Bioequivalence of Intravaginal Rings and Intrauterine Systems: Current Perspective and Future Directions

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Disclaimer

The opinions and conclusions expressed in this forum are the viewpoints of the speaker(s) and do not necessarily reflect the official position of the U.S. Food and Drug Administration.

Outline

- Background
  - Examples of intravaginal rings (IVRs) and intrauterine systems (IUSs)
- Bioequivalence approaches for IVRs and IUSs
  - Regulatory and scientific challenges and approaches
  - GDUFA regulatory science program
  - Future direction
- Summary

Background

Intravaginal Systems in the U.S.

- Estring: 0.0075 mg/24 hour, Estradiol, up to 90 days
- Annovera: 0.013mg/24 hour;0.15 mg/24 hour; Ethinyl estradiol/Segesterone acetate, up to 13 28-day cycles (1 year)
- Milprosa: 1.78 mg; Progesterone, up to 10 weeks
- Nuvaring: 0.015 mg/24 hour;0.12 mg/24 hour; Ethinyl estradiol/Etonogestrel, up to 21 days
- Eluryng: 0.015 mg/24 hour;0.12 mg/24 hour; Ethinyl estradiol;Etonogestrel, up to 21 days

Advantages

- Achieve more continuous extended drug release from weeks to months, compared to other formulations
- Improve patient compliance with a better therapeutic option

*IVRs are drug device combination products because of the delivery system.

Background (Cont.)

Intrauterine Devices and Intrauterine Systems in the U.S.

- Copper intrauterine devices (IUDs)
  - Paragard T 380A: up to 10-year use, Teva Women Health

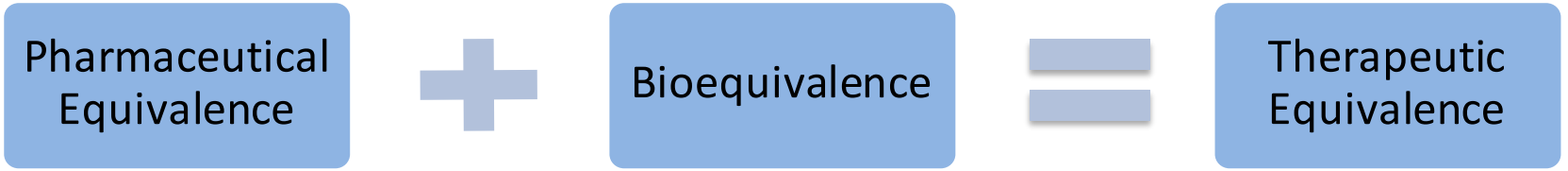
- Levonorgestrel (LNG)-releasing intrauterine systems (IUSs)
  - Mirena: 52 mg, up to 5 years use, Bayer HealthCare
  - Slyla: 13.5 mg, up to 3 years use, Bayer HealthCare
  - Kyleena: 19.5 mg, up to 5 years use, Bayer HealthCare
  - Liletta: 52 mg, up to 4 years use, Medicines360

*IUDs/IUSs are drug device combination products. However, it worth noting that FDA considers the IUD/IUS as the drug component and only the co-packaged inserter is the device component.

Advantages

- Effective, safe, and reversible contraception
- Less user dependent
- More cost-effective than oral contraception even at 1 year of use

Therapeutic Equivalence of Generic IUSs and IVRs



- Contains same active pharmaceutical ingredient (API) as the reference listed drug (RLD)
- Same dosage form (e.g., system)
- Same route of administration (e.g., intrauterine)
- Identical in strength or concentration
- Meets the same compendial standards for strength, quality, purity, and identity

- 21 CFR 320.23: Two drug products will be considered bioequivalent if the rate and extent of absorption do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions.
- For drug products that are not intended to be absorbed into the bloodstream, bioequivalence may be demonstrated by scientifically valid methods that are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.

- As intravaginal or intrauterine product differences in inactive ingredients are permissible, per 21 CFR 314.94(a)(9)(ii).

