Let's Talk MPTs

IMPT for Reproductive Health

Toxicity Study Considerations for MPT & HIV Prevention R&D

Speakers include Tom Moench, MD and Miles Brennan, PhD

Thursday, 27 May at 8:00 PT/11:00 ET/16:00 BST/17:00 CEST/17:00 SAST/18:00 EAT

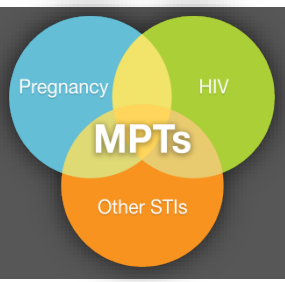
Webinar Registration Link: bit.ly/IMPTregTOX

Welcome! All participants will be muted during the presentation and discussion. Please use the chat for questions.

During the Q&A, please unmute for a question or comment, and mute if you are not speaking. Thank you!

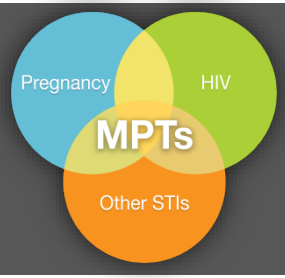
Live Webinar – Hosted by the IMPT Secretariat

Webinar Agenda



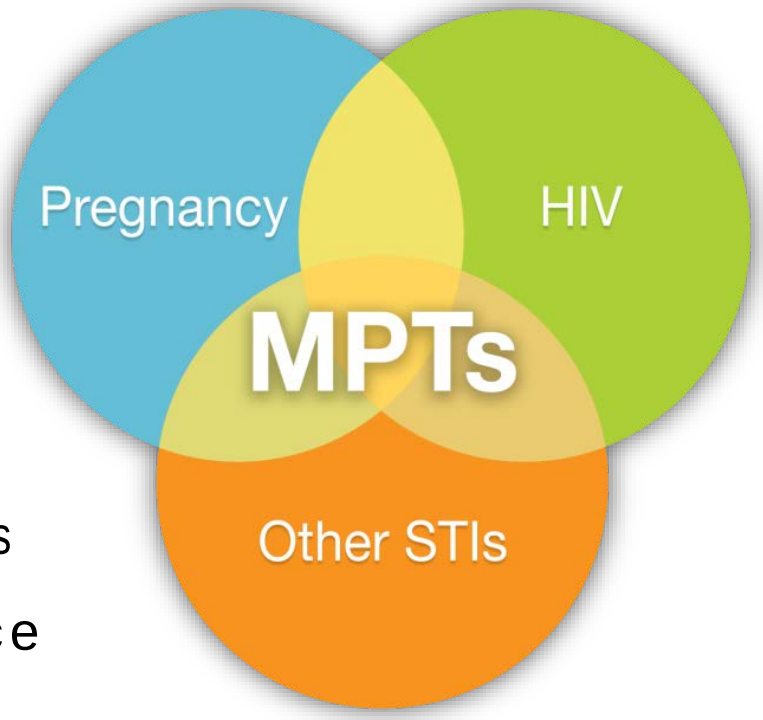
1) Welcome & Introductions
2) Presentation by Dr. Tom Moench and Dr. Miles Brennan
3) Q&A
4) Wrap Up & Adjourn

Multipurpose Prevention Technologies



MPTs <u>combine protection</u> against:

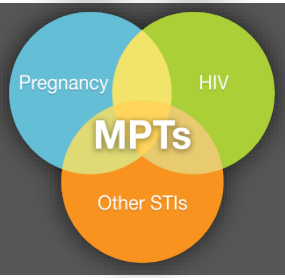
- Unintended pregnancy
- HIV
- Other STIs



MPTs have the potential to:

- Address overlapping risks
- Synergize prevention approaches
- Increase motivation for adherence
- Destigmatize HIV prevention
- Improve health & economic outcomes

What is the *Let's Talk MPTs* Discussion Series?



- A platform aimed to engage experts from diverse disciplines across the globe to help address MPT and HIV prevention R&D priorities and gaps

- Past topics include:

- Recordings and upcoming webinars available at **theIMPT.org**

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Today's Discussants

Thomas Moench, MD

Miles Brennan, PhD

Toxicity Study Considerations for MPT and HIV Prevention R&D

Thomas Moench, M.D.

Mapp Biopharmaceutical and Mucommune, LLC

Miles B. Brennan, Ph.D.

ZabBio, Inc.

Let's Talk MPTs Discussion Series
27 May 2021

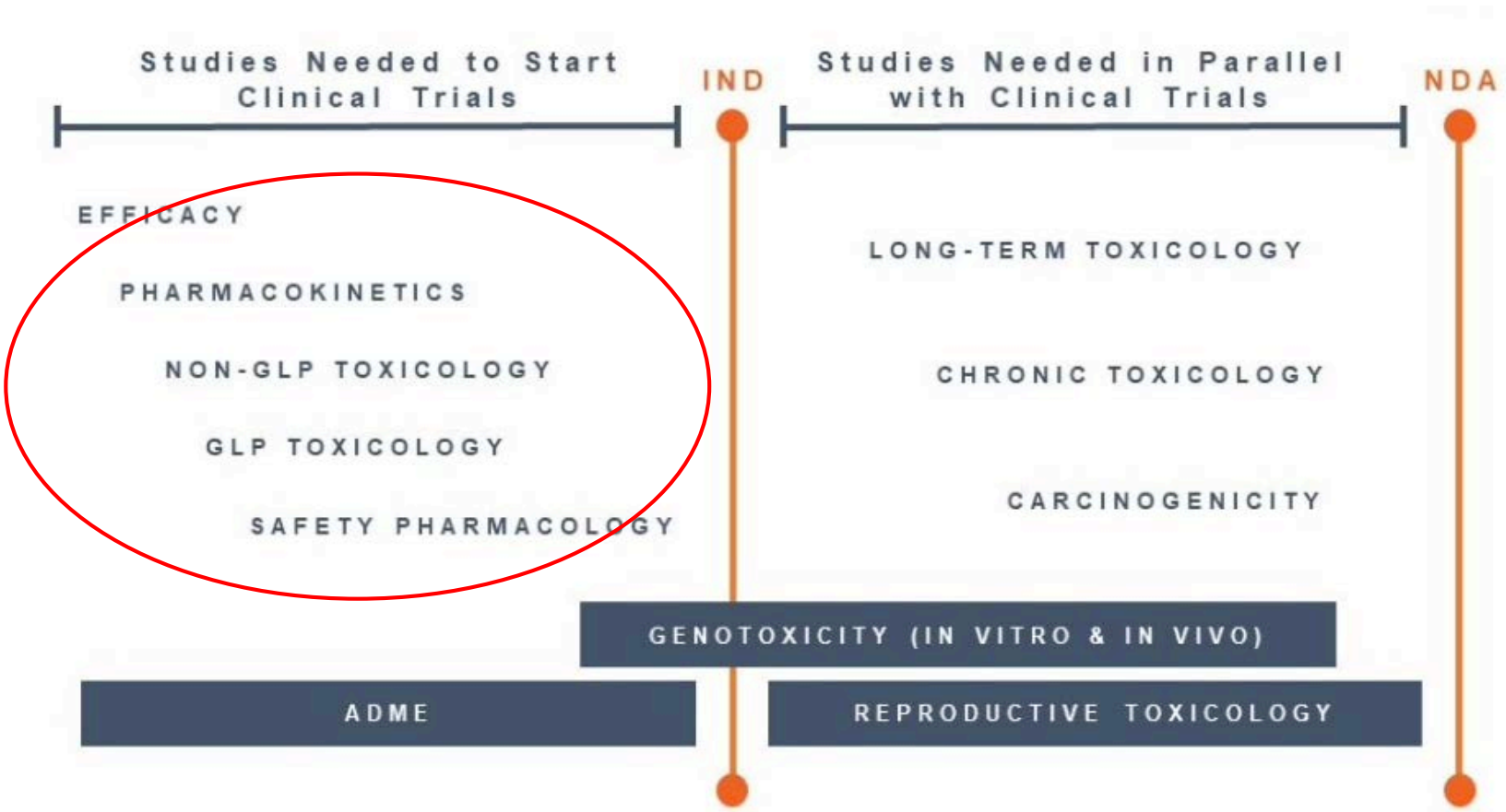
Webinar Outline

- Special vigilance for prevention products
- Toxicology study goals
- Implication of product types for toxicity testing
- Examples of typical non-clinical toxicity plans
- Resources for preparing your plan

Special vigilance for *preventive* products

- Intended for use in healthy population
- Low tolerance for side effects
- Additional concerns for risks to reproductive health

Non-clinical study timeline



Very early evaluations

- In vitro toxicity assessments
  - Preliminary studies to determine if your product has potential for reasonable safety
  - In vitro cytotoxicity in monolayers and/or 3D cultures
    - Viability, barrier function (transepithelial resistance, etc.
  - Comparing with in vitro effectiveness studies establishes therapeutic ratio
- Non significant risk device studies: https://www.fda.gov/media/75459/download
- Exploratory studies, exploratory INDs: https://www.fda.gov/media/72325/download
  - Requires less non-clinical data than full IND in order to begin a clinical study
  - Useful for proof of concept, exploration of mechanism of action, feasibility, effect size

Product formats

- Systemic
  - Oral
  - Subcutaneous or intramuscular injection
  - Intravenous infusion
  - Sustained release implants
  - Sustained release injections
- Topical
  - On demand
    - Precoital gels or films
    - Rectal douche
  - Long acting
    - Intravaginal rings
    - Long acting films

Topical vs. Systemic Pro and Con

- **Topical Pro**
  - Reduced interactions with diverse internal systems
  - Potential for "on demand" use
- **Topical Con**
  - Local toxicities may increase susceptibility to STI/HIV infection
    - Not only API, but excipients may reduce epithelial barrier function
      - Examples: high osmolality, EDTA
    - Interactions with microbiome
  - Pericoital dosing adherence challenge

- **Systemic Pro**
  - Minimal perturbation of cervicovaginal epithelium
  - Potential for very long lasting product formats: high adherence
- **Systemic Con**
  - Exposure to all body systems
    - Tolerance for side effects is very low for prophylactic products
    - May interact with other drugs as "victim" or "perpetrator" of adverse interactions

Product categories

- Small molecule drugs
- Biologicals
  - Monoclonal antibodies
  - mRNA

  } However, regulated by drug center (CDER)
- Sustained release products (drug + device combinations)
  - Vaginal rings
  - Implants
- Combination products with more than one active agent

GLP toxicology studies

Multiple goals:

- Estimate a safe starting dose in “first in human” (FIH) Phase 1
  - Establish the NOAEL (no observed adverse effect level)
- Establish maximum tolerated dose (MTD), thus inform upper dose level doses for Phase 1
  - Attempt to determine a maximum tolerated dose, but if not:
    - Achieve exposure saturation
    - Use a maximum feasible dose
    - Achieve an exposure margin 50x clinical
- Identify specific safety endpoints to monitor more closely in clinical trials

Issues addressed in later toxicology studies

- Identify possible consequences of *chronic* exposure
- Predict risks that are difficult or unethical to assess in humans
  - Carcinogenicity
  - Reproductive performance
  - Developmental toxicology

Other general principles of toxicology protocol design

- Recovery phase
- Toxicokinetics
- Duration must support the length of the planned clinical study

Recommended duration of repeated-dose toxicity studies to support the conduct of clinical trials

Maximum Duration of Clinical Trial	**Recommended Minimum Duration of Repeated-Dose Toxicity Studies to Support Clinical Trials**	
	Rodents	Non-rodents
Up to 2 weeks	2 weeks[a]	2 weeks[a]
Between 2 weeks and 6 months	Same as clinical trial[b]	Same as clinical trial[b]
> 6 months	6 months[b, c]	9 months [b, c, d]

https://www.ema.europa.eu/en/ich-m3-r2-non-clinical-safety-studies-conduct-human-clinical-trials-pharmaceuticals

Typical programs, with distinct requirements

- Small molecule systemic
- Small molecule topical
- mAb topical or systemic
- Combination product (vaginal ring)

Small molecule topical

- 2 week GLP rat toxicology study
  - Safety bloods, behavioral observations, gross pathology and histology
  - Systemic pharmacokinetics/"toxicokinetics"
  - Recovery phase group
  - Single sex (female) for microbicide/contraceptive studies
- Second species (non-rodent) toxicology study
  - For topical vaginal drugs, most often rabbit vaginal irritation study
- Additional studies if more than trace systemic bioavailability

Monoclonal antibody (topical or systemic)

- Various requirements of other systemic drugs *not* needed:
  - ADME studies (absorption, distribution, metabolism, and excretion)
  - Genotoxicity, reproductive performance and developmental toxicity, and carcinogenicity studies generally not required
- Single species generally acceptable for an anti-pathogen mAb
- Immunogenicity assessment (assays for anti drug antibodies (ADA))
  - Must be assessed in clinical studies
  - Also required in animal toxicology studies to assure that ADA does not limit "exposure" by neutralizing the mAb
- Most often mAbs directed against pathogens have low toxicity, but must look for off target binding in Tissue Cross Reactivity (TCR) studies
  - Will inform what species is appropriate for toxicology studies

GLP rat toxicology study for topical or systemic mAb

Group	Treatment	Dose Level (mg of mAb/rat)	Dose Concentration (mg/mL)	Volume (mL/rat)	Animals per Group	No. of Animals	
						Main Day 10	Recovery Day 24
1	Control Film	0	0	0.2	11	6	5
2	Active (Low)	2.2	11	0.2	9	9	---------
3	Active (High)	5	25	0.2	14	9	5
Total Number of Animals					34	24	10

Combination products: drug + device

- 2 week GLP rat toxicology study
  - Safety bloods, behavioral observations, gross pathology and histology
  - Systemic pharmacokinetics/"toxicokinetics"
  - Recovery phase group
  - Single sex (female) for microbicide/contraceptive studies
- Biocompatibility study
- Additional studies if more than trace systemic bioavailability

Biocompatibility studies https://www.fda.gov/media/85865/download

Table A.1: Biocompatibility Evaluation Endpoints

Medical device categorization by			Biological effect											
Nature of Body Contact		Contact Duration	Cytotoxicity	Sensitization	Irritation or Intracutaneous Reactivity	Acute Systemic Toxicity	Material-Mediated Pyrogenicity	Subacute/Subchronic Toxicity	Genotoxicity	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity	Reproductive/Developmental Toxicity#	Degradation@
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – permanent (> 30 d)													
Mucosal membrane		A	X	X	X										
		B	X	X	X	O	O	O		O					
		C	X	X	X	O	O	X	X	O		O			

X = ISO 10993-1:2009 recommended endpoints for consideration*

O = Additional FDA recommended endpoints for consideration*

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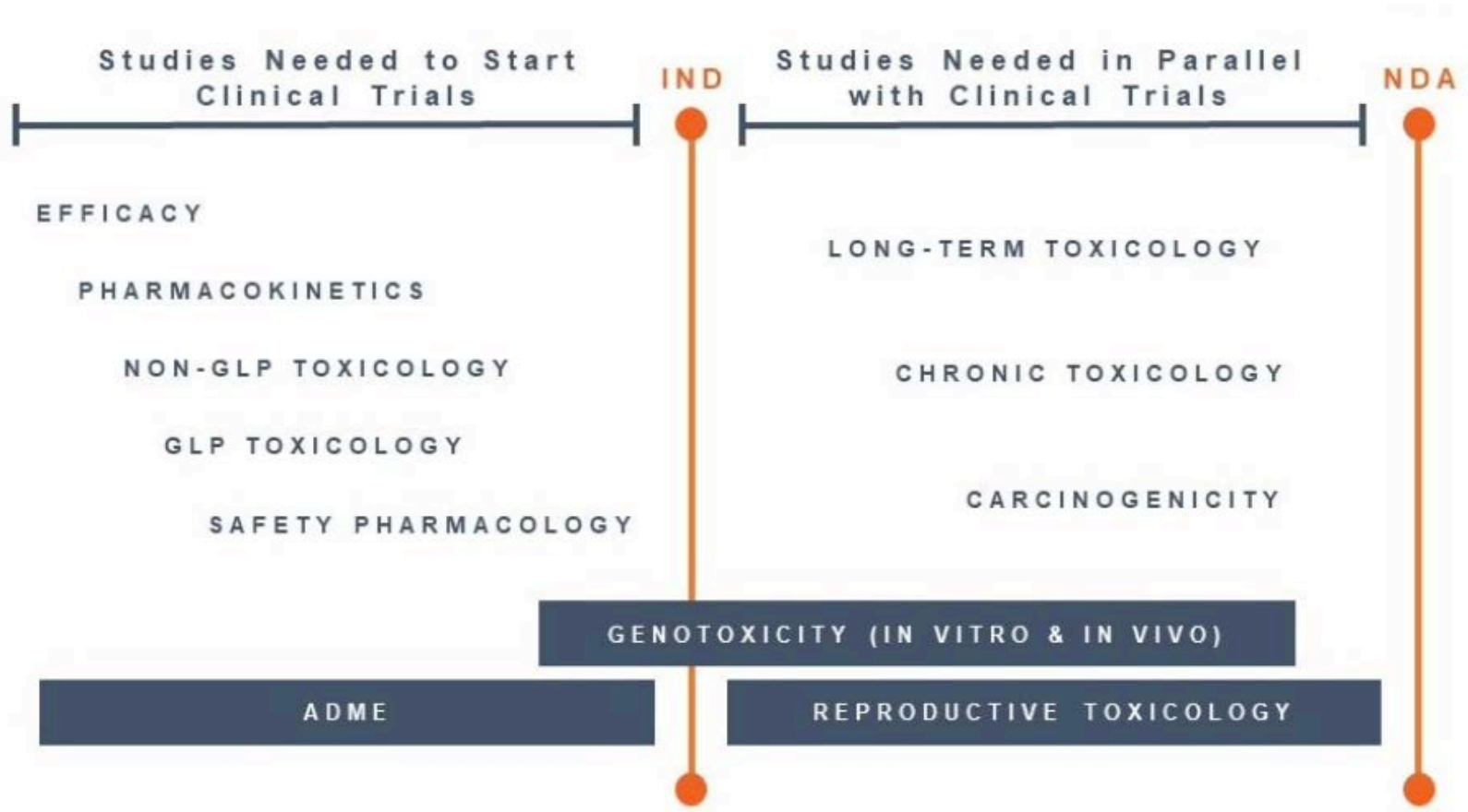
Typical pre-IND tests for topical vaginal drug + device combination product, e.g. vaginal ring

