NEW APPROACHES FOR BIOEQUIVALENCE ASSESSMENT AND GENERIC APPROVAL OF LA/ER ANTIRETROVIRAL DRUGS

Liverpool, United Kingdom
SEPTEMBER 9, 2024

leap Long-Acting/Extended Release Antiretroviral Research Resource Program

ABBREVIATIONS

AE Adverse event
AGYW Adolescent girls and young women
AI Active ingredient
ANDA Abbreviated new drug application
API Active pharmaceutical ingredient
ART Antiretroviral therapy
ARV Antiretroviral
AUC Area under the curve
AVAC AIDS vaccine advocacy coalition
AZT Azidothymidine
BA Bioavailability
BCS Biopharmaceutical classification system
BE Bioequivalence
CAB Cabotegravir
CELT Centre of excellence for long-acting therapeutics
CHAI Clinton health access initiative
CHW Community health worker
CI Confidence interval
CMC Chemistry, manufacturing, and controls
CNS Central nervous system
COGs Cost of goods
CQI Continuous quality improvement
CSA Coordinated Scientific Advice
DAA Direct-acting antiviral
DAIDS Division of AIDS
DAP Drug absorption profile
DCE Discrete choice experiment
DcNP Drug combination nanoparticles
DDI Drug-drug interaction
DE Data exclusivity
DMPA Depo-Provera
DPV Dapivirine
DSD Differentiated service delivery
DTG Dolutegravir
EFV Efavirenz
EMA or EMEA European medicines agency
EOI Expression of interest
ER Extended release
EU European Union
FAST-TB Facilitating accelerated science and translation for TB regimen development
FDA Food and drug administration
FDC Act Federal food, drug, and cosmetics Act
FDF Final dosage form
FSW Female sex worker
FTC Emtricitabine
HCP Healthcare provider
HCV Hepatitis C virus
HCW Healthcare worker
HIV Human immunodeficiency virus
HME Hot melt extrusion
HTE Highly treatment experienced
HV Healthy volunteer
IM Intramuscular
IP Intellectual property
IPT Isoniazid prevention treatment
IR Immediate release
ISL Islatrovir
IV Intravenous
JHU Johns Hopkins university
Ka Absorption constant
Kel Elimination constant
LA Long-acting
LAI Long-acting injectable
LAPaL Long-acting therapeutics, patents, and licenses
LEAP Long-acting extended release antiretroviral research program
LEN Lenacapavir
LMIC Low-middle income country
LMNC Lymphomononuclear cell
mAbs Monoclonal antibodies
MD Multiple dose
MIE Model-integrated evidence
MMF Model master file
MPP Medicines patent pool
M&S Modeling and simulation
MSM Men who have sex with men
NDA New drug application
NGO Non-governmental organization
NHP Non-human primate
NIH National institutes of health
NTP National treatment program
NVP Nevirapine
OLI Oral lead-in
pAUC Partial area under the curve
PBMC Peripheral blood mononuclear cell
PBPK Physiologically based pharmacokinetic
PD Pharmacodynamics
PEPFAR
PGLA Polyglycolic acid
PI Protease inhibitors
PK Pharmacokinetics
PLWH People living with HIV
PP Paliperidone palmitate
PPPY Per person per year
PrEP Pre-exposure prophylaxis
PSG Product-specific guidance
RA Regulatory authority
RAL Raltegravir
R&D Research and development
RCT Randomized controlled trial
RLD Reference listed drug
RLS Resource-limited setting
RPV Rilpivirine
SA South Africa
SC Subcutaneous
SD Single dose
SG&A Selling, general, & administrative
SQVr Saquinavir boosted with ritonavir
SR Sustained release
SRA Supervisory authority
SS Steady state
SSA sub-Saharan Africa
TB Tuberculosis
TDF Tenofovir
TE Therapeutic equivalence
TLC-ART Targeted long-acting and combination antiretroviral therapy
TLD Tenofovir, lamivudine, and dolutegravir
TLE Tenofovir, lamivudine, efavirenz
TPP Target product profile
WHO World Health Organization
WHO CRP WHO collaborative registration procedure
WHO PQ WHO prequalification
YW Young women
3TC Lamivudine

CONTENT

Where will we LEAP next?

On September 9, 2024 LEAP and CELT convened approximately 50 in-person and 120 virtual registrants for a one-day workshop intended to catalyze coordinated activity to streamline development and approval of generic LAI ARV products. Opening remarks from CELT, DAIDS, and LEAP leadership were followed by four Plenary Sessions and two Open Discussions. Presenters represent diverse perspectives, including: Regulatory, formulation, manufacturing, and intellectual property experts; Investigators; Clinicians; Funders; and Community advocacy groups. Topics were strategically selected to help collectively identify novel, more efficient approaches to bioequivalence assessment of low-cost generic LAI ARV products and improve access to life-saving treatments among populations and geographies with the greatest need. This report summarizes plenary session presentations and major themes from the open discussions.

Andrew Owen Co-director, Centre of Excellence for Long-acting Therapeutics (CELT)

"Funders have been catalytic in long-acting medicine development for HIV and other diseases"

Dr. Owen welcomed workshop participants to Liverpool on behalf of CELT and CELT Co-director, Steve Renard. He thanked attendees of the previous days' workshops on drug-drug interactions and antiviral pharmacology. Dr Owen expressed particular gratitude to UNITAID for the establishment of CELT and the LONGEVITY grant and to the NIH for the establishment of LEAP and other investments in the LA space.

OPENING REMARKS

Keith Crawford Program Officer, DAIDS Therapeutic Research Program

"We know [LA ARV products] work in resource-limited settings ... Nationality and which hemisphere you live in should not determine how you are able to access these types of treatments"

Dr. Crawford recognized LEAP as a valuable resource for the development of innovative LA therapeutics. He emphasized LEAP's role in helping investigators navigate the challenges of getting products into clinical trials. Citing the effectiveness of LEN and CAB-LA in NIH-supported HIV prevention and treatment trials in Africa (Near 100% protection and 98% virologic suppression), Dr Crawford identified access to LA ARV products as the critical next step. He applauded Charles Flexner and LEAP for sponsoring this forum and expressed optimism that today's discussions will help ensure effective LA treatments are available to everyone who needs them.

Charles Flexner Principle Investigator, LEAP

"We clearly have products that are positioned to radically alter the direction of the HIV epidemic, but ...
We cannot get them to the people who need them most in the parts of the world where this epidemic is still raging"

Dr. Flexner identified the availability of LA ARV formulations as the motivation for today's workshop. For 10 years, LEAP has supported the development of formulations for the prevention and treatment of HIV and related diseases. LA formulations now represent a game-changing approach ***in places where they can be used*** – a Q6m LAI formulation (LEN) is now in the same category as the most effective vaccines, offering near 100% protection from HIV (PURPOSE I). By convening key stakeholders, LEAP aims to find a pathway forward to ensure low-cost LA ARV formulations are available to those who need them and where it is most important. Dr Flexner emphasized the strategic importance of today's workshop content:

- Each plenary session builds on the last. Plenary 1 reviews learnings from low-cost LAI development in other areas; Plenary 2 pivots to LAI ARVs; Plenary 3 & 4 focus on clinical development issues and manufacturing & implementation.
- There are opportunities for rich discussion. Open discussion sessions after Plenary 2 and 3.
- A rapporteur will provide a meeting summary.
- Recordings and summaries will be available at: www.longactinghiv.org.

Special Thanks: Organizing Committee (Andrew Owen, Steve Renard [CELT], Lobna Gaayeb [MPP], Paul Domanico [CHAI], and Kimberly Struble [FDA]); Support Staff (Joe Sharp, Cheryl Westwood [CELT] and Julia Burnett, Matthew Williams [LEAP]); and Rapporteur (Polly Clayden).

Kimberly Struble Senior Analyst, Division of Antivirals at US FDA

"Regulatory considerations in the development of generic LAI formulations"

"[The Office of Generic Drugs] is very excited to work with developers in this field for LA ARVs"

Most LAI products have no generic approvals to date

- LAIs maintain drug plasma concentration longer than other dosage forms (i.e., Sustained continuous drug release over days to months).
- Reduced dosing frequency improves compliance and treatment adherence.
- Low-cost, generic LAI ARV formulations are needed to optimize HIV prevention and treatment in LMICs.

New drug application (NDA) pathways under the FDC act

Novel drugs and Modifications of approved drugs.

NDA 505(b)(1) Novel Drug	NDA 505(b)(2) Modification of Approved Drug
Drug/active ingredient that has never been studied or FDA approved.	New dosage form, strength, route, formulation, dosing regimen, combination, or indication for an FDA-approved/reference listed drug (RLD).
Applicant owns or has right of reference to all reports, including P1-3, non-clinical, and CMC packages.	Applicant does NOT have right of reference to at least some of the information required for approval
Stand-alone application.	Typically permits reliance on the literature or prior FDA review for non-clinical information plus submission of additional P1 or 2 data.
No other regulatory considerations.	**Drug product cannot have existing patents or exclusivity**.

Generic drug products.

Abbreviated NDA (ANDA) 505(j) Generic Drug
Copycat of a RLD.
Approval relies on prior FDA review of safety and efficacy information for the approved drug.
Applicant must show pharmacological equivalence and bioequivalence (i.e., Therapeutic equivalence) of the proposed drug to the RLD.
All FDA-approved drugs have a product-specific guidance (PSG) for demonstrating bioequivalence (BE).
BE limit: The calculated CI for the ratio of product averages must fall within 80-125%.
Parenteral products: Proposed and reference drug products must contain the same inactive ingredients and in the same concentrations; Differences in preservatives, buffer and antioxidant are allowed if appropriately justified.

PSGs support generic drug approval

PSG reflects current FDA expectations for showing TE.

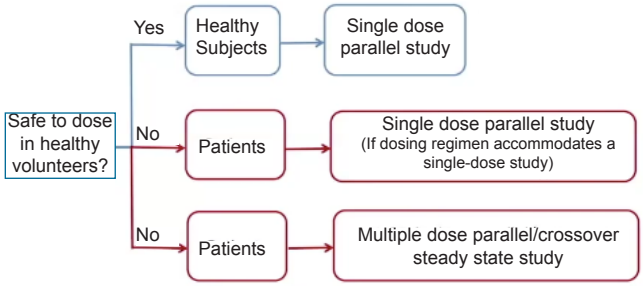
- A draft PSG is issued for every newly approved drug.
  (Available at: https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm).
- Informs the most appropriate data and methodologies for approval.
  - ◊ In vitro +/- in vivo testing; Dissolution testing; Biopharmaceutical classification system (BCS)-based waiver.

Recommended BE approach depends on the specific LAI.

- In vivo PK BE study + Q1 and Q2 sameness.
  - ◊ Q1 (Qualitative) sameness: Test and RLD product contain the same inactive ingredients.
  - ◊ Q2 (Quantitative) sameness: Concentrations of inactive ingredients in the test and RLD product are within 5%.
- In vivo PK BE study + Q1 and Q2 sameness + Q3 similarity + comparable in vitro release profile.
  - ◊ Q3 similarity: Test and RLD product have no structural and physiochemical differences that would significantly impact bioavailability (BA).
- Q3 similarity + comparable in vitro release profile (No in vivo study).
  - ◊ May be possible for Q1/Q2 formulations based on a totality of the evidence approach.

Recommended BE study design.

- Study population depends on drug/AI safety.



- SD parallel study in HVs: PSG for Medroxyprogesterone acetate, Naltrexone, Exenatide.
- SD parallel study in patients: PSG for Leuprolide acetate, Goserelin acetate, Triptorelin acetate.
- MD parallel/crossover study in patients: PSG for Paliperidone palmitate, Aripiprazole, Risperidone.

Sample PSGs for FDA-approved LAIs

Reference Listed Drug	Product-Specific Guidance
Medroxyprogesterone acetate injectable suspension	In vivo SD parallel BE study with PK endpoints.
Risperidone injection	Q1/Q2 sameness + Q3 characterization of PGLA + in vitro drug-release testing + in vivo crossover steady-state BE study with PK endpoints
PEN-G benzathine injectable suspension	Option 1: Q1/Q2 sameness + Q3 characterization + in vitro drug-release testing
	Option 2: SD parallel BE study with PK endpoints

Summary

- Today's meeting is focused on development of generic LAI products (i.e., Copycats, not modifications of FDA-approved drugs).
  - ◊ There is also much interest in developing formulations of FDA-approved drugs with longer dosing intervals, which is a different application type: NDA 505(b)(2).
- ANDA 505(j) pathway for generic drug approval.
  - ◊ **Not appropriate for new AIs, formulations, or indications.**
  - ◊ Approval relies on bioavailability and BE studies.
  - ◊ FDA PSGs provide recommendations for the type of data and studies required for approval.

