MPT Intravaginal Ring Target Product Profile

Product Name: ARV + HC MPT IVR

Please note: This dosage form TPP is designed to serve as a guiding document and tool for the general category of MPT Intravaginal Ring of the type combining ARVs with HCs. The development of a particular MPT IVR TPP will require expertise and development planning that is product specific with regard to target parameters and supporting data requirements.

Each section of the TPP contains three areas: (1) Target: Labeling language intended for product; (2) Annotations: Summary information for planned/necessary studies in support of target; and (3) Comments: Additional information to provide clarity on content in above two sections.

1) Indications & Usage

Target	Annotations
Prevention of unintended pregnancy and prevention of HIV infection through vaginal sexual exposure.	Demonstrated via cGCP phase 3 efficacy study(s) with statistical power adequate to satisfy stringent regulatory agency requirements for safety and efficacy for each indication.

Comments:

2) Dosage & Administration

Target	Annotations
i. Route of Administration: Intravaginal ii. Dosage: Drug specific per drug and indication - adequate for achieving targeted efficacies and required safety/tolerance iii. Minimum: One IVR for ≥ 28 days [1 cycle] of use. iv. Optimal: One IVR for multiple cycles [>1] of use	ii. In vitro, ex vivo, in vivo animal and human PK/PD and safety studies iii. ≥ 28 day IVR use in animals for safety and PK; Phase 1 & Phase 2 human trials to support > 28 day use for longer duration rings (e.g. 60 to 90 day ring)

Comments:

i. Self-administered by user

ii. Drug load should be sufficient to sustain the necessary level of in vivo release for the intended duration of use. The amount of excess drug should be kept as minimal as possible for environmental disposal and cost reasons.

iii. Unknowns exist around acceptability of single ring use over specific periods of time, continuous or interrupted use, ring removal issues. Consequently, these issues need to be considered in the design and development of this ring.

3) Dosage Forms & Strengths

Target	Annotations
i. Dosage Form: Intravaginal ring providing topical delivery of ARV and hormonal contraceptive APIs (see "Description, Section 11" below ii. IVR Type: Matrix, core, reservoir, segmented, sandwich, etc. iii. Strengths: TBD for the ARV and HC API specifically for individual MPT ARV iv. Use duration: ≥28 days	i. Specific details will be product specific ii. Specific details will be product specific iii. Product labeling will likely require definition of daily delivery levels of the ARV and HC API released from the ring. The label will also likely require definition of the total drug load into the IVR for each API iv. Will need to clarify continuous use, versus removal periods

Comments:

4) Contraindications

Target	Annotations
i. HIV positive women, pregnant women, girls under age 15, women prior to sexual debut, post-menopausal women ii. Possible HC related contraindications: active venous thrombosis disorder, history of severe hepatic disorder, liver tumors, hormone related malignancies, undiagnosed vaginal bleeding, cerebral vascular or coronary artery disease, severe hypertension, acute cervicitis, vaginitis (pending resolution), known or suspected carcinoma of the breast, cervix or genital tract. iii. ARV and STI drug contraindications: Will be API specific iv. Testing requirements: Recommended HIV and pregnancy testing requirements for continued product use must be defined	i. Acceptability for use by pregnant women could be established via appropriate studies or the status of the API incorporated into the IVR, however an IVR with ARV only and demonstrated safety in pregnant women would be preferable for this population ii. Likely established from existing HC contraceptive only products iii. Pending specific ARV API status, contraindications may already be defined and would be incorporated into the TPP iv. Acceptability of necessary product required testing regimens must be determined

Comments:

i. Design of MPT IVR for breastfeeding women may be feasible.
iii. Possible ARV contraindications are likely to be drug type specific (e.g., NNRTI, NRTI, etc.) and are known from treatment indications with these classes of drugs.
iv. Testing algorithms will be necessary for definition of contraindicated pregnancy or HIV positive populations (including seroconversions during product use). Specific ARV use may not be appropriate in pregnant women.

