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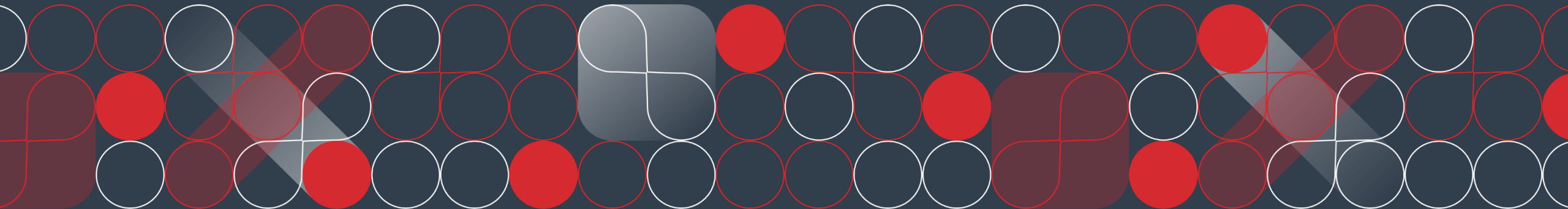
Application of mechanistic PBPK modeling to understand drug release from PLGA-based solid implants

Sub session 1: Tackling Product Complexity Through In Vitro and In Silico Approaches

Naresh Mittapelly, Senior Research Scientist



Outline

- Introduction
- Challenges to establishing equivalence
- Modeling of in vitro drug release - Nafarelin case example
- In vitro to in vivo extrapolation (IVIVE) - Buserelin case example
- Impact of CQAs on virtual bioequivalence outcome
- Summary

Introduction

- Long-acting injectable drug products(LAIs) such as polymeric implants, microparticles, and suspensions etc., are considered to be complex drug products
- The development of a generic LAI product can be challenging and at the same time rewarding
- To develop a generic version of an LAI that is equivalent to the Reference product the sponsor must establish different levels of equivalence i.e.:

Qualitative (Q1) sameness	Quantitative (Q2) sameness	Physicochemical and structural (Q3) similarity
• Same active and inactive ingredients	• Same proportion of active and inactive ingredients	• Same physical and structural properties (e.g. particle size, polymorphic form, dissolution, microstructure etc.)

Challenges to establishing equivalence

Making generic versions of LAI products presents unique scientific and regulatory challenges. These formulations require overcoming hurdles in formulation development, manufacturing, bioequivalence analysis and regulatory approval.

- Complex Formulation and manufacturing
  - *Understanding the formulation is crucial for example, for PLGA-based delivery systems, it is essential to achieve the same composition, molecular weight and drug release as that of the Reference product*
  - *Nanoparticles / Liposomes-encapsulation methods, particle size distribution impacts drug release requiring precise control over different unit operations*
  - *Particle suspensions: Particle size distribution and particles stability are two important factors to consider*
- Drug Release and PK profile matching
  - *IVIVCs – it is difficult to establish direct in vitro-in vivo correlations due to complex release mechanisms and long duration of study for LAI products*
  - *PK point of view - sponsor needs to match burst release(s) and tail phase with Reference product*
- Bioequivalence
  - *Clinical PK testing of LAI products requires different considerations for example, clinical study design - parallel vs crossover, recruitment of individuals , variability in patient response*

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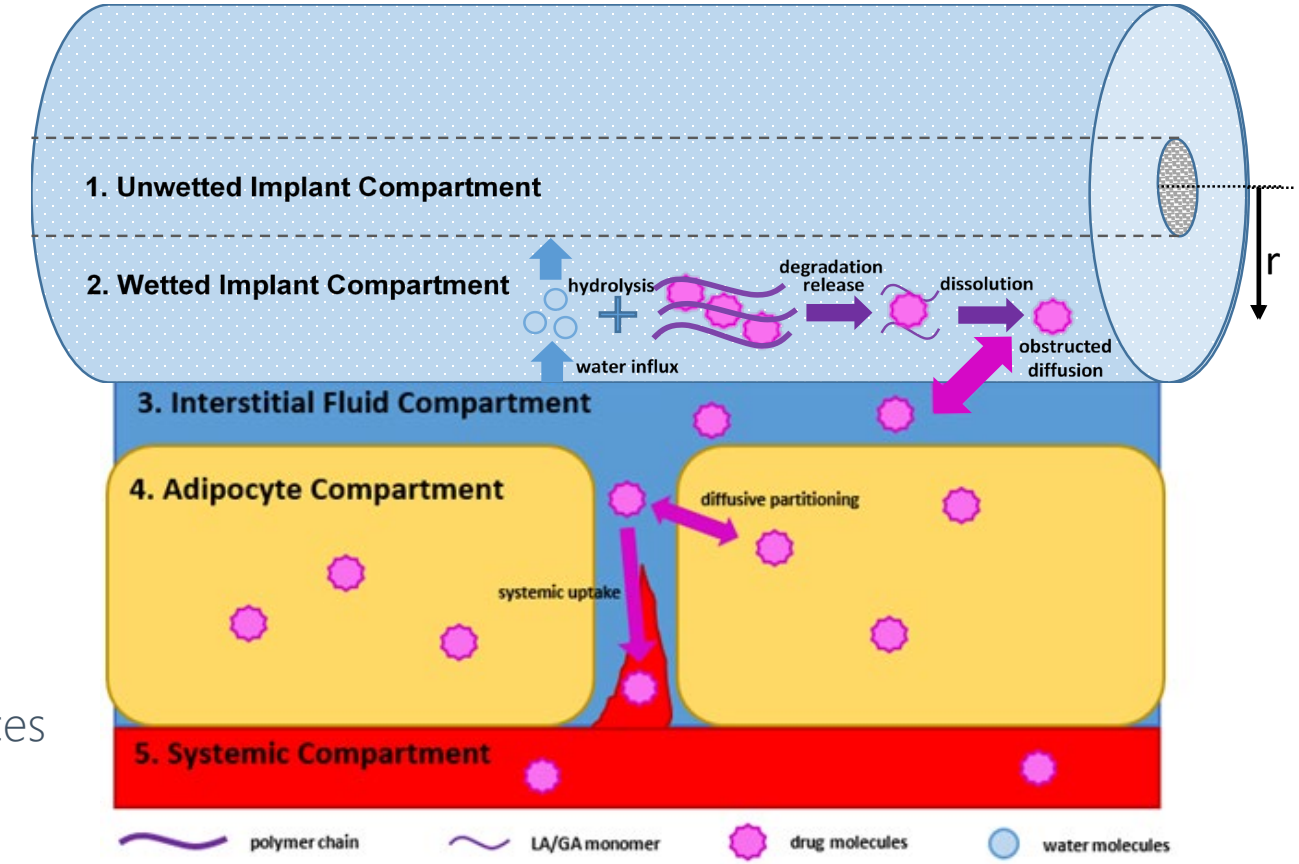
Modeling of In vitro drug release from solid implants