Melynda Watkins Senior Director at CHAI

"Hormonal contraceptive implants and injectables: What have we learned to apply to LAI ARVs?"

CHAI engagement with LA hormonal contraceptive programs for LMICs

Experience with generic development and registration.

- WHO prequalification (PQ) pathway for quality assurance.

Implant	LAI (DMPA IM and SC)
Product was in late-stage development at the time of CHAI engagement.	CHAI and partners helped the generic developer through their first WHO PQ filing.
Needed a new BE study design/Held negotiations on a sample size, duration, and data required. • Initial BE study was insufficient for WHO PQ filing. Generic partner's lack of knowledge/understanding of the requirements and new regulatory pathway caused a significant delay.	Helped plan and execute pilot and pivot BE studies. • Different study designs were needed for IM and SC products due to stage of development and the SC device.
Production capacity was a significant issue. • Manufacturing risks due to lack of back-up equipment. • Needed additional generic suppliers to ensure volumes were available and affordable.	Established appropriate manufacturing lines. • Included equipment procurement to fill the SC device.
	Prepared high-quality dossiers (to withstand WHO-PQ review) and prepared for resulting inspections.

- Development of critical follow-on country registration strategy.
  - ◊ Appropriately stage filings (i.e., Prioritize countries where the generic partner can withstand the regulatory burden).
  - ◊ Leverage mechanisms to streamline multi-country registration (i.e., WHO CRP).

Key learnings.

- Ensure early understanding of the regulatory strategy and pathway.
  - ◊ Examine development and BE study requirements (PSGs) by regulatory authority (RA) and WHO PQ based on the regulatory strategy.
    - * Even small differences in study requirements can impact acceptance by each group.
    - * Repeating studies in order to file via multiple pathways is costly and inefficient.
- Plan for long in vivo BE studies to support LA drug applications.
  - ◊ Leverage evolving mechanisms to streamline study duration and increase efficiency.
- Request early presubmission meetings and re-engage often.
  - ◊ To ensure alignment on the BE study approach or request advice.
  - ◊ Multiple mechanisms exist, depending on the RA.
- Risks to commercialization can cause serious delays.
  - ◊ Long BE study duration or study not fit for purpose.
  - ◊ Lack of back-up or duplicate equipment.
  - ◊ Low initial capacity without expansion plans (Additional BE studies may be required with scale up).
  - ◊ Long lead times for equipment (Up to 2y for new equipment).
- Country of origin can impact the overall commercialization strategy.
  - ◊ Related to generic manufacture and ultimately registration in multiple LMICs. Some countries may not accept a product from another country; There may be embargoes for equipment.

Applying learnings to LAI ARVs

Considerations for a future generic development program.

	CAB-LA	LEN
API synthesis	Straightforward (Most generics make it)	**Complex** (23 steps based on Gilead patent)
FDF manufacture	**Complex**	Straightforward
Specialized equipment	**Nanomill; Gamma irradiation**	**Spray-drying** (Tablet)
BE requirements	**Long study duration**	Biowaiver possible (FDA PSG)
Licensing	3 generics licensed via MPP	**Not yet**
Innovator approvals	PrEP: CAB-LA (single pack) Treatment: Co-pack with LA RPV.	**PrEP: Not yet filed** Treatment: In HTE individuals.
Companion oral tablet*	**Yes** (CAB-LA license requirement)	**Yes** (Required oral loading dose)
Eligible pathways	US FDA via PEPFAR WHO PQ (Leverage WHO CRP)	US FDA via PEPFAR **No WHO PQ guidance yet**

FDF, Final dosage form; HTE, Highly treatment experienced.
* A second, full development program is required for the companion oral formulation.

BE requirements by regulatory pathway.

	US FDA	WHO PQ
CAB-LA		
Guidance	Separate PSGs for LAI and tablet.	One PSG for LAI and tablet.
Study duration	Not specified in PSG. (SD parallel design)	42 weeks. (SD crossover or parallel design)
Presubmission meetings	Highly recommended.	Highly recommended.[1]
Device components	ANDA requires full comparative analysis to RLD device parts.	No additional requirements; Dossiers are reviewed as drugs.
LEN		
Guidance	Biowaiver recommended.	No PSG yet.[2]

[1] Pilot program for Coordinated Scientific Advice (CSA) is a potential mechanism (WHO Research for Health Group).
[2] LEN is not yet listed on the Expression of Interest (EOI) for the WHO therapeutic area.

Opportunities to reduce the burden of BE studies for LAIs

FDA acknowledges the challenges and is being proactive.

- 2024 FDA workshop. Considerations & potential applications for a model master file (MMF; Available at: https://www.complexgenerics.org/education-training/).
- Challenges of FDA-recommended PK BE studies for LAIs.
  - ◊ Long study duration (Several months to years) due to long half-life and time to steady state.
  - ◊ Large sample size due to high variability is complicated by recruitment difficulty and high dropout rate during a long study.
- Alternative BE approaches using model-integrated evidence (MIE).
  - ◊ Population PK modeling to enhance the efficiency of BE PK studies.
  - ◊ Mechanistic (PBPK) modeling to mediate BE decision based on in vitro studies.
  - ◊ Leverage MIE to generate pivotal evidence for BE decision:
    - * Pre-specified model-based analysis of in vitro BE study.
    - * Virtual BE study.
- MMF approach.
  - ◊ MMF. A quantitative model or modeling platform with sufficient verification and validation to be recognized as sharable IP that is acceptable for regulatory purposes.

    - * Sponsor 1 owns a validated BE study model for the RLD and submits to FDA.
    - * Sponsor 2. Generic developer of a test product has right of reference to MMF for FDA review.
    - * Information is kept confidential (i.e., Not seen but can be relied upon).
  - ◊ Value. The information is not owned by a single pharmaceutical or generic company; The same modeling approach could support different generic development programs in lieu of clinical studies.
  - ◊ Logistical questions: Who submits the MMF to FDA? How does S2 access the MMF?; Does S2 access model data? How to re-run model for test product using MMF? Can S2 perform a study with only the test product (i.e., Waive reference)? Will regulatory review time be shorter?

FDA is open to novel solutions – we need to lean into this.

- What mechanisms can we help develop with regulators to accelerate market entry for generic LAI ARVs?
  - ◊ It is critical to convene a group to bring ideas, solidify on an approach with stakeholders and collaborators, and dialogue with the FDA.
- Can we develop a MMF for CAB-LA (i.e., 42-week BE study)?
  - ◊ MMF approach is promising.
    - * There is some experience with a research group owning data that has been submitted to the FDA and relied upon by generic companies (e.g., Clinical data for efavirenz 400).
  - ◊ Some of the most preeminent modelers in the world are in the room today.

Summary

- Define the regulatory strategy, seek early engagement with RAs, and refine the approach/re-engage as needed.
  - ◊ Discuss modeling with FDA to shorten duration and reduce sample size of PK BE studies.
  - ◊ Investigate MMFs to potentially alleviate the BE burden for multiple generic partners.
    - * Could be in collaboration with the innovators who want their products to be available in LMICs.
  - ◊ Discuss approaches with WHO PQ or via CSA pilot program to align requirements.
- Utilize mechanisms to accelerate registration (e.g., PEPFAR and WHO CRP).

PLENARY 1

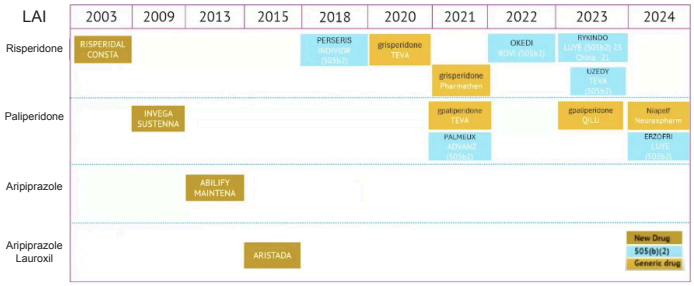
Parag Nimbolkar Medicines Patent Pool (MPP)

"Landscape analysis of approvals and market update of generic or equivalent formulations for CNS LAI medicines"

"[CNS-focused LAIs] are more commercially successful ... the idea is to collaborate and understand their journey of development"

Market analysis of CNS-focused products

Summary of EMA/FDA approvals of LAI products.



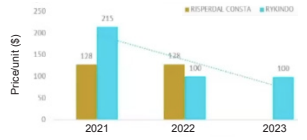
Takeaways.

- Huge delays from brand to generic and 505(b)(2) product approvals.
  - ◊ Risperidone LAI.
    - * 15 years to first 505(b)(2) product approval: Perseris (Indivior).
    - * Nearly 20 years to first generic product approval: grisperidone (TEVA).
  - ◊ Paliperidone LAI.
    - * 12 years to first 505(b)(2) and generic product approvals.
- Few therapeutically equivalent products vs 505(b)(2) products.
- Recent uptick in generic development and approvals due to improved clarity of regulatory guidance.
  - ◊ More companies are devoting resources to creating their own technology platform, "cracking" formulation complexity, and developing a therapeutically equivalent product.
  - ◊ Risperidone LAI. Generic developers have made huge strides in recent years.
  - ◊ Paliperidone palmitate LAI. At least five generic companies with tentative approvals.
- Most generic products are not present in LMICs.
  - ◊ Generics are in Australia, Canada, Europe, Japan, and US.

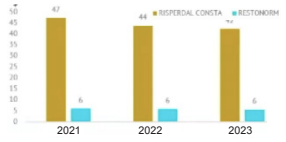
Impact of generic entry. Generally, prices decrease with benefit to the consumer.

- Risperidone LAI pricing analysis. Generic (Yellow)/alternative product (Blue) launch impacts pricing and innovator (Gold) sales; Degree of impact varies by territory.

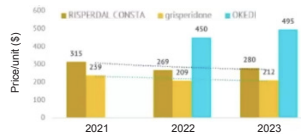
China – Generic launched at a huge discount.



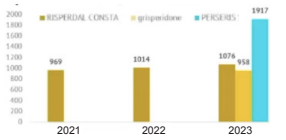
India – Huge difference in price between the innovator (Gold) and branded generic (Blue).



Germany – Generic (Yellow) priced 30% lower than the innovator (Gold).



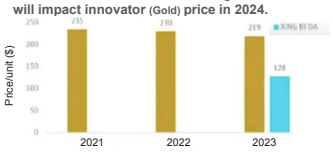
US – Generics (yellow) recently approved; The impact on price is not yet visible.



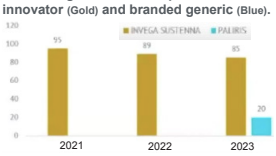
- ◊ Generics are capturing the market very fast, at least starting with high-income countries.
  - * Innovator market share decreased from 91% in 2021 to 74% by the end of 2023.

- Paliperidone palmitate pricing analysis. Impact of generic/alternative product launch on pricing will be visible in a few years.
  - ◊ Generics have only recently been launched.

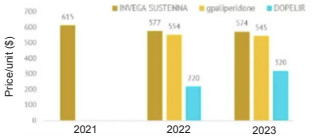
China – Generic launched at a huge discount & will impact innovator (Gold) price in 2024.



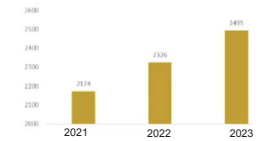
India – Huge difference in price between the innovator (Gold) and branded generic (Blue).



Germany – Generics (Yellow) may not impact price, but will greatly impact innovator (Gold) sales.



US – Generics are not commercially available due to patent protection.



Noteworthy success stories

Aristada (Aripiprazole lauroxil) IM ER suspension.

- **Submission type.** Type 1 new molecular entity.
  - ◊ Technology: Nanocrystal technology.
  - ◊ RLD: Abilify tablets.
- **Clinical path.** Alkermes submitted P3 (safety and efficacy) and SD/MD P1 PK studies.
  - ◊ Prior agency finding of safety and efficacy for oral aripiprazole was considered.
- **Value addition.** First LA atypical antipsychotic with QM and Q6W dosing options.
- **Commercial performance.** Doing well against the innovator.
  - ◊ $444M in sales vs Innovator $1.2B (2023).