5) Warnings & Precautions

Target	Annotations
TBD per product	

Comments:

6) Adverse Reactions

Target	Annotations
TBD per product: See "Comments, Clinical Safety" in section 14, below	

Comments:

7) Drug Interactions

Target	Annotations
i. Combination API compatibility; compatible with other vaginal products routinely used for treatment in target populations, and will also potentially require compatibility assessment with other commonly used systemic drugs in the target populations	i. DDI clinical trials as per FDA or other regulatory guidance; assessment of API PK effects; etc. Reg requirements to be effected by level of API absorption

Comments:
Examples: various miconazole-based products for yeast infection treatment; co-use of drugs that induce CYP3A4, increasing progestin metabolism (NNRTI effect). Further, it may be necessary to evaluate product compatibility with other commonly used drugs (e.g., TB treatment, etc.)

8) Use in Specific Populations

Target	Annotations
i. Non-pregnant women seeking protection from or at risk for HIV and unintended pregnancy ii. Other populations: adolescent reproductive age women, obese women, breast feeding	i. Adequate clinical safety data in global populations targeted for commercialization and product introduction and use; includes adolescent girls of reproductive age ii. Adequate safety studies in the specific

women	populations

Comments: Minimally, these products will target women at risk for HIV and unintended pregnancy in resource constrained parts of the world. An expanded target population could include: younger adolescent women (<18 yrs); breastfeeding women seeking protection against HIV and unintended pregnancy

9) Description

Target	Annotations
i. Silicone, poly-urethane, ethyl vinyl acetate, or other appropriately qualified biocompatible or biodegradable polymer for the ring structure ii. Dimensions: <56 mm OD; CSD and weight consistent with vaginal retention and acceptability. iii. Appearance iv. Packaging: Individually wrapped, easy open pouch v. Flexibility/Firmness	i. In vitro and in vivo ISO biocompatibility studies with IVR; impurities assessments under forced degradation and stress conditions; leachable studies while in packaging ii. Dimensions and weight tests to satisfy release specification; satisfactory insertion, retention and expulsion via clinical evaluation iii. Appearance consistent with end user acceptability and release/stability specifications; will include color specification iv. Evaluated via GMP stability studies and leachable packaging studies. v. Achieved and controlled via physical characterization of ring (compression, tensile strength, durometer rating, etc.)

Comments:
i. Qualified vendors supplying appropriate grade polymer for >30 day use as an implant; established supply chain for all raw materials
ii. Based on currently available commercial IVR
iii. Based on currently available commercial IVR
iv. As per ISO and ICH guidance

10) Clinical Pharmacology

Target	Annotations
i. Minimal systemic absorption of API (pending MOA); Necessary absorption of HC (?) ii. Demonstration of efficacy via sufficient surrogate model studies (e.g., ex vivo, animal model, human pharmacodynamic models)	i. Phase 1 PK studies targeting plasma, tissue, and genital tract fluid levels. Topical product targeting minimal systemic absorption and appropriate compartment of exposure drug levels ii. Human PK/PD studies using biopsy or fluid

	models; appropriate animal model evaluation (e.g., rabbit pregnancy model; NHP SHIV infection model, etc.)

Comments:

i. As a topical product, an MPT IVR may not require significant systemic absorption for HIV prevention efficacy; rather, the objective may be to achieve protection via local compartment levels of drug (vaginal and cervical fluids and epithelial tissue). Elevated systemic levels from IVR dosing increases risk for systemic AEs and side effects, and also increases risk of resistance selection in sero-converters. Alternatively, adequate systemic exposure of hormones may be necessary for the contraception indication.

ii. Limitations with available models are acknowledged, however justification for P3 trial investment as well as the need to present a dose/drug delivery level rationale for regulatory purposes dictates the need for meaningful surrogate of efficacy data. E.g., determination of PK/PD relationship by means of in vitro, in vivo (animal or human trials) or ex vivo models.

12.1 Mechanism of Action: For regulatory purposes it will be necessary to establish the mechanisms of action for prevention of HIV infection by the ARV as well as the hormonal contraceptive mechanism of action. This could rely on pre-existing data for each API, or may require demonstration during clinical evaluation of the combination in the MPT product. For example, prior mechanism of action studies with systemic use of a hormonal contraceptive may not equate fully to the mechanism of action with topical use.

