The Development of Two Multipurpose Prevention Technology (MPT) Products, the Regulatory Pathway for Each, and Initiation of Clinical Studies

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Rationale for MPT Products

CONRAD is developing two MPT products with contraception, HIV and HSV-2 prevention as their primary indications:

1. SILCS diaphragm plus Tenofovir (TFV) 1% gel combination (**SILCS+TFV Gel**)
2. TFV+Levonorgestrel combination Intravaginal Ring (**TFV+LNG IVR**)

Both were chosen based on:

- Combination feasibility
- Clinical advancement of the individual components

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Use of Target Product Profiles (TPPs) to Guide MPT Development

- TPPs were used that defined microbicide + contraceptive combination products intended to provide:

  1. ***Immediate (on-demand) protection***

  (SILCS+TFV gel combination product), **or**

  2. ***Continuous (longer acting) protection***

  (TFV+LNG IVR)

  against sexual acquisition of HIV, HSV-2 and unintended pregnancy

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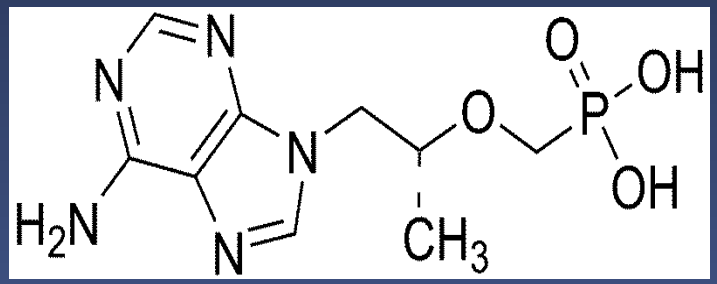
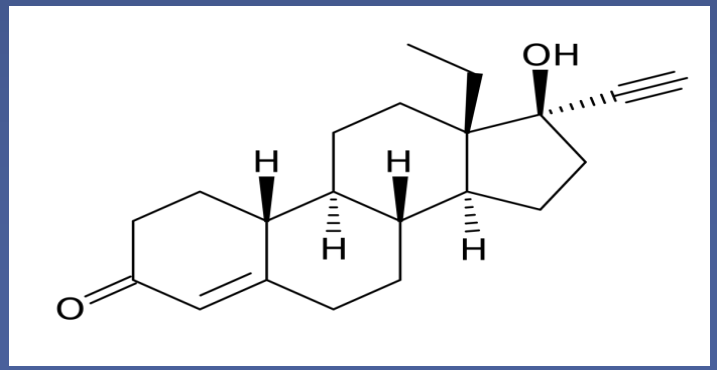
Background of Drug Components

Tenofovir (TFV)



Levonorgestrel (LNG)



- **TFV 1% gel**:
  - Successful "proof of concept" study for prevention of HIV (39%) and HSV-2 (51%)
    CAPRISA 004
  - Confirmatory study on-going
    FACTS 001
  - Positive safety, PK, and acceptability studies
- **LNG**:
  - Established track record of safety in other products
  - WHO LNG IVR experience

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MPT Product #1:

- **SILCS Diaphragm+TFV 1% gel**
  - Combination of two products in late stage development
  - Meets the TPP for providing immediate (on-demand) protection