Rytary (Carbidopa and Levodopa) ER capsule.

- **Submission type.** Type 5 new formulation or new manufacturer.
  - ◊ Technology: IR and ER beads designed for different release rates in GI tract.
  - ◊ RLD: Sinemet tablet, Sinemet CR tablet, and Stalevo tablet.
- **Clinical path.** Impax submitted two randomized P3 studies and six additional studies (i.e., PK, food effect, BA).
- **Value addition.**
  - ◊ Consistent PK profile to reduce motor fluctuations and dosing frequency.
  - ◊ Reduced time interval where patient symptoms are inadequately controlled.
  - ◊ ER formulation improves "off time" by over one hour each day.
- **Commercial performance.** Captured the market.
  - ◊ $298M in sales vs Innovator NA (2023).

Cinvanti (Aprepitant) IV emulsion.

- **Submission type.** Type 3 new dosage form.
  - ◊ Technology. Oil-in-water emulsion with improved aprepitant solubility.
  - ◊ RLD: Emend (fosaprepitant) injection.
- **Clinical Path.** Heron Therapeutics submitted two BA studies.
- **Value addition.**
  - ◊ Unique synthetic, surfactant-free formulation administered as IV push or infusion.
  - ◊ IV push saves $1.99 per push and 33 min vs 30-min IV infusion.
- **Commercial performance.** Captured the market;
  - ◊ $187M in sales vs Innovator $9M (2023).

Sublocade (Buprenorphine) SC ER injection.

- **Submission type.** Type 3 new dosage form.
  - ◊ Technology. Atrigel technology (in situ-forming gel/depot for SR over one month).
  - ◊ RLD: Subutex SL tablet
- **Clinical Path.** Indivior submitted one inpatient opioid blockade study and one RCT for safety and efficacy.
- **Value addition.**
  - ◊ Sustains therapeutic plasma concentrations for one month.
  - ◊ Blocks rewarding affects of opioids.
- **Commercial performance.** Captured the market.
  - ◊ $192M in sales vs Innovator withdrawn (2023).

Lobna Gaayeb Medicines Patent Pool (MPP)

"Unlocking the potential of the long-acting therapeutics patent and licenses (LAPaL) database to map LA therapeutics"

"The LAPaL database is another tool to see what is out there and who could be allies"

LAPaL database supports R&D of LA therapeutics

Collaborative and public health-oriented.

- Developed by MPP, UNITAID, LEAP, Univ of Liverpool, and CELT.
- Focus is LA technology platforms and compounds with potential for impact in LMICs.
  - ◊ Technical features.
  - ◊ Development status (Clinical trials and Regulatory approvals).
  - ◊ Global IP patents and licenses.
- Content is continuously updated.

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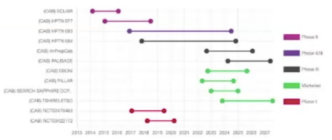
  - ◊ Enter technology name, API, or developer.
- Use drop down menus and check boxes to refine a search.
  - ◊ Frequency and/or route of administration; Type of technology or compound; Development stage; Therapeutic area; Targeted population; Ease of administration; API, etc.
- Access individual cards.
  - ◊ 29 compounds and 23 technologies to date.
- Leverage available tools with evolving functionality.

Tools.

- Clinical Trials Timeline.
  - ◊ Powerful tool for advocacy and funders.
  - ◊ Example:
    - * Can list all ongoing clinical trials for HIV PrEP.
    - * Provides insight into: What is going on; Where to invest; and Where the gaps are.

HIV PrEP



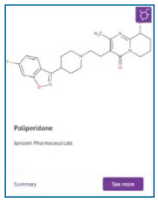
- Global IP Landscape.
  - ◊ Not limited to LMICs.
  - ◊ Focus is technologies.
  - ◊ Data are curated by IP specialists. Compound Patent Families: Patent description; Representative patent; Patent status; License with MPP.
- Regulatory Status World Map.
  - ◊ Can see all territories where a technology or compound is approved (Green) and submitted (Dark gray).
  - ◊ Filing information is more difficult to find.
- Direct Comparison **(New tool)**.
  - ◊ Compares two technologies or compounds.

Cabotegravir (CAB)

Using LAPaL to map CNS-focused LAIs

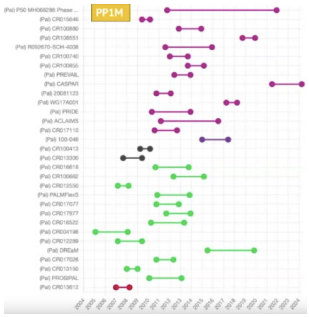
Therapeutic Area search.

- "Mental Health" yields five cards.
  - ◊ Paliperidone (Master compound from Janssen).
  - ◊ Four paliperidone palmitate (PP) formulations (LAI).
    - * Three from the innovator (PP1M, PP3M, PP6M).
    - * One generic from Luye Pharma Group (PP1M).



Clinical Trials Timeline.

- PP1M.
  - ◊ Marketed (Magenta);
  - ◊ Phase 1/2 (Purple);
  - ◊ Phase 1 (Black);
  - ◊ Phase 3 (Green);
  - ◊ Phase 2 (Red).



Regulatory Status World Map.

- PP1M.
  - ◊ Innovator is approved in 60 countries

  - ◊ **Generic is only approved in China and the US.**

- PP3M.
  - ◊ Innovator is approved in 83 countries.

- Data will continue to be filled in for PP6M and other formulations.

LAPaL scope, mission, and content

Broad scope.

- Health areas. Expanding beyond HIV towards inclusion of all areas where LA products would support the efficacy of therapy.
- Types of entries. LA therapeutics, compounds, and combinations with various routes and frequencies of administration.
- Developers. Any type (University; Pharma; Start-up; Not-for profit; Research consortia).
- Maturity. Any product at any stage of development.

Mission.

- Objectives. Facilitate collaborations; Advocate for access; and Foster development opportunities for fit-for-purpose therapeutics.
- Principles. Public health-oriented data; Data-driven; and Collaborative.
- Audience. Communities and civil society; Researchers in academia, biotechs, and pharma; Manufacturers; Caregivers; Clinicians; Policy makers; Procurement agencies; and Funders.

Content.

- Technical features. Technology highlights, Formulation aspects; Potential applications.
- Clinical trials. Interactive timelines and clinical trials data.
- IP. Global patents and licenses landscape curated by IP specialists.
- Regulatory status. Approvals and filings data.

PLENARY 2

Kimberly Struble Senior Clinical Analyst, Division of Antivirals at US FDA

"Bioequivalence of new formulations of approved antiretroviral LAI drugs: What are the regulatory considerations?"

"FDA has sought ways to minimize study duration and investigate alternative approaches to bring [generic LAIs] to market"

Complicating factors of in vivo BE study design and conduct for LAIs

General considerations for study design.

- Crossover vs parallel design.
  - ◊ SD study: parallel design helps avoid washout concerns due to long half-life.
    - * Medroxyprogesterone acetate 50d washout; Naltrexone 5 to 10d washout.
  - ◊ Multi-dose/Steady-state study: either design.
- Strength to be studied.
  - ◊ Highest strength is recommended unless safety is a concern.
  - ◊ Multiple strengths may be recommended.
  - ◊ Any strength may be used for certain products with multiple approved strengths (e.g., risperidone LAI).
- PK metrics to be evaluated.
  - ◊ SD study: Cmax; AUCt; AUCinf; and Tmax.
  - ◊ Multi-dose study: Cmax; AUCtau; Tmax; Cmin; and Fluctuation/variability.
  - ◊ Partial AUC based on clinical relevance and formulation characteristics.
    - * Naltrexone ER injectable suspension: AUC1-10 and AUC10-28 were included to account for the multi-phasic release profile and therapeutic threshold.
  - ◊ 90% CI for Cmax and AUC must be within 80 –125%.
- Injection site included.
  - ◊ Gluteal or deltoid sites based on RLD information.
    - * If both included, ensure proportions of patients are similar among test and reference product groups.
- Steady state (SS).
  - ◊ Administer sufficient doses to achieve ss.
    - * For some LA ARV products, it could take nine months to achieve ss.

Challenges in study conduct.

- Recruitment difficulty.
  - ◊ Large sample size and long study duration with high dropout rate.
- High variability for parallel studies.
  - ◊ Multiple contributing factors (e.g., Demographics, across clinical centers, etc.).
- Steady-state determination.
  - ◊ Ensure steady state is captured.
  - ◊ Safety concerns with long duration studies.
  - ◊ Ensure reserve sample retention.

Key takeaways

- Study design should account for the formulation (release-controlling mechanism), dosing frequency, and study population.
- Determine the appropriate number of doses to achieve SS and balance this with the need to minimize study duration.
- Consider the drop-out rate in the sample size estimate.
- Use an appropriate sampling scheme to accurately capture PK parameters.
- Conduct sufficient pre-study method validation examining the interference of concomitant medications (i.e., To avoid introducing confounding factors).
- Incorporate appropriate safety monitoring.
- Use an appropriate statistical approach to evaluate demographics and clinical center effect, as needed.

Next steps

New approaches to streamline in vivo BE studies.

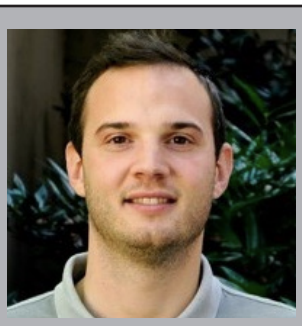
- 2021 workshop (FDA & Center for Research on Complex Generics): Establishing the suitability of model-integrated evidence (MIE) to demonstrate BE for LAIs.
  - ◊ MIE may reduce study duration and/or sample size and justify the use of alternative study designs and/or BE metrics through a model-based BE analysis framework.
  - ◊ Important considerations of using MIE for BE.
    - * Demonstrate sensitivity to detect the formulation difference with confidence.
    - * Sufficient model verification and validation.
  - ◊ MIE has been used in new drug development.
    - * Totality of evidence approach.
    - * Optimize dosing regimens, define dosing windows, select re-initiation plans, and adjust dose in subgroups.
- Model-informed vs model-integrated approaches.
  - ◊ Model-informed: M&S informs study design and analysis methods.
    - * Increase efficiency of in vivo BE studies.
    - * Assist product development and decision-making.
    - * Design/justify an appropriate sampling scheme strategy.
  - ◊ Model-integrated: M&S informs pivotal study plan and serves as pivotal evidence to support product approval.
    - * Pre-specified model-based analysis of an in vivo BE study.
    - * Virtual BE study based on M&S.
    - * Used in combination with relevant in vitro BE tests to support an alternative approach to FDA-recommended in vivo BE studies, including PK, PD, or comparative clinical endpoint BE studies.
  - ◊ Both approaches can help reduce study duration and/or sample size (i.e., Help design a more feasible BE study for an LAI product).
  - ◊ **FDA has awarded 39 research contracts and 50 grants for model-related research relevant to establishing BE for various products.**

Opportunities for MIE in generic LAI development.

- 2024 FDA workshop.
  - ◊ Strategies for alternative BE approaches supported by MIE.
    - * Enhance efficiency of in vivo PK BE studies via population PK modeling.
    - * BE decision based on in vitro studies, in lieu of PK BE study, mediated via mechanistic PBPK modeling.
  - ◊ Leverage MIE to generate pivotal evidence for BE decision (see above).
- FDA is seeing a clear demand for modeling approaches.
  - ◊ Increased use of modeling in pre-ANDA meeting requests and ANDA submissions.
- Frequent and constant communication with FDA is critical.
  - ◊ Pre-ANDA meetings are offered by the Office of Generic Drugs.
  - ◊ New MIE pilot program.
- FDA is enthusiastic about working with this group and developers in the field.
  - ◊ To bring products to the US.
  - ◊ To help others design products for use in other countries.

