Application of Modeling and Simulation in Establishing Appropriate Bioequivalence Limits for Complex Formulations

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Challenges in Establishing Bioequivalence for Complex Formulation

- Local delivery: Plasma concentration may not be appropriate surrogate of pharmacological activity.
- Long acting: High dropout rates due to long study duration
- Comparative Clinical Endpoint Study: Insensitive and large number of subjects

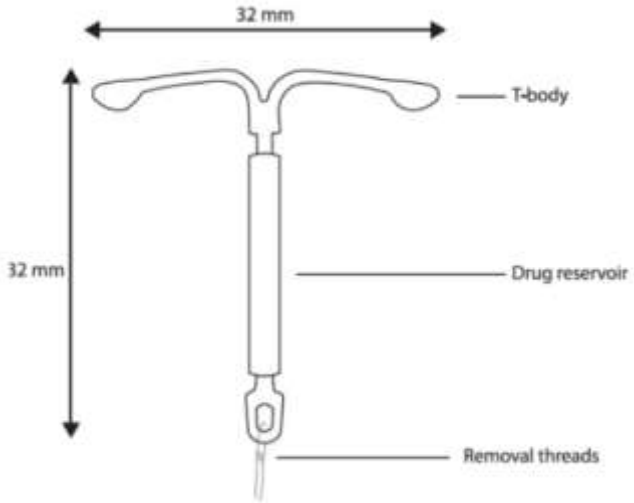
Advancing Regulatory Science with Modeling and Simulation at FDA

- Modeling and Simulation can play an important role in proposing new bioequivalence metric and approaches.

- In this direction today I will present a case study where we used modeling and simulation to propose an alternate BE criteria at 1 year for a long acting (i.e., 5 year) complex product.

Background

- Levonorgestrel (LNG) Intrauterine System (IUS): Progestin containing intrauterine system indicated for:
  - Intrauterine contraception for up to 5 years
  - Treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception
- T-body: 52 mg levonorgestrel
- Initial release rate of about 20 mcg/day which is reduced by about 50 % after 5 years.



- Approved: US (2000)

Challenges With Conventional PK Based BE Approach

- Due to local delivery of levonorgestrel, a conventional pharmacokinetic (PK)-based bioequivalence (BE) approach might not be relevant.

- In addition, considering that this product is designed to deliver LNG up to 5 years, a comparative clinical endpoint bioequivalence study lasting for 5 years may not be practically feasible.

- Accordingly, explored alternative BE study designs that involve product physicochemical characterizations and a short term BE study.

- The current presentation assesses BE metrics and statistical criteria, using quantitative modeling and simulation approaches, for the alternative in vivo BE approaches for generic LNG IUS.

Residual LNG as Potential Alternative BE Metric

- LNG IUS's local action and practical limitation with direct measurement of LNG at the site of action.

- Residual LNG, which directly relates to the absolute amount of LNG delivered while inserted, was evaluated as a potential alternative BE metric for BE determination of LNG IUS.

- We evaluated 90 % confidence intervals (CI) on residual LNG at time points up to 5 years.

- Our analysis suggests that having 90% CI of that the residual LNG amount at first one-year (12 M post insertion) is within 95-105.26% would ensure that residual LNG amount at five year is within 80 – 125 %.

Data And Quantitative Model

- Residual Levonorgestrel (LNG) data from an array of IND and NDAs with study durations of 1, 3, and 5 years

- Time course of Residual LNG was explained using:

$$\boldsymbol{Residual\ LNG = A \cdot e^{-k \cdot t}}$$

$$A = A\ constant\ representing\ LNG\ content\ (mg) at\ t = 0$$
$$k = First\ order\ constant\ (day^{-1})$$
$$t = time\ (days)$$