- The Simcyp LAI model was developed to describe the drug release from PLGA-based solid implants
- Various processes were considered
  - Wetting
  - Non-catalytic hydrolysis of PLGA
  - Autocatalysis
  - Dissolution of oligomers
  - Dissolution of drug
  - Liberation of drug
- The model requires parameters from different sources
  - Drug physicochemical properties
  - Polymer and Formulation Characteristics
  - Other



Structure of the model

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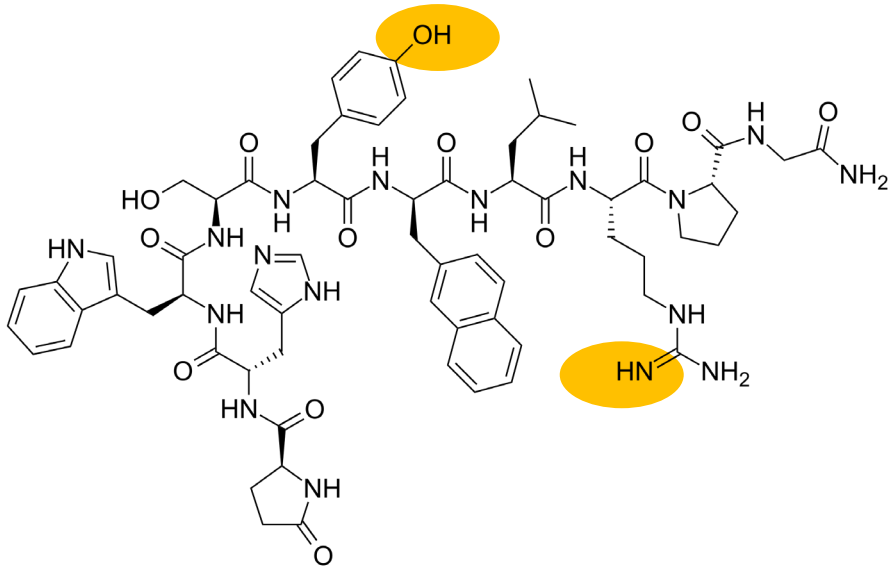
Nafarelin solid implants release model

Prolonged Controlled-Release of Nafarelin, a Luteinizing Hormone-Releasing Hormone Analogue, From Biodegradable Polymeric Implants: Influence of Composition and Molecular Weight of Polymer

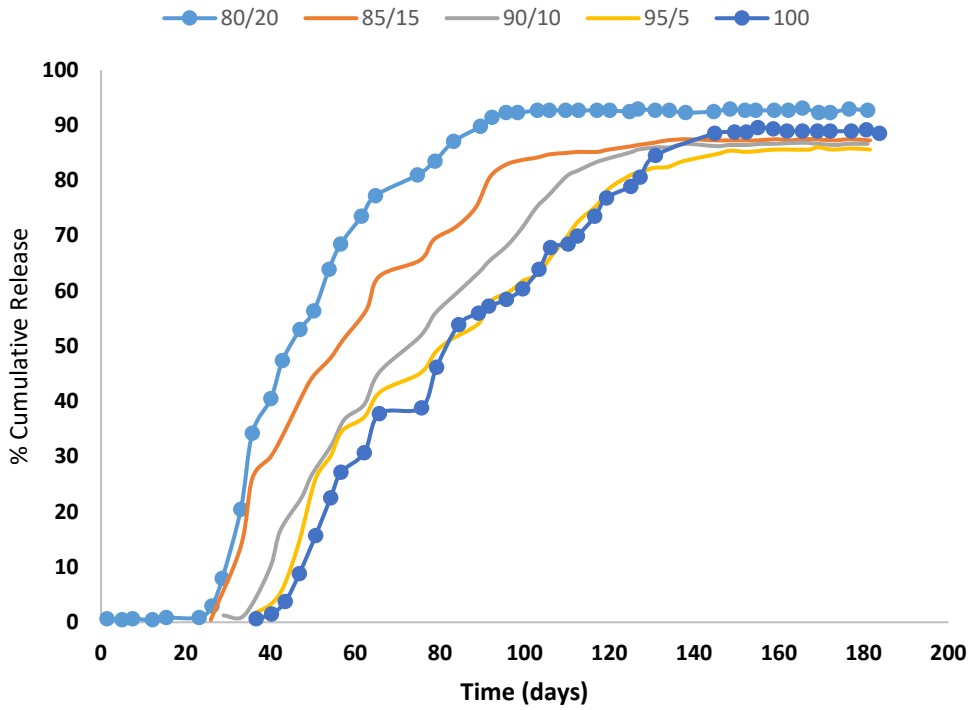
L. M. Sanders*x, B. A. Kell*, G. I. McRae*, and G. W. Whitehead‡