Product-Specific Guidance and Generic IUSs and IVRs Landscape

PSG Published

IVRs
1. Estradiol IVR
2. Ethinyl estradiol/Etonogestrel IVR

IUSs
1. Copper IUD
2. LNG IUS (referencing Mirena)

Generic Competition

IVRs
Ethinyl estradiol;Etonogestrel IVR (Amneal Pharmaceuticals LLC, approved on December 11, 2019)

IUSs

FDA's Product-Specific Guidances (PSG) for Generic Drug Development available at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

IVR: PK study

➢ Example product: **Nuvaring** (0.015 mg/24 hour;0.12 mg/24 hour; Ethinyl estradiol/Etonogestrel IVR)

Contains Nonbinding Recommendations

Draft Guidance on Ethinyl Estradiol; Etonogestrel

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Ethinyl Estradiol; Etonogestrel

Form/Route: Ring/Vaginal

Recommended studies: 1 study

Type of study: Bioequivalence (BE) Study with Pharmacokinetic (PK) Endpoints
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 0.015 mg/24 hr; 0.12 mg/24 hr
Subjects: Nonpregnant, nonsmoking healthy females aged 18 to 45 years of age and without any contraindication for contraceptive steroids.
Additional comments:

1. If the test product in not Q1/Q2 to the Reference Listed Drug (RLD) an additional clinical study or studies to identify any increased risk posed by the differing inactive ingredients or formulation differences between the test product and the RLD may be necessary.

2. Depending upon the specific clinical study or studies recommended, e.g., vaginal safety study, a test drug product that is not Q1/Q2 to the RLD may need to be submitted in a NDA to the Office of New Drugs.

Analytes to measure (in appropriate biological fluid): Ethinyl estradiol in plasma and etonogestrel in plasma

Bioequivalence based on (90% CI): Ethinyl estradiol and etonogestrel

- Potential formulation differences may require an additional clinical study or studies to identify any increased risk as a result
- Systemic action → PK study

IVR: In Vitro Studies and PK Study

➢ Example product: **Estring** (0.0075 mg/24 hour, Estradiol IVR)

Active Ingredient:	Estradiol
Dosage Form; Route:	Insert, extended release; vaginal
Strength:	0.0075 mg/24hr
Recommended Studies:	Two options: in vitro/in vivo or in vivo

I. In vitro/in vivo option:

To be eligible for this option all of the following criteria should be met:

- The test and Reference Listed Drug (RLD) formulations are qualitatively (Q1)[1] and quantitatively (Q2)[2] the same (Q1/Q2).
- Comparative physicochemical and mechanical characteristics of the test and reference standard (RS) products including, 1) degree of crosslinking of the silicone polymers; and 2) mechanical properties (hardness, tensile strength, elongation at break).
- Same dimensions as the RLD

1) Comparative in vitro drug release testing[3]
   Acceptable comparative in vitro drug release of estradiol from the test and the RS products throughout the intended period of product use (90 days).

2) Type of study: In vivo bioequivalence with pharmacokinetic (PK) endpoints
   Design: 28 days, crossover or parallel
   Strength: 0.0075 mg/24hr
   Subjects: Healthy postmenopausal women with no contraindication to estrogen therapy.

- Similar formulation (i.e., Q1Q2)
- Same dimensions
- Comparable physicochemical and mechanical properties

- In vitro drug release testing for 90 days
- In vivo PK study for 28 days
- Ex vivo study of residual of estradiol in IVR at day 28 as supportive information

IUS: In Vitro Studies and In Vivo/Ex Vivo Study

➢ Example product: **Mirena** (52 mg, Levonorgestrel IUS)

Active Ingredient:	Estradiol
Dosage Form; Route:	Insert, extended release; vaginal
Strength:	0.0075 mg/24hr
Recommended Studies:	Two options: in vitro/in vivo or in vivo