Resources

- Lenacapavir draft PSG (Feb 2024).
  - ◊ Recommended study: Request waiver for in vivo BE study requirement.
  - ◊ Waiver qualification: Test product qualitatively (Q1) and quantitatively (Q2) the same as the RLD.
  - ◊ Rationale: Dosage form is a solution; Composition does not contain any release-controlling excipients; and LA properties are not related to the formulation.
- Draft guidance for industry population PK (2019).
- Guidance for industry exposure-response relationships – study design, data analysis, and regulatory applications (2003).
- Draft guidance for industry adaptive designs for clinical trials of drugs and biologics (Nov 2019).
- Leveraging quantitative methods in reviewing complex/locally acting products (Oct 2-3, 2017).
- Contacts.
  - ◊ Pre-ANDA Meetings Program for complex generic products. For questions about submitting a meeting request, contact PreANDAHelp@fda.hhs.gov.
  - ◊ MIE Pilot Program. For questions about the program, contact MIE@fda.hhs.gov.



Simone Perazzolo Senior Scientist, TLC-ART Program at University of Washington

"Role of modeling and simulation as a tool for assessment of BE of LAI formulations"

Challenges of modeling BE for LAI products

- Extremely long duration.
- Complicated and resource intensive BE study designs.
  - ◊ Parallel design requires a very large sample size.
- Single vs multiple dosing issue – steady-state PK is important.
  - ◊ ER formulation accumulations at the end hinder SS.
  - ◊ SS can be achieved in years?
  - ◊ Is SD AUC approximately 90% of RLD?
- Depot formulations can generate variable PK (i.e., Release-controlled).
  - ◊ Is the AUC/Cmax 80-125% range too stringent?
  - ◊ What about other noncompartmental parameters (Ctau, Cmin, pAUC)? Computation requires a complex, resource intensive sampling schedule.
- What happens if APIs have a nonlinear PK?

Our experience with TLC-ART 101

Sought FDA approval via NDA 505(b)(2) pathway.

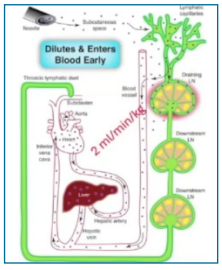
- Modification of existing products.
  - ◊ New route of administration from oral to injectable LPV/r+TFV DcNP formulation.
- Information required for approval.
  - ◊ Safety and efficacy.
    - * Relied in part on data we did not generate + new P1 study for additional PK data.
  - ◊ Evidence on how the formulation works, where it goes, and how long it stays.
    - * Mechanistic (PBPK) modeling to predict release kinetics, regional effects, and scaling.
- BE studies were not required.

Using PBPK modeling to bridge mechanistic unknowns.

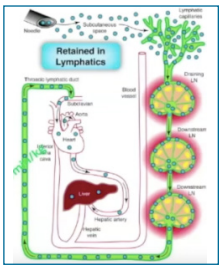
- The key is the release. Understanding the factors that control the release kinetics may better predict critical PK parameters.
  - ◊ Tmax (First peak is important for OLI).
  - ◊ AUC (Scaling).
  - ◊ Tail (Varies across LAIs).
- Focus on the injection site (Where, how, how long).
  - ◊ What happens immediately after you inject a LA-producing product?

Scenario 1
LA in solution. (Free ARV, depot, implant, etc.)
Small molecules are better suited for blood uptake. Drug dilutes in interstitial space and enters the blood early where the rate of fluid flow is more rapid (2 mL/min/kg).
How the formulation is designed to release the drug determines release kinetics for LA
Simple calculation of blood flow can yield Tmax not more than ½ hour after injection.
BE biowaiver is possible.[1]

[1] If release kinetics can be understood in vitro, there is potential to better understand PK in vivo.

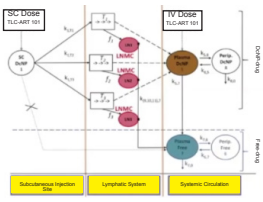


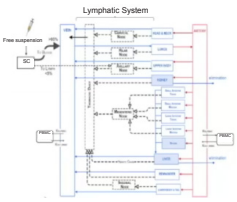
Scenario 2
Large particle or high stability formulation. (DcNP, mAbs, d-interferons, IgM)
Depot moves to lymphatics with delayed blood entry. Drug is retained in the lymphatics where the rate of fluid flow is much slower (0.02 mL/min/kg).
Leveraging this slower route can achieve LA.
From Tmax, there will be extreme slow release that will direct half-life and peaks.
Modeling to bridge mechanistic unknowns.



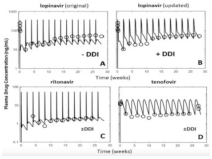
Modeling approach for TLC-ART 101 leveraging NHPs.

- Models to predict Tmax, AUC, and Tails. Incorporated data from higher mammals, tissues, cells, & IV administration (BA) in the modeling & validated.
  - ◊ Theoretical compartmental modeling to understand lymphatic transport via LMNCs.
  - ◊ Physiologically based modeling (i.e., using physiological flow volumes) to attempt realistic scale up or down by factors (From NHPs to humans and adults to pediatrics).





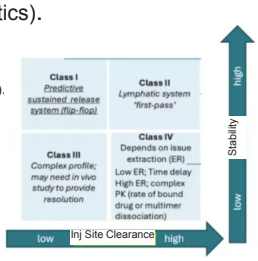
- DDI and SS modeling. We trained the model to achieve SS in NHPs and include DDIs, which provided strong evidence of behavior in humans.
  - ◊ After validation, our formulation was able to advance.
  - ◊ 6-month study of Q2w TLC-ART 101 in NHPs.
    - * TFV achieved SS with first dose
    - * LPV/r required >5w to achieve SS.
    - * DDI disturbed SS achievement.
  - ◊ **What better tool than PBPK modeling to predict SS and DDI findings and validate with a representative species for humans.**



A possible redefinition of the BCS

LA BCS based on Formulation stability and Injection site clearance (Key determinants of release kinetics).

- Class 1. Depot formulation.
  - ◊ High formulation stability.
  - ◊ Not cleared from the injection site (PK tail releases drug).
  - ◊ Potential for biowaiver.
- Class 2. DcNP formulation or bNAb.
  - ◊ High stability to exploit the lymphatic system route.
  - ◊ High injection site clearance.
  - ◊ TLC-ART 101: No depot found at the injection site, but high drug concentrations in LMNCs (Depot moved to the lymphatic system).



Summary

- Not all LAIs are the same pharmacologically speaking. (Class 1, Class 2, or Hybrid).
- Need strong mechanistic understanding and modeling.
  - ◊ Focus on understanding the release dynamics to explain Tmax, Cmax, and AUC.
  - ◊ Get to SS predictions.
  - ◊ Understand DDI and time-varying effects.
- Key parameters.
  - ◊ Formulation stability.
  - ◊ Where does the API go?
  - ◊ Where does the API stay?
  - ◊ How long does the API take?

"[Leveraging] this school of thought, we can better predict where noncompartmental parameters will fall and when the steady state will be and cut down time"

PLENARY 2

Bharat Pagi Founder and Principle Consultant at Uddipak Consultancy Private Limited

"IP issues for consideration in development of generic formulations for LMICs"

"Protecting IP is a vital part of fostering continued innovation ... This innovation must be accessible to people globally"

Role of intellectual property (IP)

Opportunity. IP drives economic growth, promotes innovation, and safeguards the hard work of inventors.

- Turns ideas into profit-making assets.
- Protects exclusive rights over novel products or brands.
- Forms an essential part of the branding strategy.
- Enhances the market value of products.
- Gives the business an edge over competitors.
- Raises money by out-licensing or selling IP.
- Encourages innovation and rewards innovators or entrepreneurs.
- Enhances chances of joint ventures and collaboration.

Challenge. IP often delays the introduction of generic products.

- Determines the earliest possible launch date.
- Helps identify the product's patent and technology landscape.
- Patent clearance is mandatory before finalizing a generic development plan to avoid or minimize future legal uncertainty.
- IP strategy should be in place before generic dossier filing to minimize risk of delayed generic launch.

IP layers relevant to generic development

Data Exclusivity (DE).

- First barrier to generic development.
  - ◊ Prevents generic manufacturers from relying on the original filer's preclinical and clinical trial data for a specific period.
  - ◊ Examples: New chemical entity exclusion (US); Data and Market exclusivity (EU); Re-examination period (Japan).
  - ◊ Typically, DE ranges from 5 to 10y (Up to 15y for an orphan drug) starting from market approval date and ending as per local law.
    - * Berdazimer sodium: New Chemical Entity exclusivity expires Jan 5, 2029 in US.
    - * Momelotinib: Orphan drug exclusivity expires Jan 26, 2034 in EU.
- Important considerations.
  - ◊ **Not classified under IP but offers the strongest form of protection for brands**.
  - ◊ **In the absence of a patent, DE can be a constraint for generic launch.** Generic approval is not possible without brand drug approval.
  - ◊ Key topic in discussions related to trade agreements (NAFTA, EU-India Free Trade Agreement).
  - ◊ Data on DE are provided by some countries. For the remaining countries, it is calculated based on market approval date.

Patents.

- Most widely used IP tool to increase value and prevent competitors. (I.e., Protect and leverage innovations)
  - ◊ Examples: API patent; Process patent; Composition patent.
- Important considerations.
  - ◊ Play a key role in product life cycle management. Enable brands to maintain market exclusivity.
  - ◊ Brands often seek to extend patent monopolies as long as possible. Maximize profitability.
  - ◊ Patents are territorial. Generics must consider patent status in manufacturing and export countries.
  - ◊ Patents may come from the innovators or third parties.
  - ◊ Generic developers must consider all patents for a given product. Expiration timelines vary.
- Most relevant patent types for generic formulations.

API	Technology	Composition	Indication	Process	Polymorph	Dosage Regimen
Combination	Drug Delivery System	Salt/Ester	Particle Size	Analytical Method	Packaging	Device

* **Red** indicates the most significant risk for delayed generic entry.

- ◊ **API patents are the strongest barrier.** No generic product is possible until API patent expiration.
- ◊ **Formulation patents are a significant barrier for complex generic LAI products.**

Registered design.

- Examples: Device, Autoinjector, and Pen designs.

Trade secrets.

- Exact manufacturing process or method of analysis. Even when processes are disclosed, details are often unclear. It is difficult for generic developers to replicate the desired specifications.

Generic LAI case studies

	VIVITROL (Naltrexone LAI)	RISPERDOL CONSTA (Risperidone LAI)	INVEGA SUSTENNA (Paliperidone palmitate LAI)
Approval and patent landscape[1]	• API patent expired before brand approval (2006). • 20 patents with expirations from 2017-2019.	• API patent expired 3y after brand approval (2003). • 19 patents with expirations from 2008-2020.	• API patent expired 5y after brand approval (2009). • All other patents expired by 2019, except one set to expire in 2031.
Rate limiter	**Composition-dose patent.** • Last patent to expire in 2019. • Independent claim 1 is related to the dosage (Naltrexone 130-480mg) and polymer used to prepare the formulation.	**Patent thickening and technology.**	**Dosage and administration patent.** • Last patent to expire in 2031. • Independent Claim 2 is related to the specific dosing regimen in adults.[2] • Drug product hydrolyzes to API; US product label (2024) recommends product dosing that corresponds to dosages already claimed.
First generic launch	**20y after brand approval even without an API patent.** • ANDA submitted by Teva in July 2020 . • Teva and Alkermes settled on a generic launch date in Jan 2027.	**20y after brand approval and 2-3y after all patents expired.** • No ANDA filed with paragraph IV certification.[3] • First generic product approved in 2023.	**Delayed until 2031 pending court decision on patent validity.** • ANDA submitted in 2018 and was approved in 2020 • **Teva contested the validity of the last remaining patent.[4]** • 505(b)(2) product was recently approved (ERZOFRI by Luye).
Takeaways	• A specific composition patent with dose can give innovators an advantage to maintain a monopoly and significantly delay generic launch.	• Generics were unable to develop a non-infringing composition. • Technical challenges exist, including BE, even with the same composition as the brand product.	• Dosage and administration patents are among the strongest IP tools for innovators to delay generic launch. • There is no possibility to change the dose/dosage of the generic label.

[1] Patent information from the FDA Orange Book.

[2] Two loading doses (150 mg-eq IM on day 1 and 100 mg-eq IM on day 8) and monthly maintenance dose (25 to 150 mg-eq IM), which correspond to the US product label (234mg IM on day1 and 156mg IM on day 8 and monthly maintenance of 39-234mg or 78-234mg IM).

[3] No patent challenge or assertion of non-infringing composition.