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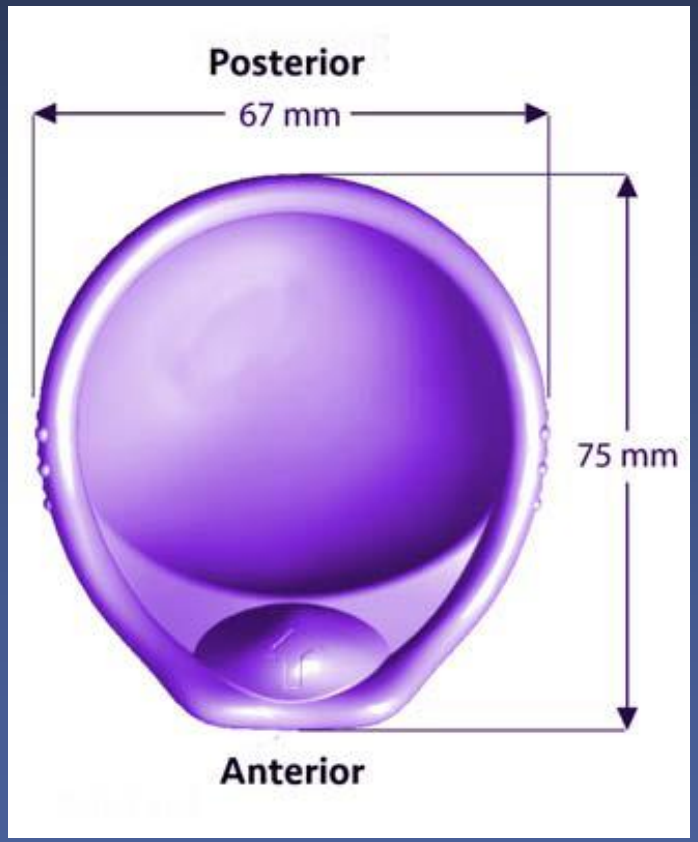
SILCS Contraceptive Diaphragm



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SILCS Diaphragm + TFV 1% gel combination product

- Both products have effectiveness data to support their individual indications
- Two clinical studies are planned to test the combination product:
  - **Post Coital Study** (PCT): Standard study of contraceptive effectiveness
  - **Safety Study** with PK/PD endpoints comparing SILCS to the current single use applicator in ability to deliver TFV 1% gel

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Regulatory Input for SILCS+TFV Gel Combination Product

- Initial feedback on the **PCT study** design from the devices group (Center for Devices and Radiological Health; CDRH) at the US Food & Drug Administration (USFDA): *a new Investigational Device Exemption (IDE) would be required*
- The **Safety + PK/PD study** protocol design has been submitted to the drug group (Center for Drug Evaluation and Research; CDER) of the USFDA, to confirm appropriateness of submitting under the existing CONRAD TFV Investigational New Drug (IND)

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Moving the SILCS+TFV Gel combination MPT forward (1)

1. If **PCT study** is "successful" (i.e., SILCS+TFV Gel prevents sufficient sperm from penetrating midcycle cervical mucus)
   - meet with the USFDA
   - propose allowing the combination to move forward once both products are (individually) approved
     - 510(k) for SILCS to be submitted end of 2013
     - NDA for TFV 1% gel end of 2016

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Moving the SILCS+TFV Gel combination MPT forward (2)

2. Compare SILCS to the current single-use applicator as a delivery system for TFV 1% gel
    - If PK, PD, and safety endpoints are similar and there are no acceptability issues, this data will be discussed with the USFDA in terms of ***bioequivalence***

MPT Product #2:

❖TFV + LNG Intravaginal Ring (IVR)