I. In vitro/in vivo option:

To be eligible for this option all of the following criteria should be met:

- The test and Reference Listed Drug (RLD) formulations are qualitatively (Q1)[1] and quantitatively (Q2)[2] the same (Q1/Q2).
- Comparative physicochemical and mechanical characteristics of the test and reference standard (RS) products including, 1) degree of crosslinking of the silicone polymers; and 2) mechanical properties (hardness, tensile strength, elongation at break).
- Same dimensions as the RLD

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- Same dimension
- Comparable physicochemical and mechanical properties

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- In vitro drug release testing for 5 years
- In vivo study for 12 months
- Residual amount of Levonorgestrel at months 12 for BE determination
- Lenonorgestrel in serum at months 1, 3, 6, and 12 as supportive data

Remaining Scientific Challenges for Developing IUSs and IVRs

Scientific Challenges

1. When Q1Q2 is recommended for vaginal products, how to establish Q1/Q2 sameness between the Test and Reference products?
2. What are the experimental parameters to be considered when developing in vitro release testing methods for IVRs and IUSs? A real time release method vs. an accelerated release method.
3. How to characterize mechanical properties of the formulation? (refer to Dr. Monica Garcia's presentation)

Regulatory and Scientific Considerations on Formulation Similarity

- Generic IVRs and IUSs do not need to establish Q1 and Q2 sameness per regulation. However, formulation similarity (no significant differences in excipients) may be recommended as part of a BE approach.
- Challenges in excipient can be:
  - Complexity in formulation structure and composition
  - Non-compendial excipient
  - Challenges in reverse engineering: ingredient extraction, analysis, and finished material may not be the same as starting material
  - Heterogeneity in ingredient structural composition and/or batch-to-batch amounts

Similarity of Polymers

- Silicone elastomer systems
- Ethylene-vinyl acetate co-polymers (EVA)
- Poly-urethanes

There is no one size fits all strategy for assessing similarity of different polymers…

Supportive Data for Formulation Similarity

- Example polymer: **Silicone elastomer**

Name of ingredient	Function	RLD		Proposed Test product	
		Qty in % w/w	mg/unit	Qty in % w/w	mg/unit
Excipient 1					
Silicone elastomer					

A composition table alone is NOT adequate to assess formulation similarity of the proposed IVR or IUS

Provide information on starting materials, polymerization chemistry of the test material and comparative physicochemical characterization data on both the silicone elastomer in the FINISHED test product and the RLD.

Supportive Data for Formulation Similarity

- Example products: **EVA**

Required information: Polymer composition

Certificates of Analysis (COA) from polymer supplier may be used as supportive information

Product Description					
This is a multi-purpose resin commonly used for flexible packaging coextrusion to provide superior sealability, opticals, and strength, high quality microcellular crosslinked foam, extrusion, injection molding, and tubing applications.					
Resin Properties	**Typical Value**	**SI Unit**	**Imperial**	**Unit**	**Test Method**
Vinyl Acetate	9	%	9	%	PTM-39
Melt Index (190 °C/2.16 kg)	2.8	g/10 min.	2.8	g/10 min.	ASTM D1238
Density	931	kg/m^3	0.931	g/cm^3	ASTM D1505 ASTM D1928 Proc A
Antioxidant	No		No		
Thermal Properties					
DSC Melt Temp	101	°C	214	°F	ASTM D3418
Vicat Softening Point	81	°C	178	°F	ASTM D1525
Film Properties					
Tensile Strength at Break MD	17	MPa	2470	psi	ASTM D882 Method A (500mm/min)
Tensile Strength at Break TD	18	MPa	2610	psi	
Elongation at Break MD	400	%	400	%	ASTM D882 Method A (500mm/min)
Elongation at Break TD	600	%	600	%	
Flexural Modulus (1% Secant)	101	MPa	14,650	psi	ASTM D790
Processing Information					
This polymer may be processed on conventional extrusion equipment. It is recommended that the melt temperature be kept below 210°C as decomposition can occur at higher temperatures.					
Regulatory Compliance					
Contact Celanese Customer Service for information about food contact or other regulatory compliance					

Scientific Challenges

1. When Q1Q2 is recommended for vaginal products, how to establish Q1/Q2 sameness between the Test and Reference products?
2. What are the experimental parameters to be considered when developing in vitro release testing methods for IVRs and IUSs? A real time release method vs. an accelerated release method.
3. How to characterize mechanical properties of the formulation?