[4] District Court of New Jersey upheld the patent validity in 2021; US Court of Appeals for the Federal Circuit rendered a split decision in 2024; Affirmed the indefiniteness determination but vacated the non-obviousness determination. Teva has one more opportunity to prove patent invalidity.

Insights for generic development

IP poses significant hurdles for achieving non-infringing formulations.

- Technology-related patents, especially if core drug technologies are protected.
- Coverage of excipients with unique properties (e.g., PGLA). Alternative products may fail to mimic the desired effected, leading to BE issues.
- Claiming all possible stability options.
- Claiming a specific particle size or drug-polymer ratio. Deviations from the RLD can lead to altered dissolution profiles with potential for BA failures or patient compliance issues.
- Protecting particle size, viscosity, and PH make it difficult to meet regulatory requirements for these characteristics without infringing.
- Trade secrets in the manufacturing process. Even when patents disclose a process, the exact details are often unclear, making it hard to replicate the desired specifications.
- Reproducibility of complex products, such as LAIs.

Options for generic developers.

- Begin development as early as possible and consider filing novel IP if there is patentability in the non-infringing product.
- Try an alternative technology with no IP or with IP that will expire before the API patent.
- Collaborate with innovators and developers in the same field and global stakeholders.
- Check patent status in the target commercial territory and manufacturing country.
- Check patent validity and explore whether the IP can be successfully circumvented or contested (More relevant for a secondary patent or incremental invention).
- Consider obtaining a license for the IP in countries where the innovator has limited commercial interest (Best option without any legal uncertainty).
- Explore voluntary, public health licensing.

OPEN DISCUSSION 1

Barriers to Generic LAI Development and Modeling

The session was dominated by potential strategies to circumvent the burden of requiring two full generic development programs for FDA approval of a single LA product (CAB-LA and the companion oral CAB formulation). Another focus was delayed generic product entry in the CNS space and the paucity of generic products in LMICs. Discussions highlighted the drivers and importance of leveraging public health licensing and collaboration to overcome commercial (IP) interests. Plenary speakers also fielded questions around long BE studies, the impact on generic development timelines, and PBPK modeling approaches.

Generic CAB-LA licensees are required to develop the companion oral formulation

Should a second, full development program be required?

- Concerns when licenses were announced and OLI made optional
  - ◊ **Other RAs may require the OLI,** even though the FDA label now states OLI as optional.
  - ◊ **The tablet is a very small market.** It is not needed after OLI.
  - ◊ **Bridging missed and "planned missed" doses.** Are there enough data to show that other oral PrEP options could be used, not just the CAB tablet?
- Global health agency perspective. **It is inefficient for ViiV and three generic licensees to be manufacturing a low-volume tablet**; We need to discuss strategies.
- Regulatory perspective. **Approval requires generics to duplicate the FDA label.**
  - ◊ FDA CAB-LA label states that the CAB tablet should be used in the case of a missed or "planned missed" dose and does not offer alternatives for bridging.
  - ◊ This is a question for the Office of Generic Drugs or those privy to patent law.
- Real-world clinical perspective. **Requiring development of a companion oral tablet that will not be used is a waste of resources and opportunities.**
  - ◊ There is a body of evidence that any oral ARV could be used as "bridging."
  - ◊ Bridging with CAB tablets does not exist in clinical practice in LMICs. People in SSA will not return to the clinic for an oral "bridging dose." They will take oral TLD they already have at home.
  - ◊ WHO guidance does not include OLI and bridging – Neither will be used.

Strategies to alleviate the burden of multiple programs.

- **Amend the FDA label** to state bridging could be done with other oral ARVs, not solely the CAB tablet.
  - ◊ There is a body of supporting evidence in the literature. Need to re-engage with ViiV, bring to the FDA, and push to change the label.
  - ◊ Regulatory: Each oral ARV option would have to be labeled for that use (i.e., Use oral CAB or any other oral ARV in the case of a missed dose).
- **One contract manufacturer supplies the CAB tablet** instead of ViiV and three generic licensees manufacturing a low-volume formulation.
  - ◊ Regulatory: Would this be a filing for the tablet alone (Indication?) or a combined filing where all generic licensees rely on the same contract manufacturer?
- **Shared product label** ("Fill and finish"). The innovator manufactures and provides bulk oral tablets for generic licensees to bottle and label.
  - ◊ Regulatory: Need to consult the FDA Office of Generic Drugs, as there is no precedent.
  - ◊ Cost: Having ViiV manufacture the tablets would be much more expensive than perhaps one or more of the generic companies.
  - ◊ Legality: There would need to be some right of reference because the labels would need to be the same.
  - ◊ The innovator would need to agree to be the sole supplier of CAB tablets – Would ViiV be responsible for implementation of the oral tablet? This concern is among the barriers to removing the requirement for a generic companion CAB tablet.

Long timeline for generic LAIs in high-income countries & further delay in LMICs

Drivers of the 17y development window for risperidal LAI.

- **IP.** The complexity and technology of LAI products have made it difficult for generic companies to achieve non-infringing compositions.
- **BE requirement**. Many generic companies dropped LAI development due to the BE requirement and product complexity.
  - ◊ Regulatory guidelines and analytic clarity evolved over time after risperidal LAI approval in 2003, then generics entered a lucrative market.
- **We may be entering a new era of generic LAI development**.
  - ◊ The recent uptick in generic LAIs reflects improved understanding and regulatory clarity.
  - ◊ Generic companies that helped "cracked the code" for risperidone are leveraging this know-how for paliperidone palmitate and other LAI products.

Drivers of limited availability of generic LAIs in LMICs.

- **Local challenges.** Few generics are developing products for LMICs due to regulatory requirements and lack of technology and/or formal understanding.
- **Innovators do not register LAIs in LMICs**, even commercially successful ones. There is market exclusivity related to it.
- **Market share shaping** needs to happen earlier, particularly for HIV.

How to accelerate generic LAI ARVs in LMICs

Licensing via MPP (A neutral, not-for-profit, public health-oriented agency), instead of direct commercial licensing.

- MPP facilitates wide access, which is critical to impact HIV incidence.
  - ◊ Need scale, low prices, and several manufacturers selected based on who is the best applicant, not "who is your partner."

Public health-oriented license	Direct bilateral commercial license
Slower initial execution	Rapid execution
Blind process selects generic partners with the highest potential to achieve speed, quality, and breadth of scope.	Top-down, one-way decision systematically selects a generic partner from a pool of preferred partners.
Wider access (Typically 100 countries; Clauses to include countries without patent protections can expand to ~140).	More limited access (A license may offer a territory of ~20 countries)

- There is concern that innovators are bypassing MPP.
  - ◊ Gilead announced a bilateral access plan without sharing details (3m ago).
    - * MPP has requested to work together to achieve more optimal and transparent licensing; There is a precedent for Gilead working with MPP, and there is time to rectify the trajectory.
  - ◊ Janssen is dropping patents in a set of countries, but no technology transfer is planned (Oral communication; No press release to date).
    - * In theory, generics could step in and manufacture RPV but not ideal without technology transfer.

MPP licensing agreements need to include data access.

- IP is not enough for complex LAI products.
  - ◊ Different MPP license types can include data and technology transfer. **The more information included, the more accelerated and less costly development will be.**

Collaborations on modeling and other approaches to help overcome property protections in favor of public-health interests.

- LEN delivery system is simple, but the synthesis is complex.
  - ◊ The innovator has placed barriers: OLI or required oral loading dose; No data access; No reference for the product other than drug substance.
- Engagement with FDA is a starting point to develop solutions.

BE study requirement

"Life happens" during a long BE study. Special considerations?

- Safety monitoring as in any clinical trial.
  - ◊ Pregnancy would likely require discontinuation.
  - ◊ Acquiring HIV infection would also be a reportable event. Enroll participants at lowest risk for acquiring HIV into a 42-week study.
  - ◊ Inclusion/exclusion criteria similar to proof-of-concept study (P2).
- Need a large sample size that considers dropout rate and variability.
  - ◊ Alternative methodologies and statistical models can help.
- PKPD changes could occur. Potential role for modeling.

Question about PBPK modeling of long BE studies.

- Can modeling be used to define a "safe space" for a LAI based on absorption kinetics before undertaking a 42-week clinical trial?
  - ◊ NHPs could be a good animal model to present real-world data and bridge it with modeling (e.g., Using NHP PBMCs and LMNCs as a surrogate for efficacy of TFV).
- How to factor the addition of excipients into the release rate?
  - ◊ Need good in vitro characterization that includes more physiologically realistic conditions to obtain a release rate constant that can be scaled to a PBPK model in vivo.

Biowaiver vs BE study and the development timeline.

- It is unclear whether we will see a generic formulation for LEN before CAB-LA.
- Every development program has a rate limiter.
  - ◊ **Long BE study** could be a rate limiter for CAB-LA, depending on when the BE study can be launched, and whether it fits into the development window.
  - ◊ **Formulation complexity** could be a rate limiter for LEN. LEN has a biowaiver, but the synthesis is complex (23 steps), and the developer must show Q1/Q2 sameness. How long will it take to establish that, scale up, and achieve stability?
  - ◊ **Cooperation and collaboration** also impact the timeline.
  - ◊ BE study for the companion oral formulation. Study duration for oral LEN (LA) is longer than an IR oral formulation, but not on the order of magnitude for a LAI, like CAB-LA.

PLENARY 3

Saye Khoo Centre for Experimental Therapeutics, University of Liverpool

"Patients vs healthy volunteers"

Regulators prefer healthy volunteers (HVs) for BE studies

Use of patients is driven by safety considerations.

- FDA (2021). Perform a BE study with patients if it cannot be safely conducted in HVs.
- EMA (2010). Explicit preference for HVs to eliminate differences unrelated to the product, unless the drug has safety concerns that make this unethical.

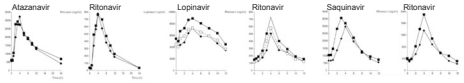
Important assumptions for the ANDA pathway.

- BE is a valid proxy for therapeutic equivalence (TE). If two products are found to be BE, it is reasonable to assume a similar therapeutic effect.
- It is reasonable to extrapolate from HVs to patients.

Differences among HVs and patients

PK differences documented in the HIV and TB fields.

- Protease inhibitors (Current opinion in HIV and AIDS, 2008; 3:296-305).



- Rifampicin (Systematic review and meta-analysis).
  - ◊ PK differences found between: HVs and adults with TB; HIV-positive and -negative status; Studies; Analytical labs; and Different generic products.

Patients are a heterogeneous group.

- The variability is not necessarily normally distributed.
- Effects of aging (Stader et al, BJCP 2021) and obesity (Bettonte et al, CID 2024) on ARV PK.
  - ◊ Modeling predicts high PK variability among HIV patients.
  - ◊ Higher RAL and DTG exposures in older (55-85y) vs younger (25-55y) patients.
  - ◊ Lower CAB and RPV exposures in patients with higher (30-50) vs lower (18.5-30) BMI.

PKPD differences point to a gap between BE and TE

Pharmacokinetics (PK).

- Lower exposures in patients (boosted PIs and many TB drugs).
- Greater inter-individual variability in patients, particularly gut-based mechanisms (DTG and RAL).
- HIV patients have relative achlorhydria and blunted DDI (SQVr+OMP and RPV+ARAs).
- **Injections remove gut-based variability but add injection-to-injection variability**.
- Disease characteristics (HCV DAAs and liver impairment).

Pharmacodynamics (PD).

- Receptor sensitivity and compensatory mechanisms (Amlodipine)
- Other: Intrinsic antagonism (anti-drug antibodies) and Concomitant disease and inflammation (QTc) are not relevant to this discussion.

Exploring the gap between BE and TE

Regulators precisely define BE around "rate and extent" based on the fundamental BE assumption (BE~TE).

- FDA (2021).
  - ◊ Being equal in rate and extent to which the API becomes available at the site of drug action.
- EMEA (2010).
  - ◊ Pharmaceutical equivalents and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits.

The BE assumption may not hold when extrapolating from HVs to patients (i.e., From least variability to most variability).

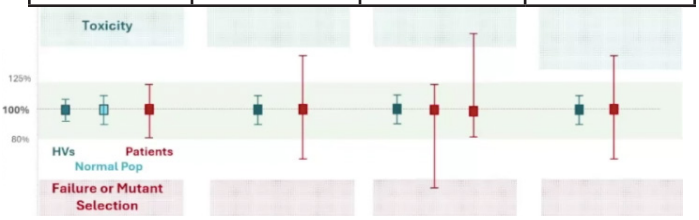
- Four potential scenarios.

