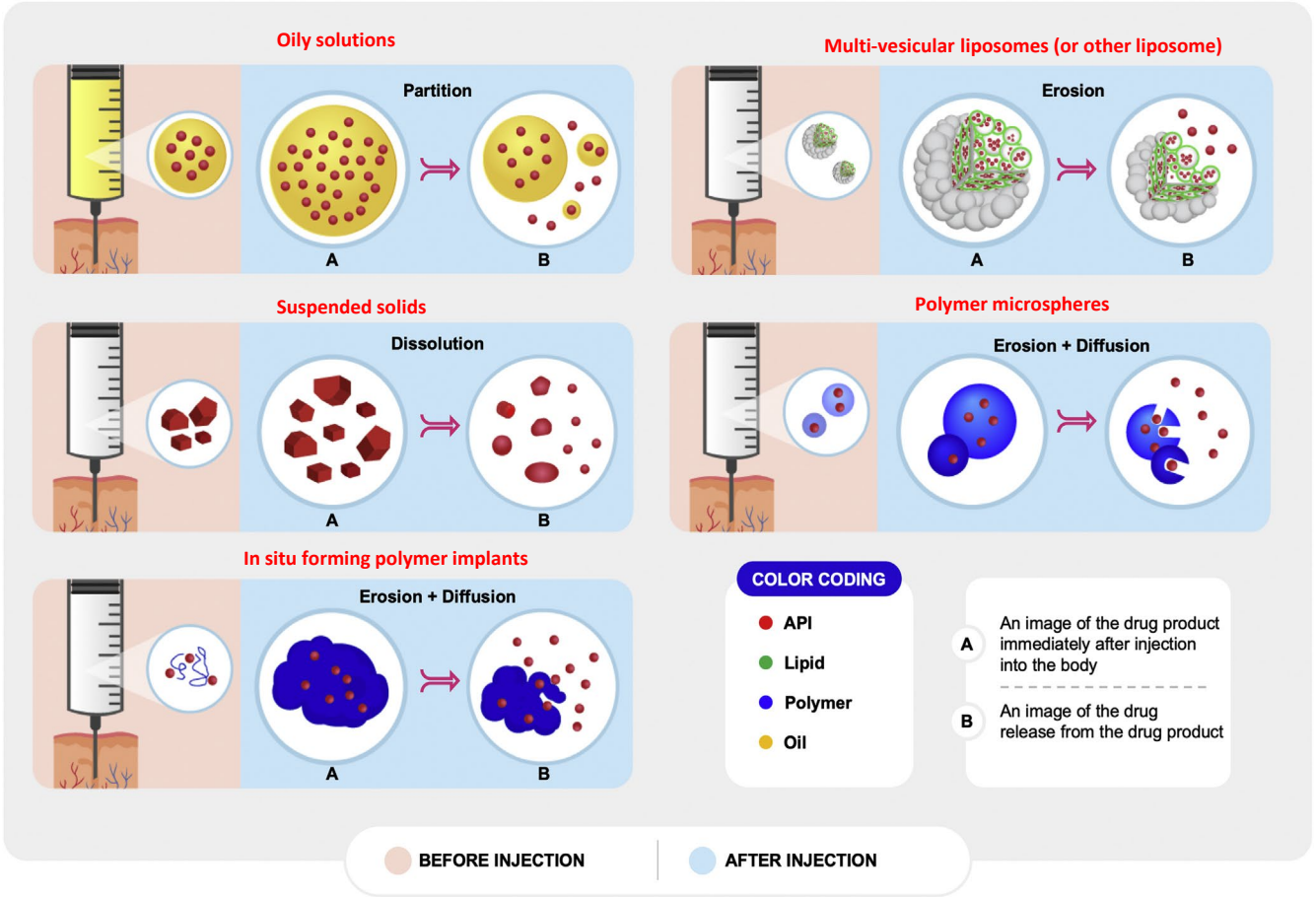
- Yuqing Gong
- Khondoker Alam
- Miyoung Yoon (*formerly*)
- Eleftheria Tsakalozou
- Lucy Fang
- Liang Zhao

BACK-UP

MMF Use Cases in Mechanistic Modeling

Each LAI formulation type is unique in terms of formulation complexity and in vivo release behavior.

- The in vivo release and subsequent absorption of API may be governed by partition, dissolution, erosion or diffusion processes.
- Depending on formulation type, complexity and route of administration, one or more process may predominate
- The PBPK model developed for certain type of LAI may not adequately describes the ADME process for other type of LAI
- PBPK model of each type of LAI has distinct formulation CQA (as input parameter) and physiology-formulation interaction
- When suitably verified, a PBPK model developed for certain LAI type may be cross-referenced for similar LAI drug products.



Journal of Controlled Release Volume 336, 10 August 2021, Pages 144-158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