Received September 23, 1985 from *Syntex Research, Palo Alto, CA 94304, and ‡ Syntex Chemicals, Boulder, CO 80301-2880. Accepted for publication February 4, 1986.

- Nafarelin is a gonadotropin-releasing hormone (GnRH) agonist used for the treatment of endometriosis and early puberty



Ampholyte, pKa1 - 9.49 and pKa2 - 13.26



Cumulative release of nafarelin acetate from different PLGA implants in vitro

https://doi.org/10.1002/jps.2600750407

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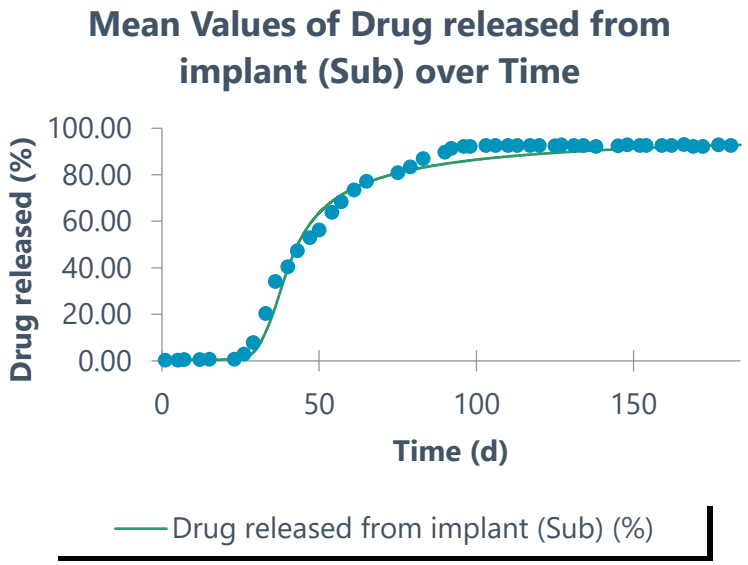
Nafarelin(Cont.,)