11) Nonclinical Toxicology

Target	Annotations
i. Acute tox in animals; dose ranging	i. Rodent species; systemic and topical exposure
ii. Non-genotoxic/non-mutagenic	ii. Ames test, chromosome aberrations test, micronucleus testing, etc.
iii. No sensitivity findings	iii. Guinea pig sensitization model
iv. Non-teratogenic	iv. Segs 1,2,3 reprotoxicity testing
v. No effects on return to fertility	v. Appropriate animal models for contraceptive reversibility
vi. Non-carcinogenic	vi. FDA approved carcinogenicity protocol
vii. No chronic toxicity findings	vii. Minimum of 6-9 month duration chronic tox study in rodent and non-rodent species at dose levels above planned clinical exposure (possible topical and/or systemic exposure)

Comments: The requirement for and nature of such studies will be a function of possible pre-existing data for the API used in the MPT IVR product

12) Clinical Studies

Target	Annotations
Efficacy: i. Minimally acceptable efficacy: >50% for prevention of HIV infection; >90% for prevention of unintended pregnancy ii. Reversibility: For HIV susceptibility- drug specific; fecundity within 3 months iii. Special efficacy: Active against resistant isolates of HIV; active in the presence of seminal and cervico-vaginal fluids iv. In vitro/in vivo mechanism of action studies	***Efficacy:*** i. Appropriately powered, statistically significant cGCP phase 3 trial(s) per indication ii. Appropriate fecundity studies (as part of planned trials or with independent clinical studies) iii. In vitro/ex vivo infection models for resistant isolate potency, and activity in the presence of GT fluids/semen. iv. Full in vitro/ex vivo characterization for new API' cross reference for approved API
Preclinical Safety: i. No vaginal epithelial damage or other toxicity of the vagina, cervix, uterus, ovaries, bladder, spleen or liver ii. No deleterious effects on normal vaginal flora, particularly lactobacilli iii. No penile irritation iv. No vaginal irritation	***Preclinical Safety:*** i. Rabbit vaginal irritation study; rabbit penile irritation study; acute tox, repeat dose tox, dose escalation; Toxicokinetic studies ii. In vitro toxicity testing with relevant lacto strains; appropriate animal model data and quantitative microbiological assessments in phase 1 human trials iii. GLP RPI study iv. Appropriate animal model vaginal irritation (e.g., sheep) using the ring formulation; study duration consistent with intended P1 trials
Clinical Safety: i. No vaginal epithelial damage; no systemic toxicity; optimally, no effects on the FGT microbiome, transcriptome, or proteome; no significant induction of inflammatory response markers; no unacceptable effects on daily life style or schedule; no social harm effects/AEs ii. AE's: Minimally acceptable- No possibly product related grade 3 AEs or higher observed during trials; No higher than grade 2 AE that are product related and acceptable to target population; AE frequency no higher than ARV treatment or observed with HC contraception products with similar APIs iii. Side Effects: The side effects profile should target fewer side effects and lesser intensity than that seen with related API products,	***Clinical Safety:*** i. Appropriate Phase 1 thru Phase 3 clinical trials with necessary pharmacovigilence studies post approval. ii. Phase 1 safety and PK studies in women; Expanded safety phase 2 trials with necessary sub-studies in the target or other specific populations iii. Phase 1 safety and PK studies in women; Expanded safety phase 2 trials with necessary sub-studies in the target or other specific populations

and should occur at or below the frequency observed with single indication products with similar drugs. No irreversible effects on ability to conceive. No systemic toxicity findings.	

Comments:

Efficacy:

i. Stated efficacies are minimally acceptable and based on the specific target efficacy for dapivirine IVR as per the ASPIRE trial (HIV) & Nuvaring (contraception). Preferred efficacy for HIV would be greater than 70% as per oral Truvada. Pre-phase 3 studies involving surrogates for efficacy (animal, PK/PD models, ex vivo, etc.) for dose determination/justification, and end-user acceptability will be required.

ii. Return to HIV susceptibility will depend on the half-life and potency of drug in the compartments of exposure. The longer the prevention interval after cessation of product use, the better. However, the risk of persistent drug levels below the protective level but capable of resistance selection in cases of sero-conversion must be understood and addressed

iii. Phase III trials will require non-use of other vaginal products. Consequently, this will likely be reflected in the label, pending data from co-use studies. Phase I studies designed to evaluate PK/PD in the context of sexual intercourse could be considered.