	BE	TE	BE Assumption
Scenario 1	Similar DAP	TE	Holds
Scenario 2	**Dissimilar DAP**	**TE**	**Gap**
Scenario 3	**Similar DAP**	**Not TE**	**Gap**
Scenario 4	Dissimilar DAP	Not TE	Holds

DAP, Drug absorption profile.

- BE assumption vs real life.

Scenario 1	Real Life		
HVs are a good proxy for patients	Much more patient variability	Population coverage issues	Altered PD
• Patients have more variability. • BE assumption holds.	• Due to patient or disease characteristics. • Gastric PH, BMI, injection-to-injection variability, etc.	• Variability is not normally distributed. • Subgroups more susceptible to failure or toxicity.	• Patients are more sensitive to toxicity. • The target group and use case is important

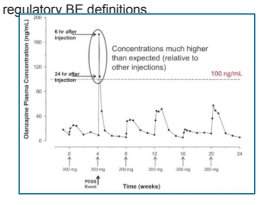


What modulates the gap between patients and HVs?

- There are only questions.
  - ◊ Highly variable drugs (Inter-subject variability>30%). Do they widen the gap? Is this the case with LAIs?
  - ◊ **Multiple dosing. Does it accentuate the difference between patients and HVs?**
  - ◊ Formulations containing combinations. Are they expected to behave the same way in HVs and patients? (Probably a reasonable assumption).
  - ◊ Eliminating first pass metabolism and gut-based interactions (i.e., Injections). Does it make a difference given the addition of other factors, such as injection-to-injection variability?
  - ◊ Indication. Treatment vs prophylaxis vs chemoprophylaxis?
  - ◊ Study design. Long BE study?

The multi-dose issue is interesting.

- Use pAUCs to examine drug coverage over total treatment duration.
  - ◊ Then, need to know what happens in patients, patients with liver disease, etc. Evaluations of TE are dependent on a comparator and outside the scope of regulatory BE definitions.
- Injection-to-injection variability.
  - ◊ Injection events will be a reality of life (e.g., Hit a blood vessel, blood extravasates, and seals the release).
  - ◊ What is the impact on treatment?
  - ◊ How will this be managed?
  - ◊ **Olanzapine example.** Burst release after an injection event changed Cmax and the shape of the curve relative to other injections.



Summary

- BE is only one aspect of therapeutic equivalence.
  - ◊ The problem is that many of the factors we are worried about have been "designed out" through the use of HVs.
- Use of patients is primarily driven by safety considerations.
  - ◊ A number of FDA PSGs for recent LAIs recommend BE studies with patients.
    - * These are primarily related to hormones, opiates, anti-psychotics and chemotherapy.
    - * Leuprolide 2021; Buprenorphine SC 2020; Paliperidone 2021.
  - ◊ Ethical considerations of long BE studies.
    - * Need to cover the tail if you are going to use patients.

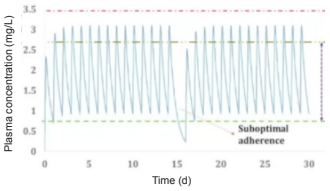
Marta Boffito Chelsea and Westminster Hospital NHS Foundation Trust

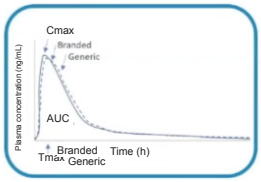
"Managing the PK tail in BE studies"

Bioequivalence

Traditional BE studies were for oral drugs.

- Plasma concentration-time curve.

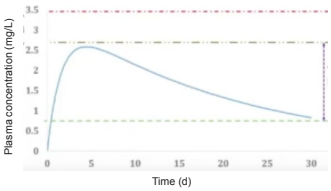




- BE limit: Generic and brand formulations are BE if the 90% CI for GMR of Cmax and AUC (log transformed) is within 80-125%.

BE studies for LAIs.

- Plasma concentration-time curve.



What about the tail?
We also care about the end of the PK curve, not just the beginning

- **Traditional BE does not consider the PK tail phase.**

LAIs behave very differently than oral formulations.

- Release-dependent (flip-flop) PK.
  - ◊ The rate of absorption is slower than the rate of elimination.
  - ◊ The elimination half-life is much longer following extra vascular (Appropriate LAI route) vs IV dosing.
- The PK tail is pharmacologically important and highly variable.
  - ◊ Terminal slope is controlled by BA and absorption rate, not clearance and Vd.
  - ◊ Absorption rate depends on many characteristics, varies widely across different drugs and formulations, and has significant inter-individual variability.
- **Is the traditional 80-125% BE limit appropriate for LAIs?**
  - ◊ When elimination depends on absorption, does it matter whether Cmax is within the BE limit if the decay is similar and concentrations are well-above therapeutic cut-offs?

Challenges around the design of in vivo PK BE studies of LA agents

Single dose (SD) vs multiple dose.

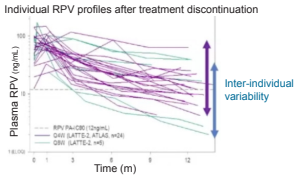
- Is steady state necessary for ARVs?
  - ◊ Some LA ARVs have loading doses, which are known to have significantly more inter-individual variability than later doses (e.g. Differences in males vs females during first 6m).
  - ◊ Time to steady state may not be realistic.
- SD provides no information on intra-individual variability.

Standard two-period crossover design.

- Washout period for controlled-release products is 8.5 half-lives.
  - ◊ SD parallel design avoids long washout period, but high intra- and inter-individual variability is a concern.
  - ◊ **It would take 3y to conduct a cross-over PK BE study of RPV at steady state (RPV half life ~ 29w).**

Recruitment and retention of study participants.

- High inter-individual variability in the PK tail and long PK washout are important to consider when selecting healthy volunteers or PLWH.
  - ◊ Data from P3 trials of RPV+CAB LA.
    - * For some, RPV quickly drops below the minimum effective concentration but is present for many months. **Risk for HIV infection and resistance.**
    - * For others, very high RPV concentrations are maintained for 1y. **RPV will be present for years, not months.**



- Long follow-up period ≥ 1y. To maintain a low drop-out rate, you must consider many circumstances (How much and when you pay and transparency matter).

Healthy volunteers vs patients.

- Choice is driven by safety and ethical considerations.
  - ◊ Fasting vs fed; Biological matrix; Highest dosage or multiple; Parent drug/metabolite.
- Active metabolites are a complicating factor.
  - ◊ PK curve, tail and behavior may be completely different for LAIs vs oral formulations. Concentrations depend on drug release and absorption, and time to steady state is unknown.

Lessons from veterinary medicine.

BE studies of oxytetratcycline IM.

- Test and brand formulations were bioequivalent in pigs.
- Formulations behaved similarly in cows but not bioequivalent.
  - ◊ Tmax and AUC met BE criteria.
  - ◊ Cmax was not within the BE limit (90% CI of test:reference: 65.04–134.97%). High inter-individual variability in drug exposures.
  - ◊ More studies needed: Larger sample size? Lower dose?

80-125% limit complicates the simplification of BE studies.

- Inter-individual variability in LAI exposures requires larger studies.

Potential solutions & areas for research

Role of the in vitro component in studying BE.

- Each LAI is different. Developing a better understanding of the in vitro-in vivo correlation is important (i.e., How to administer? Adequate dosing interval? PK tail duration for safety?).

Partial AUC assessment.

- May be difficult for time- and concentration-dependent drugs (i.e., Many anti-infective drugs). We care what happens at the end of the dosing interval.
- Ctrough is not included in BE criteria. Is it different for LAIs?
- Do we need BE data during the tail? What sampling frequency?
- Injection site/procedure effect. How the drug is formulated impacts absorption, elimination/tail, and inter-individual variability.
- Dropout rate and participant safety. Risk of resistance and developing HIV with exposure to low drug concentrations.

Modeling approaches.

- FDA workshop (2021): Model-integrated evidence to demonstrate BE of LAIs.

Summary

- Understanding the PK tail of different LAI formulations is important. Don't get fixated on traditional BE concepts.
- PK tail depends on absorption (high inter-individual variability).
- Parallel design is more realistic than crossover. Sample size increases due to wide inter-individual variability.
- Ideally assess BE beyond the loading dose. Steady state may be too long.
- Volunteer retention is important. Need to include different populations if there are differences (e.g., age, weight, women, men, etc.).
- PK tail is a challenge for BE/generic development but achievable.
- Increase our knowledge of half-lives and tools to predict the PK tail. No need to sample for years.

PLENARY 3

Charles Flexner Johns Hopkins University

"How long does a BE study need to be for a LAI ARV?"

"We need to flip flop how we think about BE for LA formulations as compared to oral drugs"

What is "steady state" (SS) for LAIs?

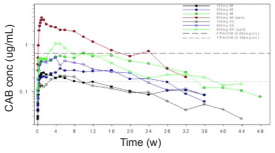
Achieving SS within BE studies may not even be relevant.

- It takes a very long time for most LAI formulations to reach SS.
- FDA did not require CAB-LA or LEN to reach SS in P1 or P3 studies.
- LAIs have different PK principles than oral formulations.
  - ◊ LAIs exhibit absorption-dependent (flip flop) kinetics: Rate of absorption (Ka) is much slower than the rate of elimination (Kel).

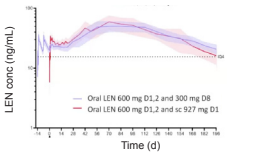
	Oral	LAI
Systemic exposure	• Depends on the rate of absorption (From GI tract) and clearance (Hepatic).	• Depends more on the release rate (From IM/SC depot) and absorption than clearance (Hepatic or renal).
Important PK parameters for BE	• Cmax and AUC.	• **Absorption rate.**

Why are we thinking about BE in the same way for LAI and oral formulations?

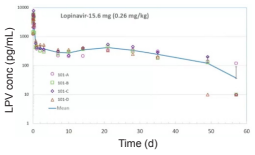
- Shouldn't BE be focused on absorption for LAIs?
  - ◊ Particularly if Ka does not change significantly over time.
  - ◊ As long as the drugs are safe, Cmax and AUC are not the important PK parameters.
- Absorption curves for LAI ARVs.
  - ◊ SD CAB-LA (100-800mg) IM.
    WR Spreen et al, Curr Op HIV AIDS 2013
    * A complex formulation with remarkably **constant drug absorption for nearly 1y**.



  - ◊ SD LEN (927mg) SC.
    Jogiraju V et al, IAS AIDS 2022
    * Substantially more complex formulation in terms of distribution and absorption.
    * Once the distribution phase is complete (~ 8w), **constant drug absorption for 4m.**



  - ◊ SD TLC-ART 101 SC.
    Bender Ignacio R et al, Int AIDS Congress 2024
    * Intermediate complexity between CAB-LA and LEN.
    * Rapid LPV release during the distribution phase (First 4-5d), then **constant LPV release and absorption for nearly 2m**.



Does BE for LAIs require PK sampling over the entire period of detectability?

Why not accept Ka as evidence of equivalence if it remains unchanged for a "reasonable" amount of time?

- CAB-LA (See absorption curve above).
  - ◊ Modeling the absorption rate for any of the CAB-LA curves would yield a similar Ka, and that Ka does not change for almost 1y.
- LEN (See absorption curve above).
  - ◊ Measuring Ka at any time point during the 4-month interval after the distribution phase would yield a similar result.

BE (As defined by RAs) is a probability statement.

- The degree of confidence one needs determines how much data must be collected.
  - ◊ Measuring PK properties of one formulation vs another using standard statistics within a predetermined confidence bound assures us that two formulations are similar enough to warrant using one in place of the other in a clinical setting.
- **At what point can we be confident that a new formulation has reproduced the absorption curve of the originator? (e.g. CAB-LA).**

BE as a Bayesian probability statement

Bayesian vs traditional frequentist statistics.

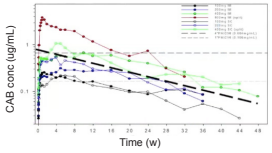
- Bayes' postulate: A probability statement is likely to be more accurate if it takes into account that which has already occurred (Bayesian prior).
- Bayesian probability thought experiment.
  - ◊ Fill a box with 50 black and 50 white balls, then remove balls one at a time in a blinded fashion.
  - ◊ What is the probability at any moment in time that you will remove a black or white ball?

Frequentist Thinking	Bayesian Thinking
• **The probability is always 50:50.**	• It is highly unlikely that one would pull out 50 black balls then 50 white balls. • **The make up of the first 50 balls drawn changes the probability of any ball picked later.**

- **We are all Bayesian thinkers. Why aren't we all Bayesian statisticians?**
  - ◊ Complexity. Incorporating prior data into a probability statement is much more complicated than traditional frequentist probability analysis.
  - ◊ Limited exposure. Bayesian statistics are not typically taught in medical or graduate schools.
  - ◊ Controversy regarding what constitutes a Bayesian prior.

Applying Bayesian probability analysis to BE studies.

- Pre-existing PK data are Bayesian priors that all can agree on.
- Partial AUCs (pAUC) are a good idea.
  - ◊ How much of a pAUC is needed to reach a reasonable consensus on BE?
  - ◊ CAB-LA example (i.e., A "well-behaved" formulation).
    * Would you agree to receive a new formulation with a 2-month prior? 3 months? 6 weeks?
    * Given the Ka stability, the probability that Ka 0.02 at 2m would be 0.05 or 0.01 at 6m is vanishingly small.

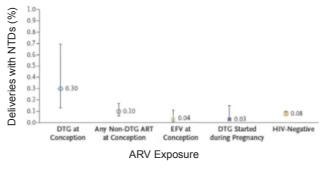


- Possibility of Bayesian drug regulation.
  - ◊ Collect partial data.
  - ◊ Inform recipients about the level of confidence for the probability of equivalence rather than accumulating all data and conducting a huge frequentist BE analysis.
  - ◊ Obtain informed consent early in drug development. Individuals agree to receive the low-cost formulation knowing that absolute BE determinants have not yet been met from a regulatory point of view but that data collection will continue with updates on BE status.

Our statistical philosophy impacts our clinical philosophy

A cautionary tale: Frequentist data analysis has sometimes led us astray.

- *Neural-tube defects and ARV treatment regimens in Botswana*.
- Frequentist analysis (Zash R et al, NEJM 2019) led to a regulatory decision that DTG should not be given to women of reproductive potential (i.e., They received less effective ARVs).
  - ◊ Counted the number of infants with neural-tube defects (NTDs) per number of exposures.
    * **Statistically significant increase in NTDs after DTG exposure at conception.**
- Bayesian analysis of same data (JHU).
  - ◊ Incorporated all known pregnancies with DTG exposure from prior clinical trials and published studies (Bayesian priors).
    * **The difference in neural-tube defects does not meet statistically significant bounds.**



OPEN DISCUSSION 2

Clinical Considerations

Kimberly Struble kicked off the discussion by affirming FDA openness to new ideas for BE assessment of LAI formulations. Attendees voiced specific concerns about the current approach to BE determination and highlighted challenges posed by LA formulations. Throughout the discussion, there was a sense of urgency to leverage this group's expertise and collaborate to design new methodologies and hold discussions with the FDA as well as regulatory agencies in other countries and global stakeholders.

"What is the alternative approach to evaluating [BE] ... The FDA is inviting some of this novel thinking in order to move forward"

We need a new set of target parameters to determine BE for LAI formulations

LAIs behave differently. BE for short-acting formulations cannot be used as a place holder.

- LAIs exhibit release-dependent PK.
- Massive inter-individual variability is inherent in LAI products.

Concern about missing opportunities for generic approval if BE confidence bounds are too rigid (i.e., 85-125%).

- Need to allow for therapeutic equivalence if BE is not met.
  - ◊ Example: BE study is conducted in a slightly different population; Drug absorption curve is similar to the innovator but does not meet confidence bounds for BE due to more variability.
- FDA. A built-in safeguard via modeling the Ka to prove we aren't giving up any efficacy based on some variability not accounted for in traditional BE.
  - ◊ Virtual BE studies or a supplemental package could be very helpful.
- There is a precedent for applying criteria to drugs with very wide inter-individual variability that are wider than traditional BE.

Bayesian approach.

- FDA Office of Generic drugs just wants applicants to show that the two formulations are the same given the inherent biological variation.
- BE based on priors (PK data from the existing formulation) and what you think you know about the proposed generic formulation.
  - ◊ If we can craft a line through the PK curve, and the line for the innovator and proposed generic are the same, that is sufficient for BE, even if there is variability in the data.
  - ◊ A statistical test would not be used to say the formulations are different – They are not.

pAUC and inferring BE.

- A challenge is that a small difference in a LAI formulation can have a profound impact over a 2-3m dosing interval.
  - ◊ The terminal half-life is going to look different.
  - ◊ Many LAI products have multi-modal PK.
- **How long does it take to figure this out?**
  - ◊ It is obvious when you have a full dataset (i.e., CAB), and you can draw a line through it.
  - ◊ With BE, you are collecting a small piece of data (pAUC) at the point of making a decision. **You cannot just extrapolate from here.**
  - ◊ Example of multi-dose olanzepine: Each dose has a different PK (i.e., Same formulation over time in the same individual).
- Fundamental research is needed to understand how much of the terminal half-life we need to collect to have confidence in a BE determination.

Different parameters are needed, but regulators do not change quickly

Generic ARV products will need to meet BE criteria for the foreseeable future.

- If BE is not met, there may still be an opportunity to prove equal activity via a clinical trial.

Could we influence BE study duration for CAB-LA or are we talking about more in the future?

- CAB-LA BE studies are set to begin in 2025.
- A simple change in methodology might be possible, but a radical proposal will take time.

Call to action to design innovative methodologies for BE

If we don't do it, no one will.

- Generic companies are conservative; They need support.
- We have many ideas and experts in this room. Let's study designs, put ideas together, and have conversations with the FDA to generate some of these concepts.
- FDA is looking for innovation from people like us.

Don't wait. There is no more compelling time than right now.

- FDA sounds receptive to change now, then it will go down the traditional path.
  - ◊ Do not miss this opportunity to impact the path in a positive direction.
- If we cannot make LEN and CAB-LA available for PrEP where most of the infections are, then we are basically giving up.

There is a precedent for proposing new methodology to FDA.

- In recent years, the Forum for Collaborative Research has proposed new methodology to the FDA for DAA trials and studies on PrEP and background infection rates.
- The Office of Generic Drugs has been open to different methods.
  - ◊ Need to show that your method has the correct predictive power.
  - ◊ The statistical analysis plan and underlying assumptions need to be completely and thoroughly laid out.

Getting generics into LMICs extends beyond FDA – need buy-in from other agencies and interested parties.

- Need to convene additional meetings to educate a mass amount of people at the same time and foster discussion.
  - ◊ Regulators, key opinion leaders, and purchasers in other countries.
  - ◊ New methodologies could be foreign territory for many.
  - ◊ Include access to modelers and statisticians and this group to explain some of the concerns and how we will work through them.
- Potential shorter term targets for engagement:
  - ◊ PQ and FDA-tentative approval will open procurement with PEPFAR and Global Fund.
  - ◊ License for CAB-LA requires PQ or SRA approval (FDA-tentative approval, sometimes EMA and article 58).

Negative consequences of ARV drug resistance are huge

The frequency of resistance mutations depends on duration of failure.

- Resistance profiles are limited in clinical trials due to early detection.
- In clinical practice, people fail for longer periods.

Administration issues can impact drug concentrations and resistance.

- Especially when drugs are supplied on a larger scale.

Concern around the idea of informed consent (Before BE criteria met) and follow-up.

- If we give patients a "bad" or under-performing formulation, then we have selected a number of integrase mutations in those patients.

PLENARY 4

Paul Domanico Senior Director, Global Health Sciences at CHAI

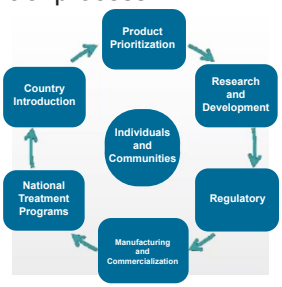
"The importance of partnerships across the continuum of care"

"Learnings from FAST-TB (how to accelerate the introduction of better TB regimens) are very relevant to what we are talking about today"

Partnerships across the continuum of care

Drug discovery, development and introduction is a complex technical, logistical, cultural and financial process.

- Timely product delivery requires a large group of diverse players.
- Academics, innovators, governments, and regulatory bodies around the world must remain coordinated and aligned for years.
- There are many opportunities to go slower – It is so much work to go faster.
- **It is our collective responsibility to ensure all voices are in the room.**

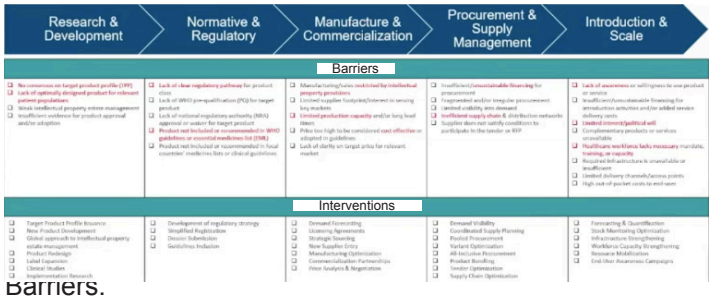


CHAI brings business acumen to global health.

- We apply learnings from any relevant discipline to:
  - ◊ Improve access to better medicines and diagnostics.
  - ◊ Tune care models in country.
  - ◊ Deliver value to the patients we serve.

Product access: Barriers, interventions, and partnerships

Overview of the product development life cycle.



Barriers.

- All the ways you can fail across the life cycle.
  - ◊ Lead to time and money poorly spent, disconnect among organizations, and misunderstandings (Language or clarity of thought).
- Highlighted challenges.
  - ◊ R&D: Lack of consensus on a TPP.
  - ◊ Normative & Regulatory: Unclear regulatory pathway.
  - ◊ Manufacture & Commercialization: Problems with IP; Limited production capacity; New product type requiring new capabilities.
  - ◊ Procurement & Supply Management: Concerns over sustainability; Fragmented supply chain.
  - ◊ Introduction & Sale: Patient population is unaware of the solution (Cure or better way to manage their disease); Variable political will.

Interventions.

- CHAI assembles expert teams to address each challenge.

Partnerships.

- Convene all parties for the conversation (Lesson learned from HIV).
- **The voice of the patient is mission critical.**
- Partners.
  - ◊ Academia.
  - ◊ Donors.
  - ◊ Industry (Innovators and generics).
  - ◊ Ministries (Discuss priorities, commitment, and political will to a disease).
  - ◊ Non governmental organizations (In-country and international role).
  - ◊ National Treatment Programs (NTPs).
  - ◊ Patients (Building strong civil societies for many diseases).
  - ◊ SRAs and normative bodies (Harmonization among FDA, EMA, WHO PQ and RAs in RLS).
  - ◊ WHO.

FAST-TB program

Overview.

- CHAI in partnership with Peter Kim.
- Convened key players across the continuum (n=50-70).
  - ◊ Designers of clinical trials for TB regimens.
  - ◊ Biomarker investigators. Improve patient monitoring during clinical trials; Understand patient position in their disease journey; Denote disease severity.
  - ◊ Modelers. Discuss better ways to model clinical trials and epidemiology in the countries we serve.
  - ◊ Various community voices: TB survivors; Civil society; and NTPs.

Learnings with particular relevance to today's meeting.