- Segmented, Polyurethane, Reservoir Ring

➢Meets the TPP for providing continuous (longer acting) protection

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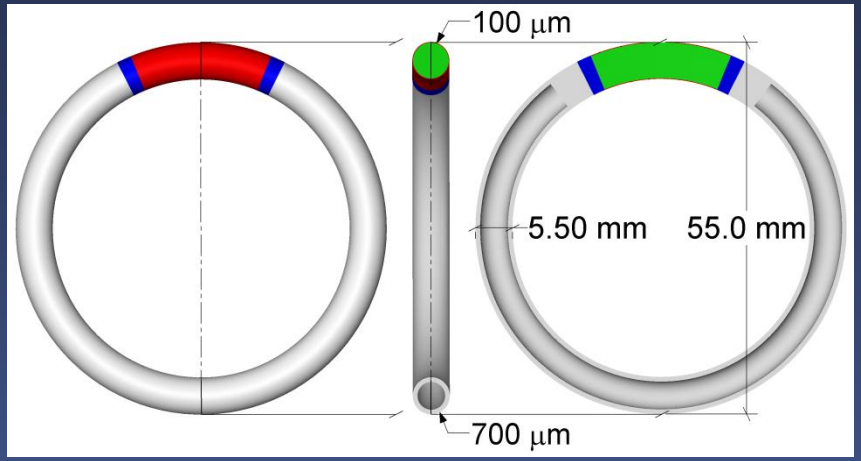
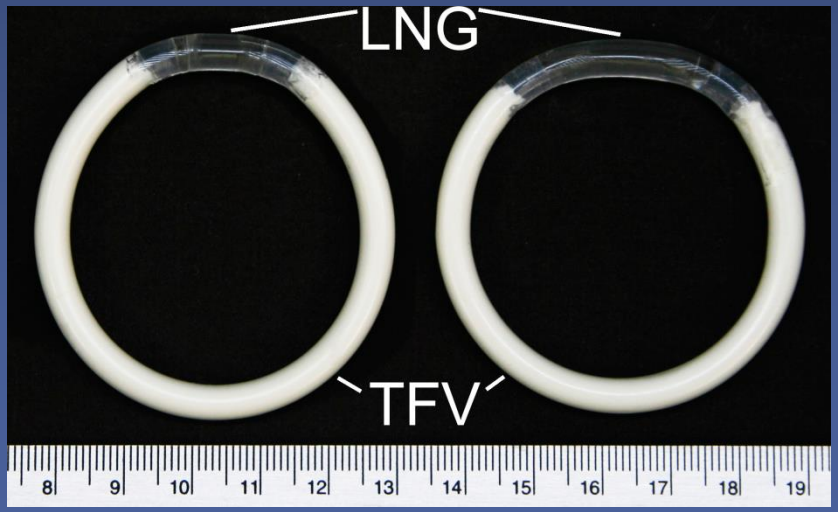
Segmented TFV+LNG IVR

Target:

- 10 mg TFV/d and 20 µg LNG/d for at least 90 days
- LNG release rate modulated by changing segment length
- TFV-only IVR also in development
- 55 mm (2.2”) outer diameter, 5.5 mm (0.2”) cross-sectional diameter
- IVR development in collaboration with Dr. Patrick Kiser, formerly of the University of Utah and currently at Northwestern





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Early Regulatory Input: IVRs

Pre-IND meeting for TFV+LNG IVR

- Background package for USFDA review included preclinical program, manufacturing information, and proposed initial clinical study

FDA feedback:

- Initial clinical study – 30 days for 90-day ring
- Preclinical program sufficient – cytotoxicity, genotoxicity (Studies: 2 in vitro and 1 in vivo) and sensitization tests
- Present detail CMC information in IND
- Submit 2 separate IVR INDs:
  1. TFV+LNG
  2. TFV alone

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Clinical Plan for TFV+LNG IVR (1)

One-month study of 90-day combination IVR

- **Arms:** TFV+LNG IVR, TFV IVR, Placebo IVR; 2:1:1 ratio
- **Endpoints**: Safety, PK (LNG & TFV), PD (LNG & TFV), and acceptability
- **Study population:** 56 ovulatory women enrolled in two sites (EVMS, Norfolk, VA; & PROFAMILIA, DR)
- Residual drug will be measured in returned IVRs

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Clinical Plan for TFV+LNG IVR (2)

- Initial one-month study to be followed by Phase I study in sexually active women using the ring for the full 90 days
- Socio-behavioral study of placebo IVRs in African women is planned
- Phase II in sexually active, HIV-uninfected women (200 in the U.S. and 100 in Africa) will follow.
  - Objectives: safety, PK, PD, adherence, and acceptability

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Program Conclusions

SILCS+TFV 1%Gel Combination MPT:

- Diaphragm plus gel combination is a familiar “on demand” contraceptive system that has the potential advantage of protecting against HIV and HSV-2
- Regulatory approval tied to TFV Gel approval, 2016

TFV+LNG IVR Combination MPT:

- Offers continuous (90-day) protection against pregnancy, HIV & HSV-2 in a woman-controlled, sustained release format; clinical testing to begin early 2014

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A Potential Wrinkle

Gel Reformulation Program:

- TFV 1% gel was not developed as a contraceptive
- There is an on-going reformulation program to add contraceptive activity by changing the TFV gel excipients
- Regulatory issues will become much more complex if the reformulated gel varies substantially from the original TFV 1% gel

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