iv. Will depend on available information from the individual drugs

Preclinical Safety:

i-iv. The need for these studies will be dependent upon what is available from the component API in the MPT IVR. Exacerbating effects of the combination of drugs will need to be ruled out via appropriate tox studies and DDI studies in animals prior to human trials. Studies may require gel formulations to achieve the necessary dose interval

vi. Findings may occur at test doses significantly above the targeted human dose. Likely will require a gel formulation for this study in animals (and in humans)

vii. Typically, FDA calls for rabbit vaginal irritation studies with topical vaginal products, however the agency has accepted sheep model studies with IVR. NHP studies may also be acceptable. Gel studies may be appropriate as a precursor to IVR evaluations for vaginal safety assessment

viii. Findings may occur at the test doses significantly above the targeted human dose. Likely will require gel studies in animals to achieve an exposure interval above the dose of the IVR product

Clinical Safety:

i. The minimally acceptable general safety profile should be equivalent to current comparable products (e.g. Nuvaring, or other HC contraceptive based products and currently available ARV treatment products).

ii. Vaginal bleeding or spotting profile and general cycle effects must be acceptable to the target population. Reported AEs cannot be of greater severity or frequency than those reported for single indication products using the same API (or API class) in the MPT IVR.

iii. Studies indicate long term sustained and adherent use of products are highly dependent on the side effect profile. Note: Ipsos marketing study identified specific side effects that are of concern to end users: migraines, diarrhea, irregular/no bleeding, etc.

13) Useful References

Holt, J.D. & Nuttall, J.P. (2014). Preclinical safety evaluation. *Current Topics in Microbiology and Immunology,* 383, 55-78.

Doncel, G.F. & Clark, M.R. (2010). Preclinical evaluation of anti-HIV microbicide products: New models and biomarkers. *Antiviral Research*, 88(Suppl. 1), S10-S18.

Lard-Whiteford, S.L., Matecka, D., O'Rear, J.J., Yuen, I.S., Litterst, C., et al. (2004). Recommendations for the nonclinical development of topical microbicides for prevention of HIV transmission: an update. *Journal of Acquired Immune Deficiency Syndromes (JAIDS)*, 36(1), 541-52.

Merck. (2001). NuvaRing [package insert]. Whitehouse Station, NJ.

Tebbey., P.W. & Rink, C. (2009). Target Product Profile: A Renaissance for its Definition and Use. *Journal of Medical Marketing,* 9(4), 301-307.

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry and Review Staff: Target Product Profile – A Strategic Development Process Tool. (2007).

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry - Vaginal Microbicides: Development for the Prevention of HIV Infection. (2014).

14) How Supplied/Storage & Handling

Target	Annotations
Stability and Storage:	***Stability and Storage:***
i. Shelf Life: Minimum 36 months; preferred 60 months at ambient conditions	i. Appropriate ICH stability studies with finalized specifications and validated test methods
ii. Storage conditions: minimum 30°C, 65% RH; Preferred zone 4b conditions; light stable	ii. Appropriate ICH stability studies with finalized specifications and validated test methods
iii. Primary and secondary packaging description	iii. Necessary packaging compatibility studies (extracables/leachables, etc) will be required. Stability data in primary packaging will be required

Comments:
Stability and Storage: Temperature cycling, freeze-thaw, transport and appropriate excursion studies will be required

15) Patient Counseling Information

Target	Annotations
i. This product should be used in the context of safe sex practices (e.g., condom use) ii. Correct and consistent product use is necessary for efficacy and safety iii. End users will be counseled on the need for follow up testing for HIV infection (and possibly pregnancy) iv. Counselling regarding ring expulsion, removal, cleaning, storage, and disposal	The P3 efficacy and safety trails will be conducted in the context of safe sex counseling and the provision of condoms. Further, all clinical studies will be conducted with meaningful counseling on correct and consistent product use in an adherent fashion. Product removal tolerance, if any (e.g., during menses, during sex, after expulsion), will need to be determined on a product specific basis. HIV and pregnancy testing will be required to avoid risk of resistance selection in sero-convertors using these products, or possible fetal exposure to ARV drugs

Comments: