DRUG DEVELOPMENT FOR GLOBAL HEALTH

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BILL & MELINDA GATES foundation

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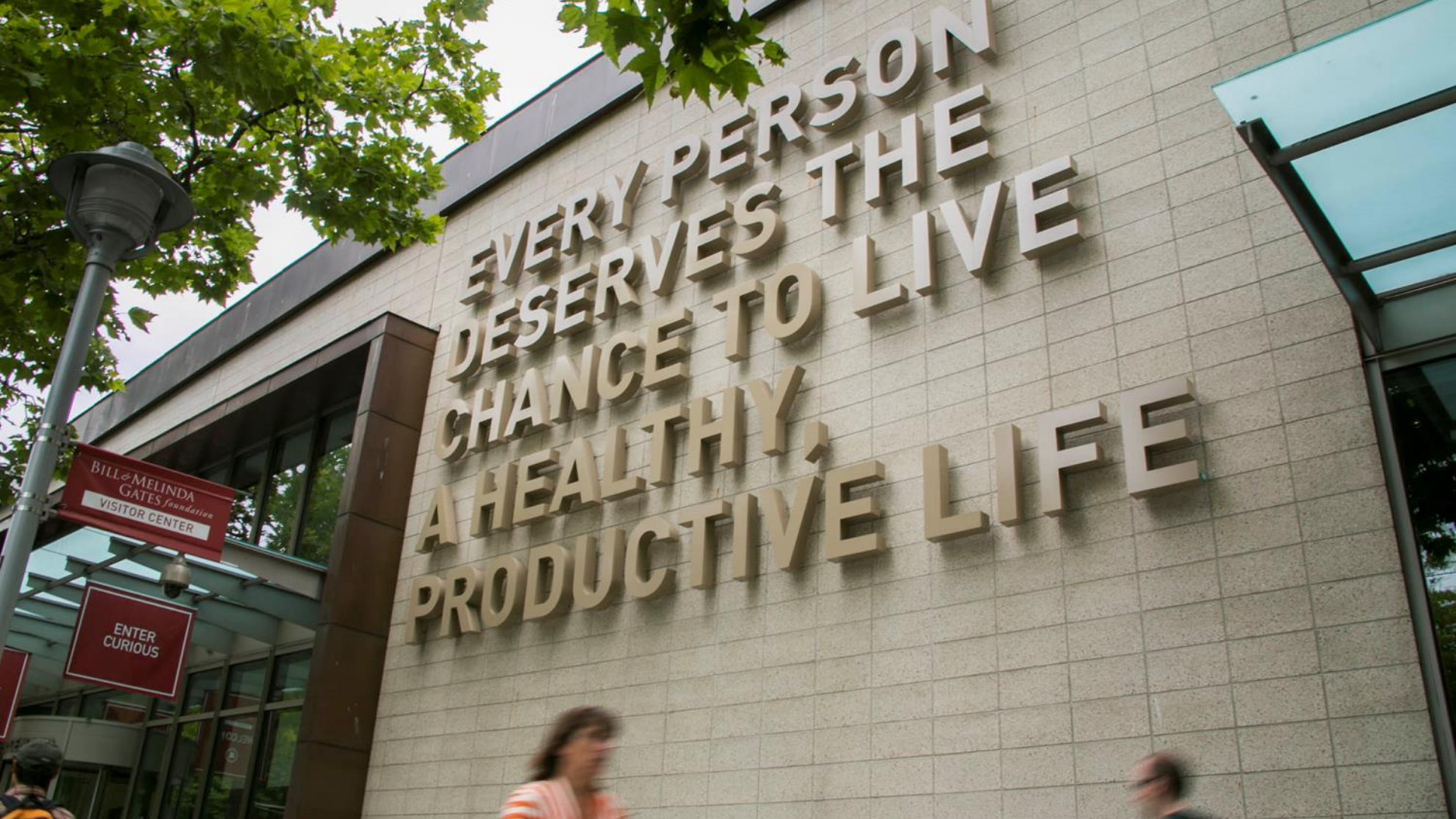

EVERY PERSON
DESERVES THE
CHANCE TO LIVE
A HEALTHY,
PRODUCTIVE LIFE
BILL & MELINDA GATES foundation
VISITOR CENTER
ENTER
CURIOUS

OUR GLOBAL REACH AND PRESENCE

$40B
Trust endowment

1,541
2017 employees worldwide

$4.7B
2017 grant payments

1,089
2017 active grantees

WHAT WE FOCUS ON

Areas of greatest need

Where we can have the greatest impact

Making science happen for people

The Last Mile

UNDERSTANDING HEALTHCARE SYSTEM AND INFRASTRUCTURE REQUIREMENTS IS KEY TO REALIZING PRODUCT IMPACT

Important to understand as product developers

Shortage of healthcare providers

- Sub-Saharan Africa has only 2% of the world's supply of physicians; nurses also in scare supply.
- Healthcare provider may have a couple of years training beyond college – or even high school

Weak supply chains

- Stock outs are frequent
- Puts premium on FDC's, prefilled injection devices and other all-in-one, ready-to-use formats

Transportation – last mile may be literally on the back of a donkey or motorcycle

- Requires rugged products; premium on lightweight compact formats

Healthcare facilities may be hard to access

- May be days walk away for rural patients
- Overburdened facilities / long waits for urban patients
- Very high barriers for the most vulnerable who must work every day

Additional infrastructure that supports a well functioning healthcare system may be absent as well

- Cold chain is sporadic or absent outside the best hospitals in the largest cities; requires ambient temperature stability for 3-5 years under extreme climate conditions
- Even electricity may be lacking or sporadic – procedures that require equipment beyond a microscope may be out of reach

Global Health settings often need different product formats to address patient needs and gaps in healthcare systems and infrastructure – but must be *cost effective* and *affordable* as well

BILL & MELINDA GATES *foundation*

FAMILY PLANNING

"Family planning and access to contraception - including information, supplies, and services - is an issue that I am passionate about, and it has become one of my personal priorities at the foundation. I believe it's one of the most urgent issues of our time."

Melinda Gates

THE CHALLENGE

- 220 million+ women in developing countries lack access to modern contraceptives leading to an estimated 80 million women with an unintended pregnancy.

THE OPPORTUNITY

- Reduction in unintended pregnancy by 70% (50M annually)
- Maternal deaths would drop by 67% (200,000 fewer deaths)
- New born deaths would drop by 77% (2.3M annually)

CONTRACEPTIVE USE AND CHALLENGES IN SUB-SAHARAN AFRICA

Contraceptive Use in Sub-Saharan Africa

- More than 1/3 of contraceptive users in SSA choose injectable depots
  - Durations range from 1-3 months
  - Cost is ~ $0.80/dose
- Non-degradable implants are also widely used
  - Durations range from 3-5 years

Delivery Challenges for Current Injectable Depots

- Most common reason for unplanned pregnancy for users of injectable depots is missed dosing
- Need to access clinic 4-12 times a year
- Shipping costs and stock-outs of drug and/or supplies
- Need for healthcare worker training

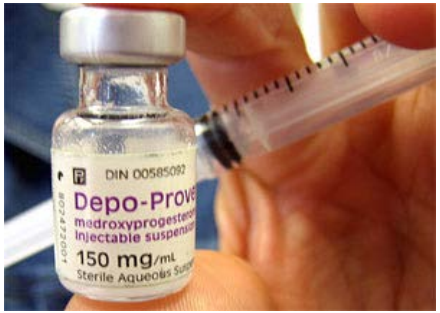
Delivery Challenges for 3-5 year Implants

- Need for healthcare worker training for implant and removal
- Requires surgical removal at end of delivery duration
- Inflexible interval is a barrier for spacing children

Cost Remains a Barrier to Access

- Procurement budgets are fixed and do not cover needs of all women who desire access to modern contraceptives

Injectable Depot



Non-degradable Implant

BMGF INVESTMENTS: CREATING NEW OPTIONS

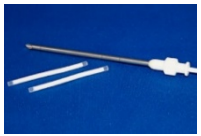
Long-Acting Injectable and Implantable CT Products in Development

Sayana Press: 3-month DMPA injectable in Uniject
Approved 2011 by MHRA
(Depo-Provera approved 1992 by US FDA)

Jadelle: 5-year LNG implant
Approved 1996 by US FDA

Implanon: 3-year ENG implant
Approved 2006 by US FDA

Commercial products
Investments



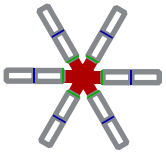
Monthly oral

3-month injectable

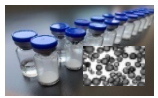
6 to 24 month injectables &/or bioerodible implants

3 - 5 year implants

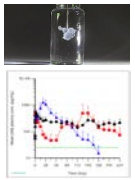
Very long-acting controllable



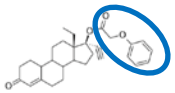
Lyndra
Long-acting delivery



FHI360 / SIPPR
PLGA microparticles and implant



MedinCell
Injectable polymeric hydrogel



Evestra
LNG & ENG pro-drugs

DelSiTech
Injectable silica matrix

FHI360 / pH Sciences
Biodegradable implant

MicroCHIPS
Programable implant

PRODUCT DEVELOPMENT AND MANUFACTURING CHALLENGES

- Complex dosage forms requiring sophisticated manufacturing technologies, e.g.
  - Suspension filling in Uniject device
  - Microparticles
  - Extrusion technology
  - Complex assembly
- Majority also have device requirements
  - Combination products in prefilled injection device
  - Insertion aids for implants

- Potent compound handling requirements for API's
- Aseptic manufacturing or terminal sterilization required
- A shelf-life of at least 3 years under ambient zone 4b storage conditions is required for procurement
  - 5 year shelf-life preferred
- WHO Prequalification or equivalent stringent regulatory agency approval
- Cost of goods not to exceed current methods on a per patient per year basis

➢ *All product candidates make use of well characterized contraceptive hormones with established track records of safe and effective long-term administration.*

➢ *How can we take advantage of well understood PKPD or exposure-response relationships to streamline development costs and timelines for these much needed global health product innovations?*

CAN MIDD ACCELERATE REGULATORY PATHWAY IN CT?

Traditional Scenario	Pre-clinical	Phase I	Phase II	Phase III	SRA	WHO PQ & NRA Approval
Duration (years)	1-3	1-3	2	Up to 4	1-1.5	4-7
		n<100, PK+safety	n=100-300 (PKPD)	n≥400 (20k cycles)		

Hypothetical MIDD Scenarios for Well-characterized APIs

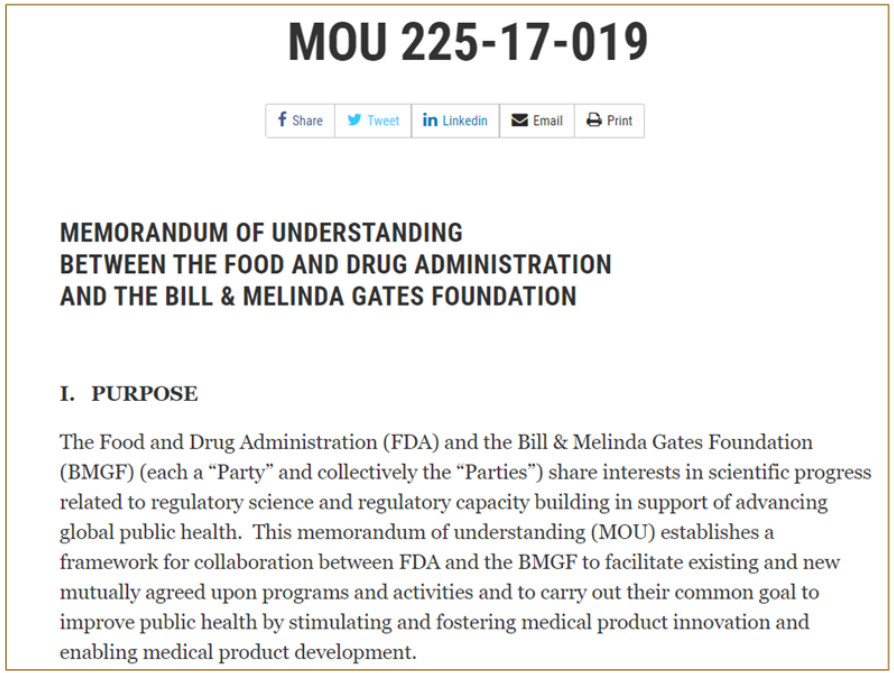
FDA 505(b)(2)	Pre-clinical	Phase I	Phase III	SRA	WHO PQ & CP
Duration (years)	1-3	1-3	3-4	1	1-2.5
Size		n<100, PK+safety	n≥200 (10k cycles)		

Full PK Bracketing	Pre-clinical	Phase I	Definitive PK	SRA	WHO PQ & CP
Duration (years)	1-3	2	2-3	1	1-2.5
Size		n<100, PK+safety	n<200 PK+Safety		

Reduced trial burden; Streamlined program (decrease $ and time), potentially de-risking for pharma partners

MIDD = Model informed drug development; CT= Contraceptive Technologies; SRA = Stringent Regulatory Authority; PQ = Pre-Qualification; NRA = National Regulatory Authorities; CP = Collaborative Procedure