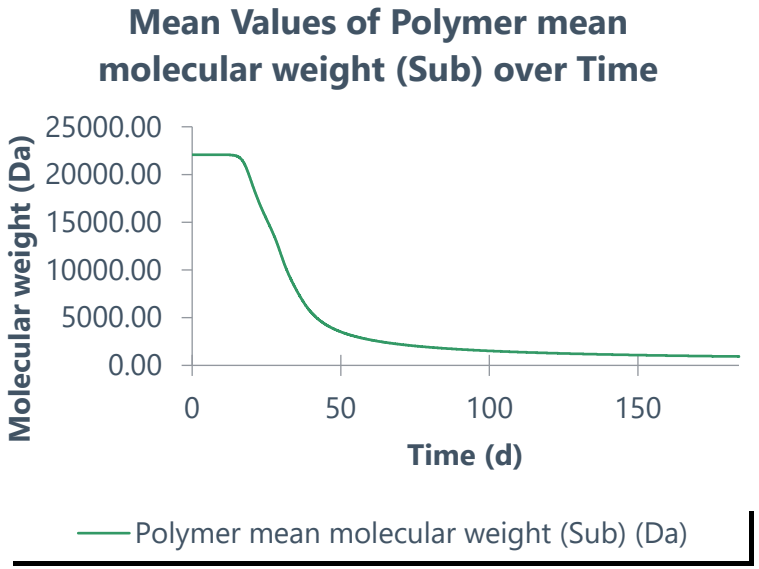
Parameterization of the model

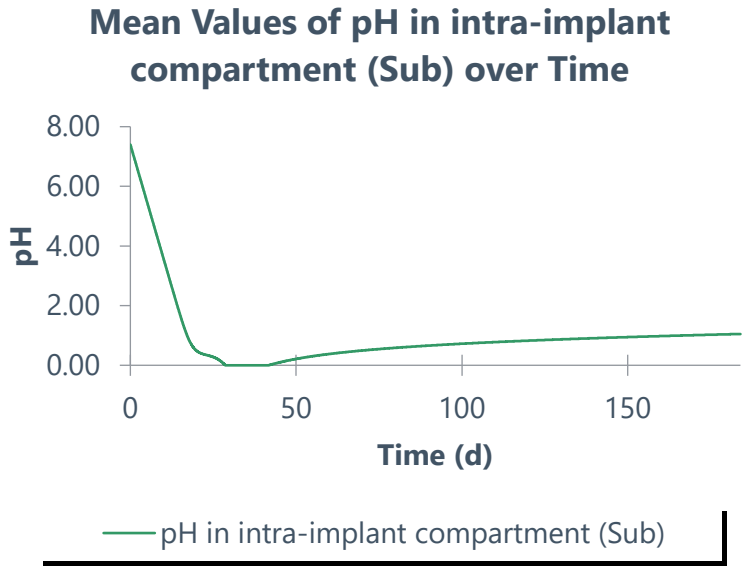
- Implant Parameters
  - ✓ *Length – 1.77 mm*
  - ✓ *Diameter - 3 mm*
  - ✓ *Mass of the implant - 20 mg and Drug loading - 5% w/w*
- Formulation Characteristics
  - ✓ *Lactide to glycolide ratio-80:20,85:15,90:10 and 100:0*
  - ✓ *Intrinsic viscosity of PLGA- 0.33-0.38 dL/g(5% solution in hexafluoro isopropyl alcohol)*
  - ✓ *Immediate releasable fraction ?*
  - ✓ *Fractional volumetric porosity ? - assumed to be 5%*
- In vitro release conditions
  - *pH 7.4 ethanolic phosphate buffer @ 37 degC*
  - *Volume of media ? - assumed to be 10 mL*

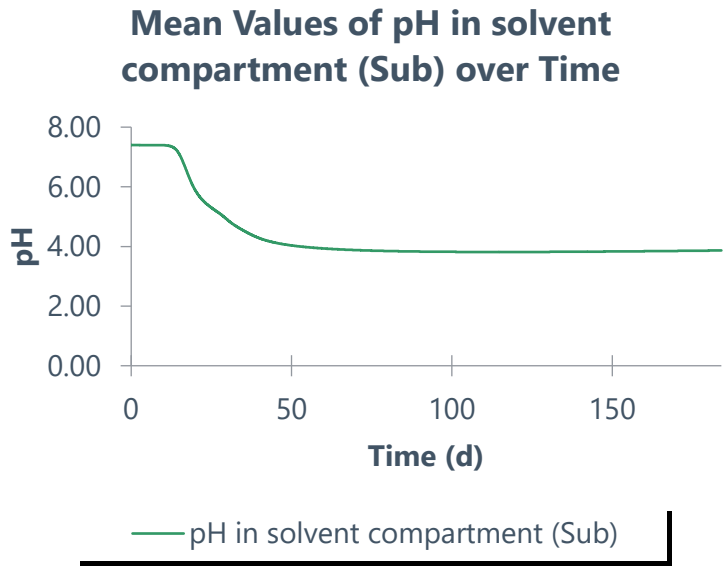
Nafarelin(Cont.,)

Results









- ✓ The model development was performed by adjusting the parameters "ionization proportionality constant", "de-ionization constant" and initial porosity of implant, using 80/20 formulation data,
- ✓ For other formulations, the drug release was simulated by changing the PLGA polymer-related parameters

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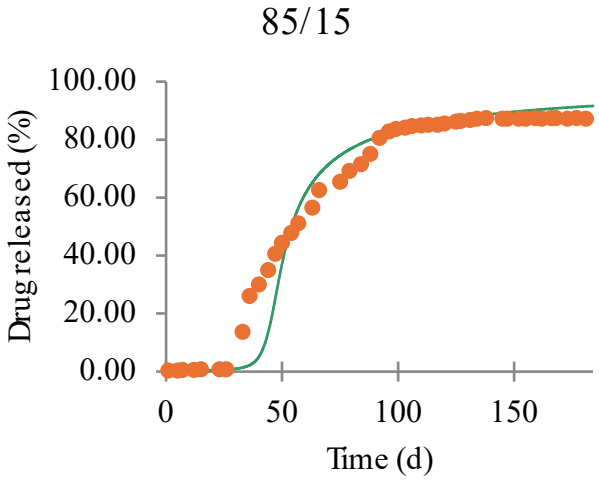
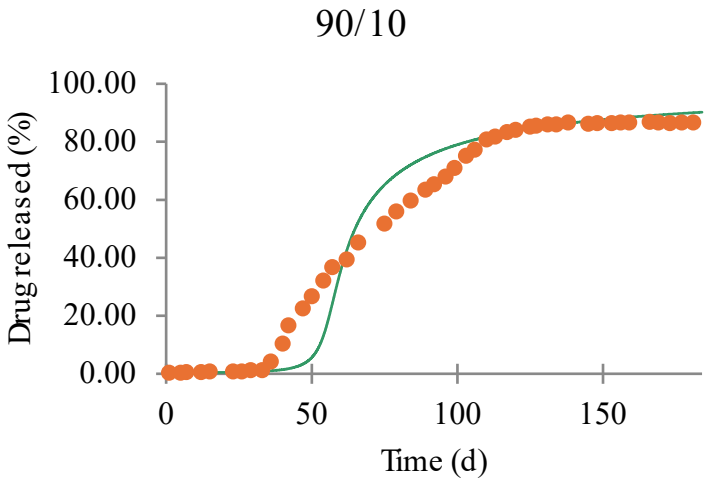
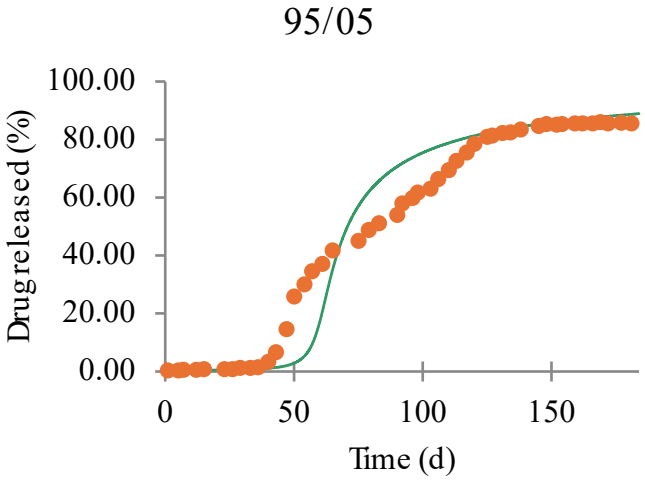
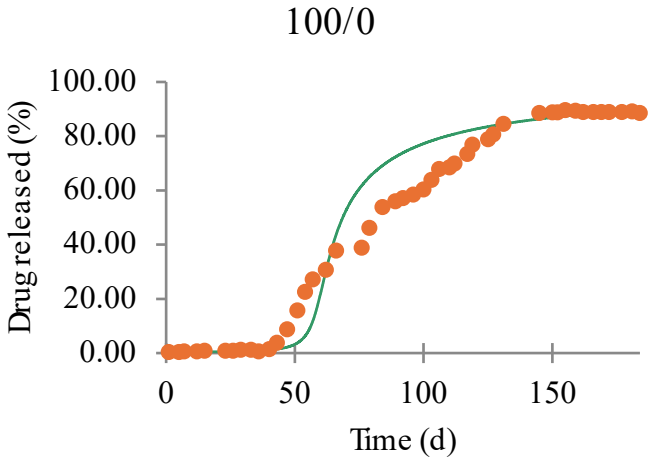
Nafarelin(Cont.,)

Results





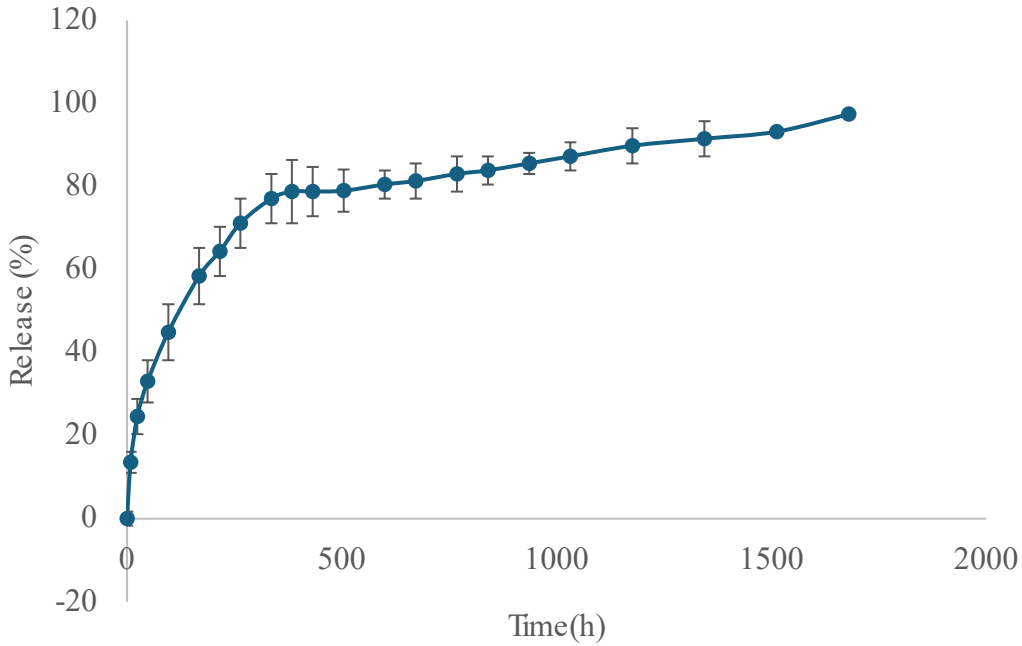




- ✓ The simulation results are close to the observations
- ✓ As the lactide content in the formulation increases, there is a delay in drug release
- ✓ It is possible that certain formulation parameters, for example, porosity, can be different between these formulations at the moment, we assumed Q3 is same for all these formulations

In vitro to in vivo extrapolation (IVIVE)-Buserelin

- Buserelin implant is marketed in Canada under the brand name Suprefact for the palliative treatment of advanced prostate cancer
- In vitro release was reported by Schliecker et al, where the experiment was carried out with 12 mL PBS (0.05 M, pH 7.4) containing benzalkonium chloride and sodium azide at 37 deg C. The vials were only shaken for 5s at sampling time
- Implant dimension and formulation information were taken from the Schliecker et al publication



Release of buserelin from commercial implant reported by Schliecker et al.

Schliecker G, Schmidt C, Fuchs S, Ehinger A, Sandow J, Kissel T. In vitro and in vivo correlation of buserelin release from biodegradable implants using statistical moment analysis. J Control Release. 2004 Jan 8;94(1):25-37. doi: 10.1016/j.jconrel.2003.09.003. PMID: 14684269.

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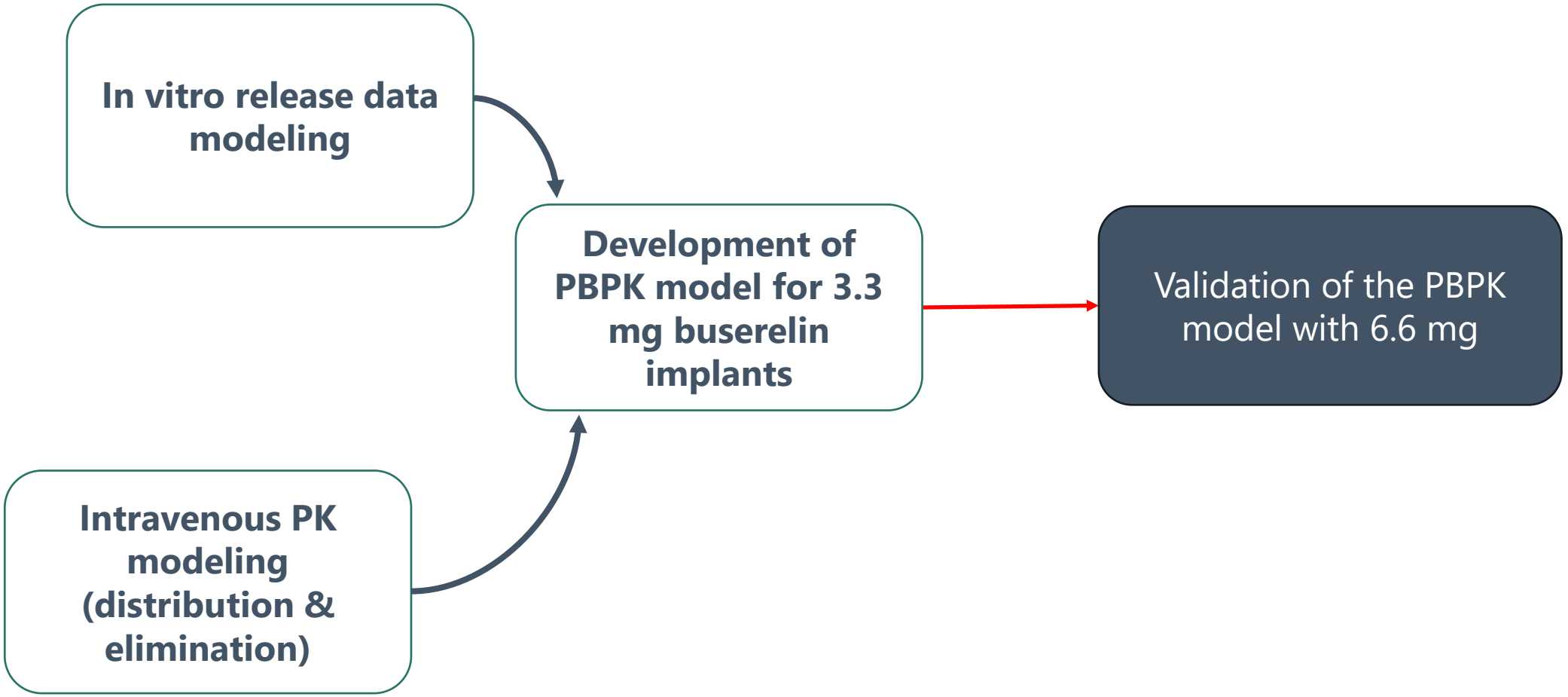
In vitro to in vivo extrapolation (IVIVE)-Buserelin

Workflow



The workflow presenting development and validation of the PBPK model for buserelin solid implants

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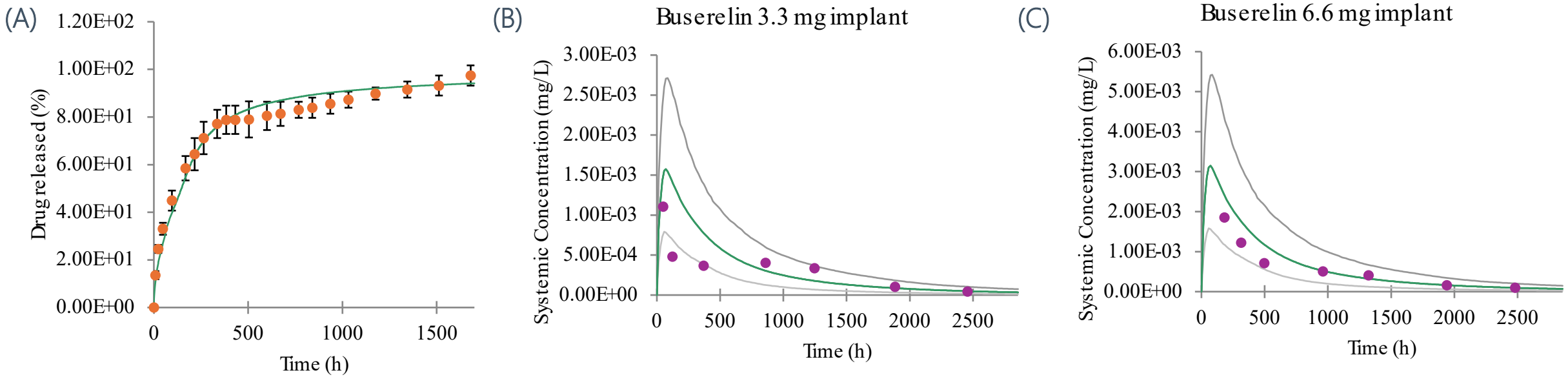
In vitro to in vivo extrapolation (IVIVE)-Buserelin

Results



Simulation results (A) in vitro release 3.3 mg buserelin solid implant, in vivo pharmacokinetics (B) 3.3 mg implant (n=1000) and (C) 6.6. mg implant (n=1000)

- ✓ The in vitro release model was developed using the observed data.
- ✓ Later, the in vitro model parameters were transferred to the in vivo model, assuming the in vitro method is bio-predictive in nature
- ✓ The absorption-related parameters(partition coefficients/diffusion coefficients) were adjusted to develop the 3.3 mg implant model
- ✓ The model was validated using 6.6 mg solid implant clinical PK data

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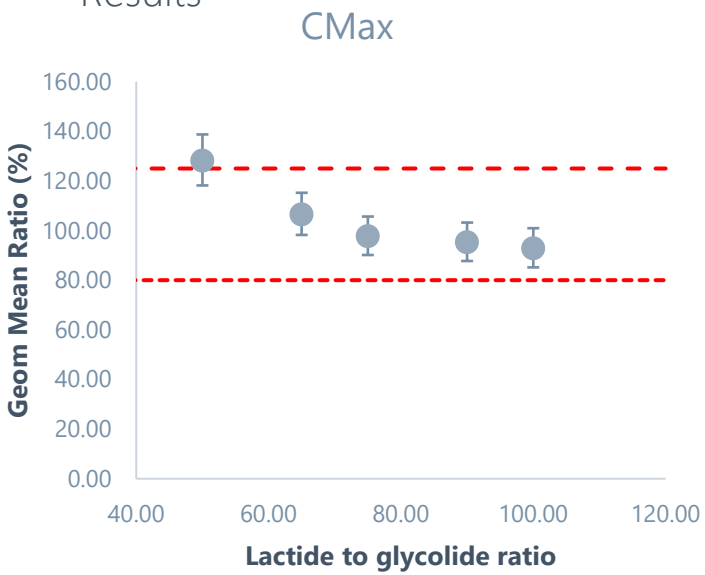
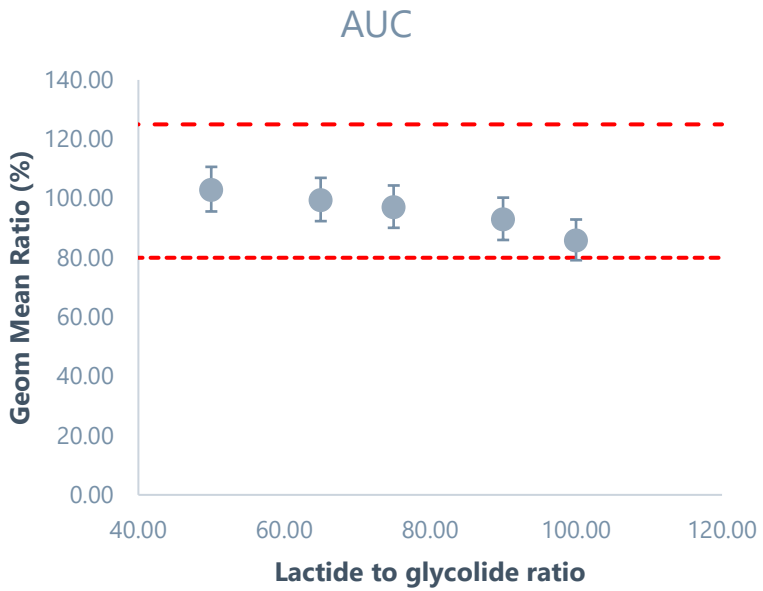
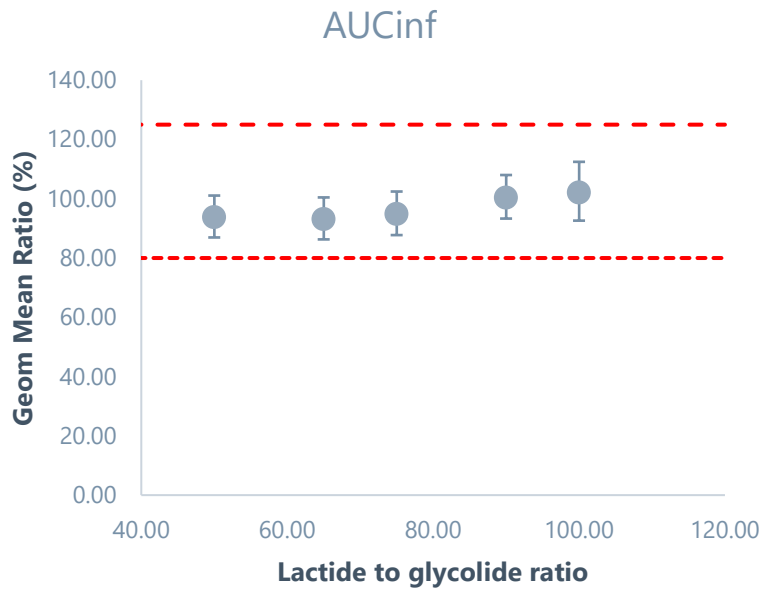
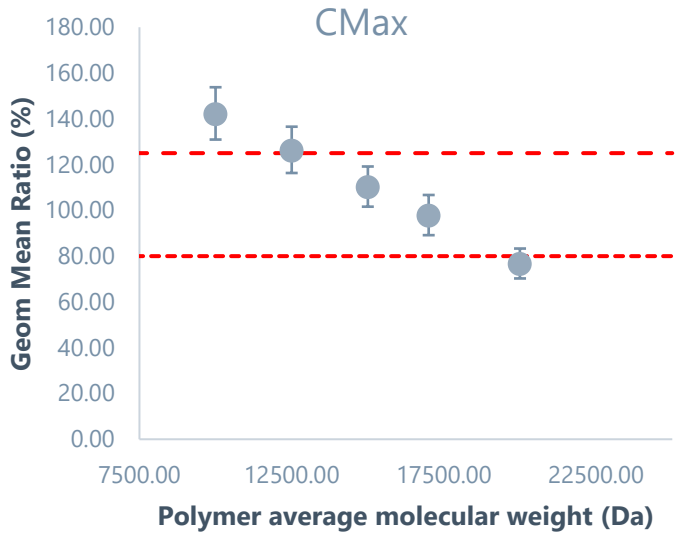
Impact of CQAs on virtual bioequivalence (buserelin implants)