Model Assumptions

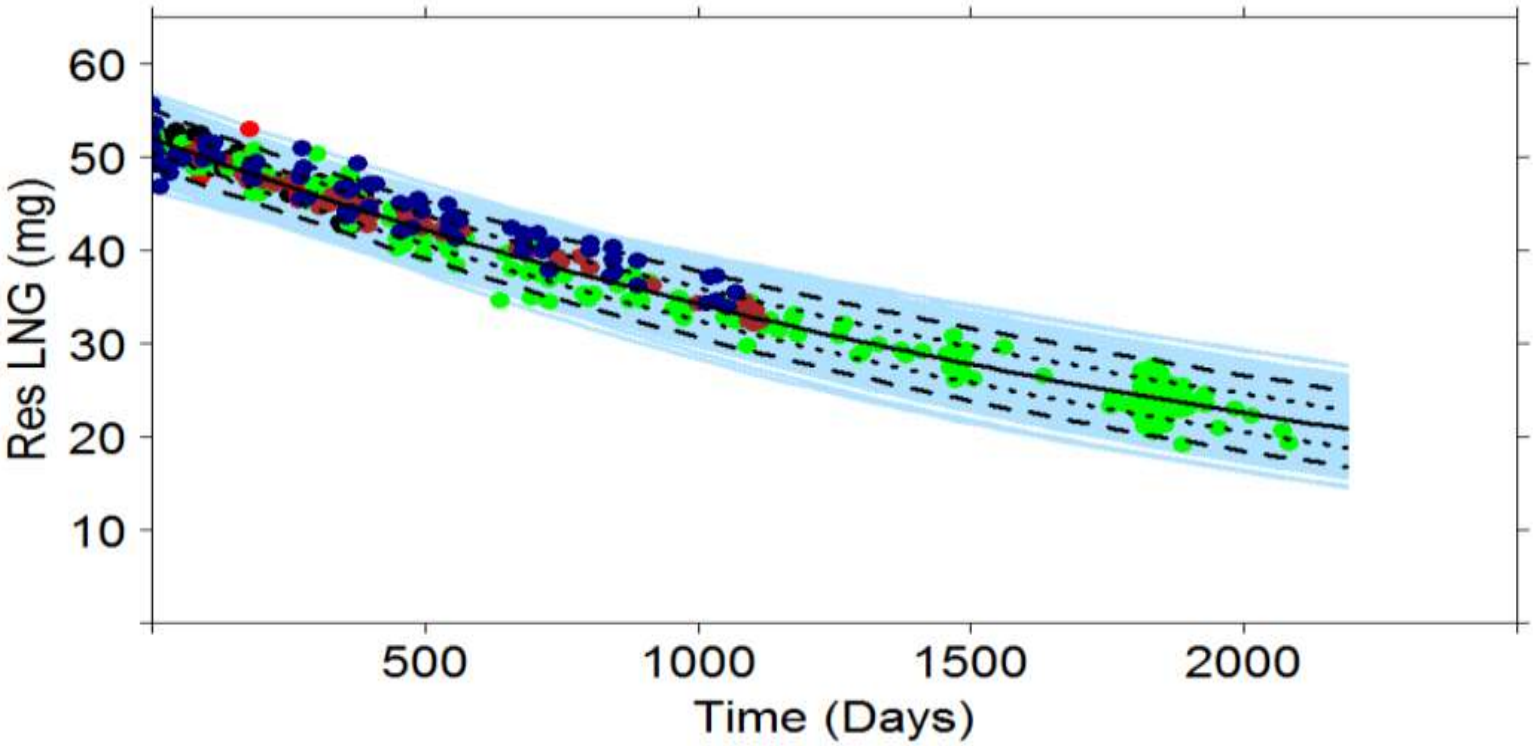
- Product Specification: The initial content of Levonorgestrel was assumed to be between 47 – 57 mg/system.

- Virtual population incorporating the variability, under following assumptions:

    1. CV of 3% for A (mean 52 mg) provided a range of initial LNG in 47 – 57 mg/system.

    2. For release rate constant different CVs (i.e. 5 %, 10% and 15%) for k were tested and a CV of 10 % with a mean release rate constant of 4.2×10^{-4} per day provided a reasonable explanation of observed residual LNG.

Residual LNG from Virtual Population (n = 1000) and Observed data



Study Design

- Hypothetical generic test products with release rate constants differing by 5% up to 100% (δ) as compared to RLD were generated (i.e. $\mu_R \pm \delta \times \mu_R$)

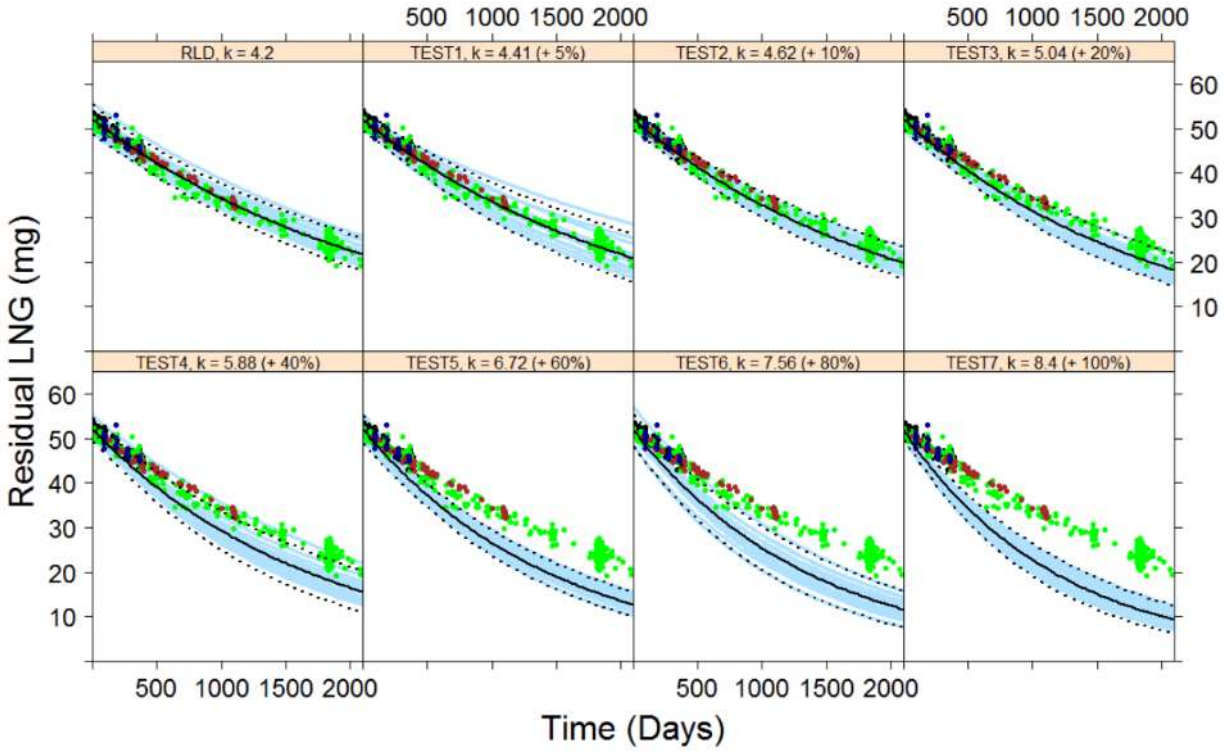
- BE analysis was performed on residual LNG from virtual subjects (n = 20) for RLD and hypothetical generics using 80% - 125% BE limit.

- Then 90% confidence interval of geometric mean ratio of the RLD and TEST at 1 year and 5 years were computed and the procedure was repeated 1000 times simulating 1000 studies.

Parallel BE Study Results at 1 Year and 5 Year for Hypothetical Generics with Faster Release

		$\mu_R + \delta\mu_R$	
δ (%)		1 Year	5 Years
0 (0%)	GMR (Lower, Upper)	100.00 (98.47, 101.56)	100.03 (95.90, 104.35)
0.05 (5%)	GMR (Lower, Upper)	99.25 (97.72, 100.80)	96.33 (92.26, 100.58)
0.1 (10%)	GMR (Lower, Upper)	98.50 (96.97, 100.05)	92.74 (88.73, 96.92)
0.2 (20%)	GMR (Lower, Upper)	97.02 (95.49, 98.58)	86.00 (82.11, 90.07)
0.4 (40%)	GMR (Lower, Upper)	94.14 (92.61, 95.70)	73.97 (70.32, 77.81)
0.6 (60%)	GMR (Lower, Upper)	91.34 (89.80, 92.90)	63.59 (60.17, 67.20)
0.8 (80%)	GMR (Lower, Upper)	88.61 (87.06, 90.18)	54.64 (51.46, 58.02)
1.0 (100%)	GMR (Lower, Upper)	85.97 (84.41, 87.56)	46.98 (44.02, 50.14)

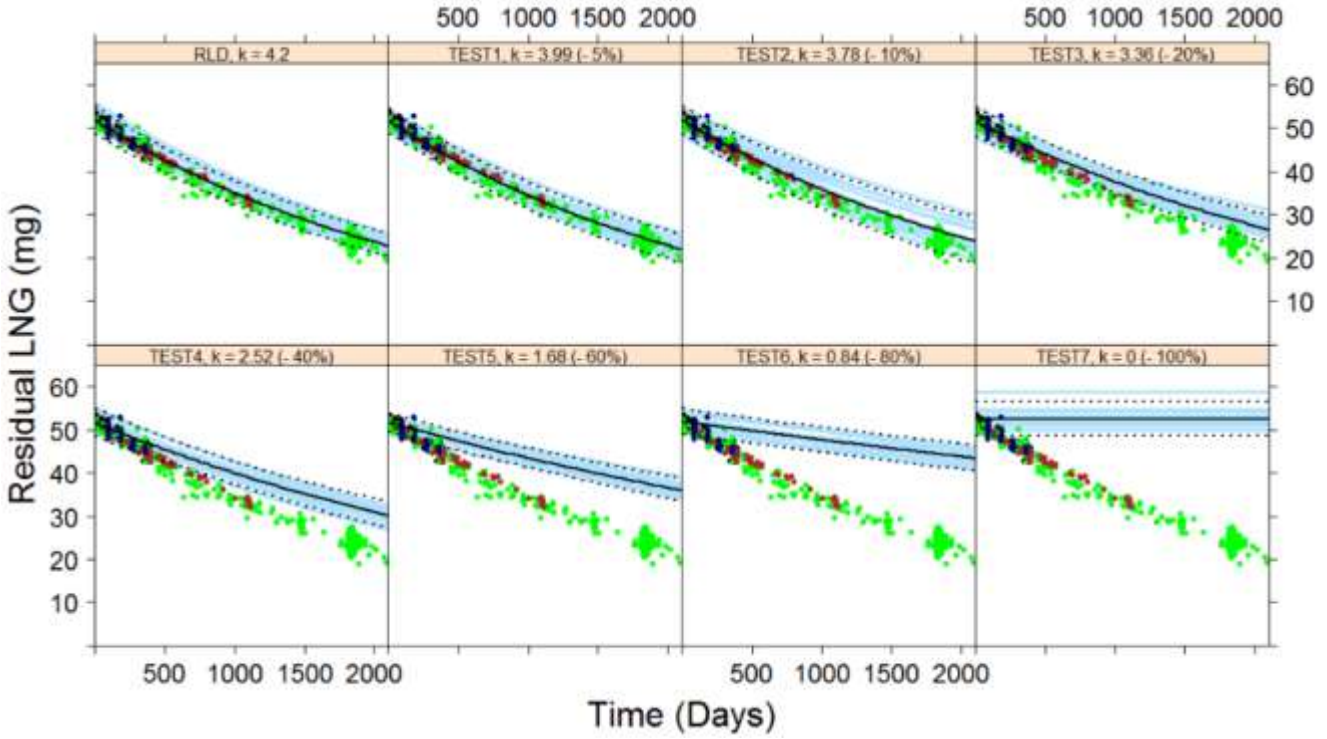
Observed Residual LNG from Different Formulations and Model Simulated Residual LNG in Virtual Population with Hypothetical Generic Formulations



Parallel BE Study Results at 1 Year and 5 Year for Hypothetical Generics with Slower Release

		$\mu_R - \delta\mu_R$	
δ (%)		1 Year	5 Years
0 (0%)	GMR (Lower, Upper)	100.00 (98.46, 101.55)	100.01 (95.87, 104.32)
0.05 (5%)	GMR (Lower, Upper)	100.76 (99.23, 102.31)	103.87 (99.67, 108.25)
0.1 (10%)	GMR (Lower, Upper)	101.53 (100.00, 103.08)	107.89 (103.62, 112.33)
0.2 (20%)	GMR (Lower, Upper)	103.06 (101.52, 104.62)	116.29 (111.88, 120.87)
0.4 (40%)	GMR (Lower, Upper)	106.24 (104.69, 107.82)	135.39 (130.65, 140.31)
0.6 (60%)	GMR (Lower, Upper)	109.50 (107.92, 111.10)	157.44 (152.26, 162.79)
0.8 (80%)	GMR (Lower, Upper)	112.86 (111.24, 114.49)	183.10 (177.32, 189.07)
1.0 (100%)	GMR (Lower, Upper)	116.32 (114.67, 118.00)	213.00 (206.37, 219.86)

Observed Residual LNG from Tested Formulations and Model Simulated Residual LNG in Virtual Population with Hypothetical Generic Formulations

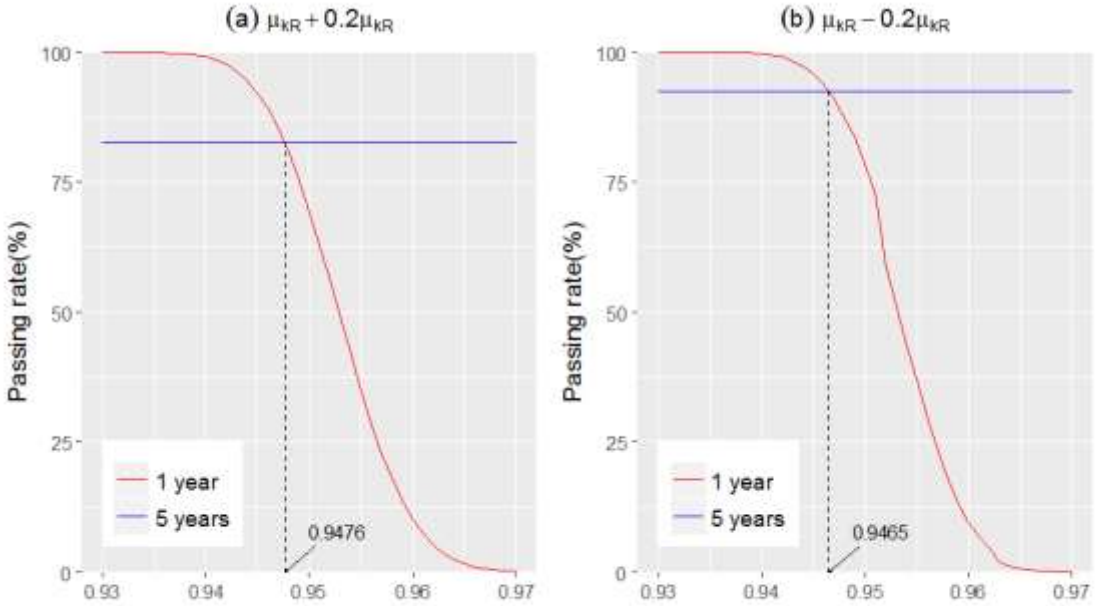


Selection of Potential BE Limit at One Year

- Purpose of this approach was to find BE limit at one year which will ensure similar passing rate at 5 years, assuming conventional 80% - 125% BE criteria applied to residual LNG at 5 years.

- Then 90% confidence interval of geometric mean ratio of the RLD and TEST at 1 year and 5 years were computed and the procedure was repeated 1000 times simulating 1000 studies.

Selection of Potential BE Limit at One Year



n = 20, CV(A) = 3%, CV(k) = 10%

- BE Limit of 95 – 105.26 for Residual LNG at 1 year can be proposed to ensure BE limit of 80 – 125 at 5 year.

Evaluation of the Proposed (95% – 100/0.95%) BE Criteria at 1 Year

- Observed residual LNG data at one year was retrieved and parallel BE comparison was conducted.
- Residual LNG data in between 330 to 390 days were considered for one year analysis.
- Two cases were evaluated and BE analysis showed that criteria were met:
  - Formulation C vs formulation D
  - Formulation D vs Similar product

Evaluation of the Proposed (95% – 100/0.95%) BE Criteria at 1 Year

- Results from parallel BE study comparing 1 Year observed Residual LNG data of Formulation C and Formulation D.

TIME	GMR	Lower	Upper
1 Year	99.54	97.47	101.64

- Results parallel BE study comparing 1 Year observed Residual LNG data of Formulation D and Similar product.

TIME	GMR	Lower	Upper
1 Year	100.50	98.04	103.02

Summary

- Modeling and simulation was used to assess potential BE metrics and statistical criteria for a 5-year LNG IUS.

- Our analysis suggests that having 90% CI of that the residual LNG amount at first one-year (12 M post insertion) is within 95-105.26% can ensure that residual LNG amount at five year is within 80 – 125 %.

- A one year in vivo BE study would significantly shorten product development time and could potentially encourage generic competition in the LNG IUS product category.

What ANDA Applicants Can Do?

- Models published or publicly available in NDA reviews.
- Key model parameters that can influence rate and extent of absorption can be identified and simulated to support your alternative BE proposal.
- Design/justify a shorter duration BE study, bio-inequivalent scenarios, sample size.

Thank You!

- Alternative approaches to demonstrate bioequivalence: Applicants can submit their proposal through FDA's preANDA program.

- For questions about submitting Pre-ANDA meeting requests for complex generic drug products online please contact PreANDAHelp@fda.hhs.gov

- Pre-ANDA Program Information: https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/ucm578012.htm

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