- 2 week rat toxicology study of the active agent
- Non-GLP or GLP 2 week sheep study of the ring
- Biocompatibility study (requirement for devices (CDRH))

Other issues

- Excipients
  - FDA list of inactive ingredients https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm
    - Helpful if your excipients are on this list in the dosage form and quantity used in another approved product
  - Excipients can cause toxicities, particularly in topicals
    - Caution on humectants/osmolytes
    - Caution on EDTA
- Choice of the control to use in toxicity (and clinical) testing
  - Vehicle control vs. ”certifiably bland control”

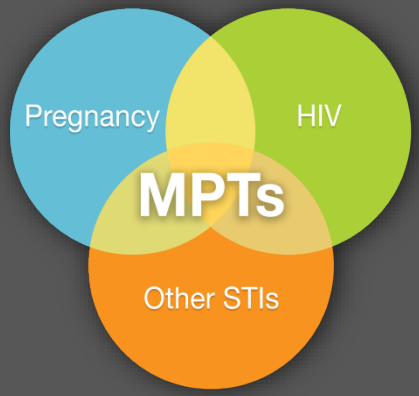
Non-clinical study timeline



Summary: Preparing a plan for your product

- Need for customization and consultation/negotiation with FDA
- Review FDA and ICH guidance documents
  - See links provided with this Webinar
- Engage appropriate consultants
  - Toxicologist
  - Regulatory affairs
- Potential NIAID resources for IND enabling studies (CRMP)
  - https://www.niaid.nih.gov/research/resources-hiv-microbicides-biomedical-prevention
- Obtain FDA feedback via a pre-IND package
  - Make a proposal and seek FDA comment

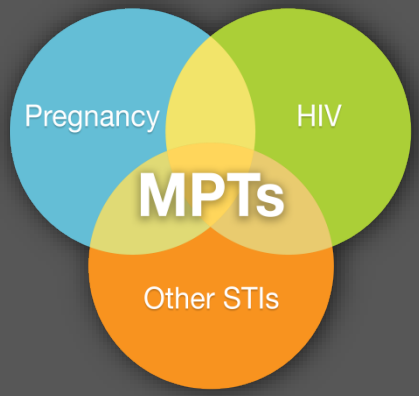
Q&A



All

- Please submit questions to the chat
- Please unmute for questions or comments.
- Please announce your name and affiliation when speaking.

Other Items & Wrap Up



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PEPFAR U.S. President's Emergency Plan for AIDS Relief

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