Comparative In Vitro Studies

- In vitro drug release testing
  - Ability to discriminate formulation differences within a reasonable time frame
  - Accelerated vs Real time in vitro drug release testing
    - Correlation between accelerated and real time in terms of drug release mechanisms

GDUFA Research Program

Dissolution methods for long-acting LNG IUS

"The objective of this study is to investigate dissolution methods, both real time and accelerated conditions, for levonorgestrel intrauterine systems (5-year application) and to analyze their capability of detecting manufacturing differences, predicting in vivo performance, and to evaluate method robustness."

- 1U01FD005443: A grant was award to Dr. Diane Burgess from the University of Connecticut in 2015.

GDUFA Research Results

International Journal of Pharmaceutics 550 (2018) 447–454

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International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Manufacturing and characterization of long-acting levonorgestrel intrauterine systems

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ARTICLE INFO

Keywords:
Intrauterine device
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Manufacturing
In vitro drug release

ABSTRACT

Mirena® is long-acting (5 years) contraceptive intrauterine device. It is composed of a hollow cylindrical drug reservoir (containing Levonorgestrel and polydimethylsiloxane), which is covered with a release rate controlling silicone membrane. This structure presents a manufacturing challenge and to date, there have been no literature reports on the manufacturing, product design and quality evaluation of these hollow cylindrical intrauterine devices. It is vital to develop a reproducible and robust manufacturing process for these long-acting intrauterine devices or systems to obtain an understanding the *in vitro* and *in vivo* performance of such drug-device combinations. In this study, a twin-syringe method with a customized mold was developed to manufacture hollow cylindrical polydimethylsiloxane (PDMS)-based levonorgestrel intrauterine systems (LNG-IUSs). Different mold materials, curing temperatures and times were screened to fabricate PDMS-drug reservoirs with good quality characteristics (easy demolding, good appearance and appropriate physicochemical characteristics). The prepared PDMS-drug reservoirs were covered with the release rate controlling membrane to fabricate the LNG-IUSs.

- A twin-syringe method with a customized mold was developed to manufacture IUS.
- IUSs with various drug loading were prepared and characterized.
- Real-time in vitro drug release from the IUSs with different drug loading showed zero-order release kinetics and the release rate was inversely proportional to the drug loading.

GDUFA Research Results (Cont.)

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Drug release testing of long-acting intrauterine systems

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Two-phase drug release modeling
Zero-order
First-order
Higuchi
Polymer swelling ratio

ABSTRACT

Performance evaluation of polydimethylsiloxane (PDMS) based long-acting (*e.g.* 3–5 years) levonorgestrel (LNG) intrauterine systems (IUSs), such as Mirena®, is challenging due to their complex formulation, locally-acting feature, and extremely long duration of drug release. To achieve such long-term release, a large amount of drug (up to 52 mg in Mirena®) must be incorporated as a drug reservoir in the IUS. Consequently, dose dumping or unanticipated changes in the LNG-IUS *in vivo* release characteristics may give rise to adverse product safety and efficacy. Therefore, it is crucial to understand, and have appropriate control over, the physicochemical properties and *in vitro* release characteristics of these products. This requires an understanding of the LNG-IUSs drug release mechanism and the development of a sensitive yet robust *in vitro* release testing method. There have been no previous reports on *in vitro* drug release and the release mechanism from LNG-IUSs. This is probably a consequence of the extremely slow drug release rate of LNG-IUSs under real-time in-use conditions (*e.g.*, 3–5 years) and therefore it is impractical to obtain complete release profiles (*e.g.* there is only 60% release in 5 years for Mirena®). Therefore, the development of appropriate accelerated *in vitro* release methods is imperative. Following preparation of LNG-IUSs, similar to Mirena®, real-time release was tested in (0.9% *w/v* NaCl) media in a water shaker bath at 37 °C for over 2 years. Addition of surfactant (sodium dodecyl sulfate (SDS)), elevation of temperature, addition of organic solvents (ethanol (EtOH), isopropanol (IPA), tert-butanol (TBA) and tetrahydrofuran (THF)) and a combination thereof were utilized as release media to accelerate drug release for LNG-IUSs. Complete drug release was achieved in 32 and 672 days in THF and TBA hydro-organic media, respectively. The release profile in THF was considered too fast as it may result in change of release mechanism, whereas the release profile in TBA was deemed suitable following model fitting. Model fitting was performed to understand the release characteristics as well as the release mechanisms. The release rate in the hydro-alcoholic media was linearly proportional to the swelling ratio of the PDMS in the corresponding organic solvents. Zero-

- Various organic solvents and surfactants were evaluated for developing accelerated in vitro drug release testing methods.
- The release rate in the hydro-alcoholic media was linearly proportional to the swelling ratio of the PDMS in the corresponding organic solvents.
- If the release becomes too fast under an accelerated condition, there may be change in release mechanism.

GDUFA Research Results (Cont.)

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Impact of product design parameters on *in vitro* release from intrauterine systems

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Source variation
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USP apparatus 2

ABSTRACT

Polydimethylsiloxane (PDMS)-based levonorgestrel intrauterine systems (LNG-IUSs) contain a large amount of potent LNG, and therefore it is important to understand the impact of product design parameters on the *in vitro* and *in vivo* performance to ensure safety and efficacy, as well as to avoid serious side effects resulting from dose dumping. LNG-IUS is a complex drug-device combination product, and its formulation design, requires consideration of additional factors such as device configuration and dimensions, in addition to formulation and processing parameters. In this study, ten qualitatively (Q1) and quantitatively (Q2) equivalent LNG-IUSs were manufactured with differences in source (supplier) and dimensions (*i.e.*, thickness) of the outer membrane, drug particle size, dimensions of the drug reservoir (*i.e.*, inner diameter), as well as configuration of the entire IUS. A real-time *in vitro* release testing method was developed for the LNG-IUSs. In addition, an accelerated release testing method was developed using hydro-alcoholic media in order to reduce the time associated with formulation design. Source variations and thickness of their outer membranes had a great impact on the *in vitro* drug release from the LNG-IUSs. It was demonstrated that the thicker the outer membrane, the slower the drug release rate. The physicochemical properties of the outer membranes obtained from different sources were

- Ten Q1Q2 equivalent IUSs were manufactured with differences in source and dimensions of the outer membrane, drug particle size, dimensions of the drug reservoir, as well as configuration of the entire IUS.
- A real time release testing method was developed.
- The results showed that the placement of outer membrane was significant, i.e. whether the ends of the drug reservoir were covered or not.

Future Directions

- Exploring new analytical tools for characterizing polymeric excipients and formulations
- Investigating the impact of variation in polymer characteristics on physicochemical/mechanical properties and drug release of IVRs and IUSs
- Developing novel real time and accelerated in vitro drug release testing methods
- Developing new modeling and simulation tools to improve BE study design

Summary

- IVRs and IUSs have unique complexity and challenges for generic product development and approval
- The prolonged application durations of IUSs and IVRs prompt development of alternative approaches for establishing BE
- When formulation similarity is recommended for a BE approach, comprehensive polymer characterization on test and reference products may be needed
- Discuss potential formulation differences and alternative BE approach via controlled correspondences or pre-ANDA meeting requests early in development
- GDUFA research program is helpful for addressing remaining scientific gaps

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