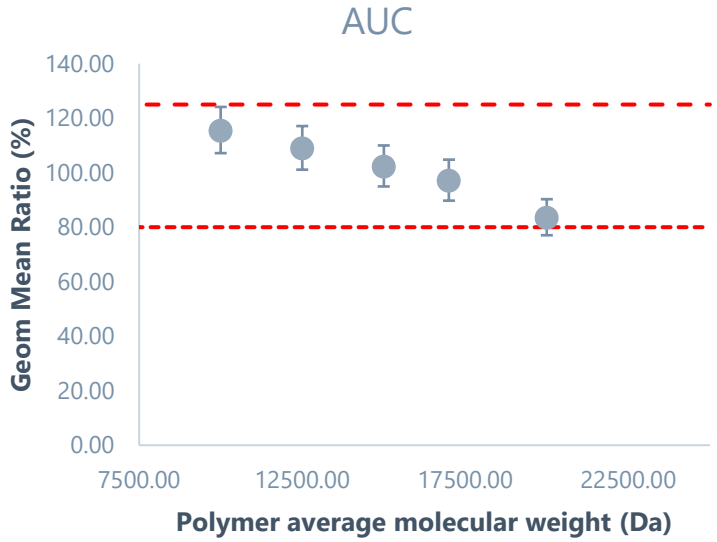
Results

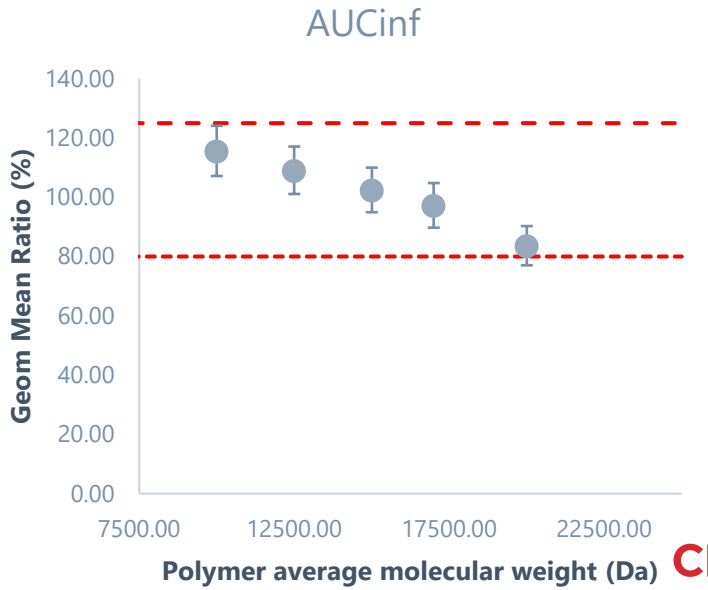












Summary

- Discussed different challenges for the development of generic LAI products
- Gaps identified
  - *Reverse engineering of solid implants/characterization of implants of Q1,Q2 and Q3*
  - *Testing of implants using bio-relevant/bio-predictive methods*
  - *Characterization of implants for mechanistic understanding of drug release by studying changes in PLGA molecular weight, water uptake profile, porosity/pore size characterisation, implant pH profile, etc*
  - *Development and study of alternate formulations can provide mechanistic insights to help in advancing the model*
- The in silco modeling & simulation can go hand in hand with empirical release testing, to enhance the understanding of release mechanisms and product behavior during optimization.

Acknowledgements

✓ Certara Predictive Technologies

Team

Alexandre Djehizian

Clairissa Corpstein

Krishna Chaitanya Telaprolu

Kevin McNalley

Natlie Morris

James Clark

Supervisors

Frederic Bois (Retired)

Sebastian Polak

Masoud Jamei

✓ US Food and Drug Administration (FDA)

✓ Collaborators

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Thank you