EXPOSURE-BASED PARADIGM TO DEVELOP LONG ACTING CONTRACEPTIVES



MOU 225-17-019

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MEMORANDUM OF UNDERSTANDING BETWEEN THE FOOD AND DRUG ADMINISTRATION AND THE BILL & MELINDA GATES FOUNDATION

I. PURPOSE

The Food and Drug Administration (FDA) and the Bill & Melinda Gates Foundation (BMGF) (each a "Party" and collectively the "Parties") share interests in scientific progress related to regulatory science and regulatory capacity building in support of advancing global public health. This memorandum of understanding (MOU) establishes a framework for collaboration between FDA and the BMGF to facilitate existing and new mutually agreed upon programs and activities and to carry out their common goal to improve public health by stimulating and fostering medical product innovation and enabling medical product development.

Outcome

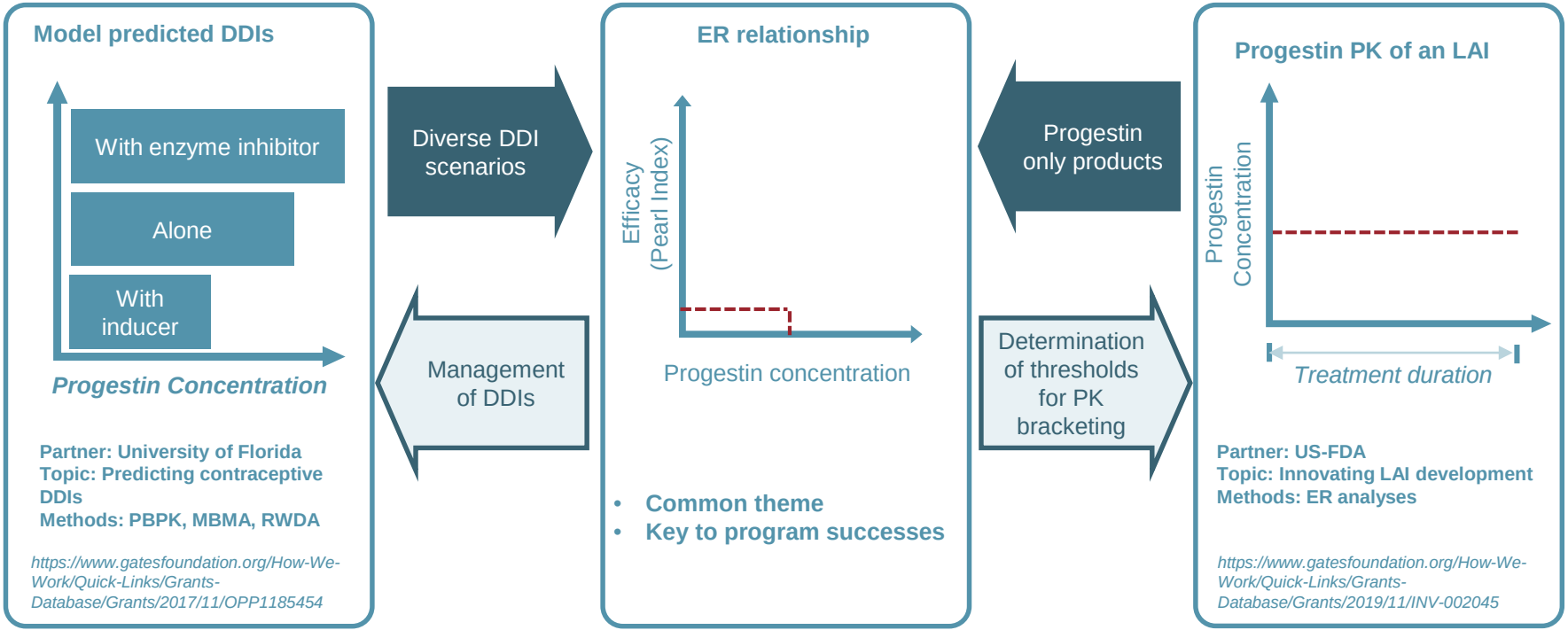
An innovated approval pathway for alternative delivery products of well-studied hormonal contraceptives

Methods

Modeling and simulation research to assess the feasibility of an exposure-based paradigm for the development and review of these products

https://www.fda.gov/about-fda/non-profit-and-other-mous/mou-225-17-019

FACILITATING KNOWLEDGE SHARING AND COLLABORATIONS



DDI = Drug-drug interactions; ER = exposure response analyses; PBPK= Physiologically-based PK; MBMA = model-based meta-analyses; RWDA = real-world data analyses; LAI = long acting injectables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THANK YOU