- Voice of the community is critical to better understand different aspects of the patient's journey and empower end-users to shape the research agenda.
- Inclusive subject selection goes beyond including all patient sub-populations that would benefit from a medicine/treatment.
  - ◊ The study population must inform the variability represented in the populations you serve.
  - ◊ Ensure inclusion criteria are as real-world as possible. Being too proscriptive about removing patients (i.e., Lost-to-follow-up or a particular AE) limits trial validity when translating to care in country.
    - * 'The trial does not represent how I care for patients, the patients I see, or the patient journey I see.'
    - * 'Often times the people dismissed from a trial are actually my challenge in my clinic – They are the patients I have to serve, and your trial did not help me understand how to do that.'
- Alignment, transparency and coordination between groups to ensure community voices are included across the entire journey, not only at the start.
  - ◊ This is critical for communities to attain confidence in work done on their behalf.
  - ◊ The trust needed to improve and sustain product uptake cannot be built in the absence of continuous community involvement (e.g., HIV concept, "Nothing for me without me").
- Donor and policy priorities will be addressed in another presentation.
- Market shaping. A lot of work is needed to transform care, especially with LA products.
  - ◊ A strategy for introducing a product for treatment and prevention needs to consider:
    - * What cultures are you are trying to bring a solution to? How is it you have a relationship with them?
    - * The number of patients per unit time informs the relationship or deals made with generics so that expectations are understood (i.e., Number of tablets, injections, metric tons of API, etc. per unit time).
- Person-centered care. The desire to deliver choice/personalized care is an essential mindset for success.
  - ◊ We need to better understand patient adherence challenges for LA products.
    - * LA products are going to be a boon, but they must be re-administered. The x-axis is only changing from days to months (Individuals will still need care for years)).
  - ◊ The goal of hearing what person-centered care translates into becomes very important.
    - * The story we tell, the advocacy we promote, how we wrap health care around that patient, and where that patient seeks care.
- Other relevant topics.
  - ◊ Research.
  - ◊ Diagnostics.
  - ◊ Regimen development and clinician role.
  - ◊ Product approval.
  - ◊ Product information.
  - ◊ Translation of evidence and implementation research.
  - ◊ Capacity building.

René Holm Department of Physics, Chemistry, and Pharmacy at University of Southern Denmark

"How difficult is it to manufacture a LAI formulation, really?"

"[Ease of manufacture] really depends on the technology that comes into play"

Background

Range of LAI technologies.

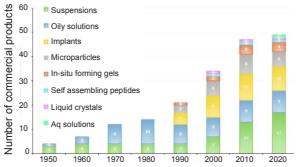
- Solutions: Haldol 5mg/mL.
- Microencapsulation: Risperdal CONSTA.
- Solid-state implants: Zoladex.
- In-situ forming depots: Eligard.
- Suspensions: Depo-Provera; Abilify Maintena; CABENUVA.

Each technology has a very different manufacturing plan.

- Delayed generic development of Risperdal CONSTA may have had more to do with manufacturability than IP.

Evolving landscape of commercial LAI products (1950-2024).

- Growing list of applied technologies.
  - ◊ 1950-1990. No major development beyond Suspensions and Oily solutions.
  - ◊ 1990s. Implants, Microparticles, & In-situ forming gels.
  - ◊ 2000- 2010. Self-assembling peptides & liquid crystals.
  - ◊ 2023. Aqueous solutions.



- Expanding therapeutic areas.
  - ◊ Schizophrenia (17); Oncology/palliative care (13); Contraception (6); Hormonal disorder/ deficiencies (8); Infectious diseases – Not HIV (4)/HIV(4); Opioid dependence (3); Diabetes-related disorders (3); Anti-inflammatory (2); Other (3).

How to select a LAI technology

Compound properties.

- Intrinsic properties for slow release (e.g., CAB). Compound can be injected "as is" as a suspension; Size can be adjusted.
- Need to control the release. Start working with polymer chemistry.

Advantages and limitations of each technology.*

	Advantages	Disadvantages
Solution	• **Process scale-up (Simple).** • **Manufacturability (Cost).** • **Sterilization strategies.** • Simple preparation & manufacturing	• Limited release duration. • Administration (Viscosity). • Drug loading.
Microencapsulation	• Drug-release modifications. • Hydrophobic & hydrophilic drugs	• **Process scale-up (Complex).** • **Manufacturability (Expensive).** • **Aseptic processing.** • Initial drug release. • Drug loading limitations.
Solid-state implant	• Drug-release modifications. • Hydrophobic & hydrophilic drugs	• **Manufacturability (Expensive).** • **Aseptic processing.** • Invasive administration. • Size/drug-loading limitations
In situ forming depot	• **Process scale-up (Relatively simple).** • **Manufacturability (Cost).** • **Sterilization strategies.** • Drug-release modifications. • Simpler preparation.	• Organic (Biocompatible solvents). • Initial drug release. • Stability (API, polymer). • Administration (Viscosity). • Drug-loading limitations.
In situ hydrophobic API depot	• Simple preparation. • Simple formulations. • High drug-loading possible.	• **Process scale-up (Particle size).** • Drug-release control. • Particle size. • API modifications.

* Blue indicates factors more relevant to manufacturing.

Consider product price in a price-sensitive market.

- Older, oil-based solutions are the cheapest products on the market.
  - ◊ Easiest to manufacture; Excipient is inexpensive; and Thermal sterilization is possible.

Aseptic processing costs & technical complications should not be underestimated.

- Consider the sterile manufacturing plan early.
  - ◊ Global sterilization guidelines are ethically aligned and enforced as of P1.
  - ◊ EMA (2019): 1. Autoclaving (Fastest & most effective); 2. Dry sterilization (Oil formulations); **3. Aseptic processing** (Selected technology/compound properties do not allow terminal sterilization).
- Aseptic processing and API sourcing requirements.
  - ◊ Sterile API requires infrastructure. Gamma-irradiation or sterile filtration and aseptic crystallization.
- Finding a plant that can generate cheap generics can be a challenge.
  - ◊ **Generic manufacturers are price-dependent and cannot install every technology.** They will focus on achieving excellence in a particular technology.
  - ◊ **Technologies created at universities are not restricted by infrastructure.** The process may not be installed in aseptic conditions.

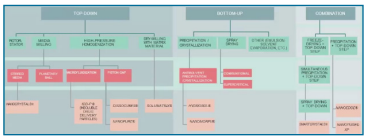
Manufacturing schema by technology

Solutions and in-situ forming gels (Low complexity).

- Dispensing; Mixing; Filling; Sterilization.
- Scale-up and sterilization are relatively easy. Scale up using mathematical models (i.e., From 1mL to 4 tons); Sterilization via autoclaving (Most manufacturers have this).

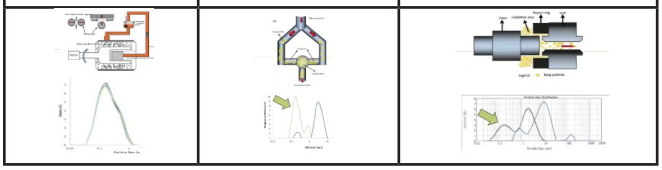
Suspensions (More complex).

- Many options for Top-down, Bottom-up, & Combination methods.
  - ◊ Top-down via media milling or high-pressure homogenization is ideal. (i.e, Used for commercial products).
  - ◊ Combination method adds to cost & complexity (i.e., Additional technologies).
  - ◊ Nanonization milling to target is robust and scalable (e.g., CAB).
    - * A 4L chamber can manufacture 150-200L. (Need to invest in the technology); Custom equipment for small (R&D) or large scale (Operations).
    - * Broad application to other LAIs.
    - * Key process parameters are understood: Agitator speed; Milling media (Type, size, charge); Milling Time; Suspension Flow; API (Particle size, concentration).



- The production approach for micro- and nano-suspensions matters.

Media Milling	Microfluidization	High-pressure homogenization
Most likely to be used	Not used commercially	Used for a few commercial products



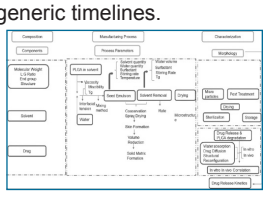
  - ◊ **Different milling technologies yield different particle-size distributions (Same API).** Important for compounds with huge sensitivity on the release.
  - ◊ Scale-up is possible by modeling breakage behavior.
    1. Frontal impacts (Breakage) and Shear stresses (Break agglomerates/brittle material): Probability of stressing.
    2. Brittleness: Low stress energy (SE) values break all particle sizes for brittle materials.
    3. Stress number: Above a minimum SE value, breakage rate depends on the number of stress events.
  - ◊ **Technology interchange is not necessarily possible**. A copycat formulation can be difficult to obtain if not truly copied all the way.

Implants (Intermediate complexity).

- Dispensing; Mixing; Extrusion; Cutting; Sterilization. HME is often used.

Microspheres (Most complex).

- Manufacturing complexity can drive long generic timelines.
  - ◊ Systems are robust and well-understood, but many process parameters define the release.
  - ◊ Microfluidization yields more consistent production but is not widely implemented.
  - ◊ 20-year delay in generic Risperdol was likely due to manufacturing complexity.
    - * The first generic was an in-situ forming gel. (i.e., A "Short cut" when they could not make it work)



PLENARY 4

Zack Panos Associate Director, HIV Treatment & Market Intelligence at CHAI

"The adoption and business case for LA ARVs: HIV as a case study"

"How governments and partners think about adoption of new products ... everything they weigh"

LA products face a high barrier to entry and widespread adoption in LMICs

LAIs will require an overhaul of all systems in place for HIV.

- The HIV response has been designed around daily oral ART for 20y.
  - ◊ From supply chain to service delivery, prevention, and treatment.
- Current products are affordable and highly effective.

Framework for evaluating and creating new products.

- Strong Clinical Profile; Simple Logistics; Affordable Cost; Meets User Preferences; Plugs Remaining Gaps.

Strong clinical profile

Current SOC regimens are effective, well-tolerated, and can be used across the population.

- DTG-based regimens for HIV treatment.
  - ◊ 96-97% viral suppression among adults/high 80% among children in PEPFAR countries.
  - ◊ 95% of adults (~24M) are taking a DTG-based regimen in LMICs.
- Oral PrEP for HIV prevention.
  - ◊ 99% effective when taken as directed.

Simple logistics

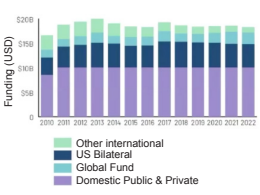
Ministries will weigh the benefits of new LA products vs new logistical requirements and challenges.

- Potential challenges with LA products.
  - ◊ Additional burdens on HCPs.
  - ◊ Additional requirements for consumables (e.g., Needles, sharps boxes, etc.).
  - ◊ Potential changes in monitoring requirements.
  - ◊ **Increased number of visits and facility touch points.**
  - ◊ New complexities in distribution/storage (e.g., Cold chain; LA formulations may not be as forgiving as oral ARVs).
- Current DSD models have moved care for HIV treatment outside the facility and reduced contact points with HCWs (Especially since COVID).
  - ◊ Most countries have endorsed a community DSD model (Only two countries have solely facility-based care models).
    - * Instead of monthly facility-based ART visits (pre-COVID), one person picks up ARVs for multiple people or a community health worker distributes medicine in a community setting.
  - ◊ Less frequent clinical consultation within DSD.
    - * Q6M is most common; A few countries have moved to Q1Y; Only three countries have Q3M.
- LAIs will likely require facility-based administration.
  - ◊ Q8W injection would require a huge change for increasingly overburdened and underfunded healthcare systems.
  - ◊ **How do we address this gap?**

Affordable cost

Current HIV landscape in LMICs.

- Stagnant funding for decades.
- Growing need. The number of people started on treatment or prevention increases by millions each year.
- TLD currently costs 10 cents/day.
  - ◊ TLD (Oral treatment) $37 PPPY.
  - ◊ TDF/FTC (Oral PrEP) $40 PPPY.



The cost of LA products must compete with current oral regimens to achieve broad uptake.

- COGs analysis of LEN (Andrew Hill) and CAB-LA (CHAI) show low-cost generic production is feasible, but the cost will still limit uptake.
  - ◊ CAB-LA (API synthesis, formulation, and sterilization).
    $30-40 PPPY at launch vs $14-18 PPPY at medium-scale volumes (~800,000 annual users).
  - ◊ LEN (API cost, formulation, and excipients).
    $145 PPPY current vs $61 PPPY at launch vs $29 PPPY at year 3.
  - ◊ **Combination of CAB and LEN would be 2-fold higher than TLD.**
    $50 to $70 PPPY.
- Low cost is an important determinant of uptake for any product.
  - ◊ Historic uptake of TLD after first approval and volume guarantee in 2017.
    TLD was introduced at a lower price than TLE/TEE and achieved 50% of the market share in 3y.
  - ◊ Contraceptive implant scale-up after access agreement and volume guarantee (2012).
    Steady increase in market share from 2011 to 2020; Implants account for most of the increase in couple-years of protection from 2011 to 2020.

Meets user preferences

We don't really know what people want for their own care.

- Patients are not a homogeneous group.
- Literature review on user preferences for HIV prevention (CHAI).
  - ◊ Product effectiveness is consistently most important, but the extent that it dominates decision-making varies widely across populations and geographies.
    - * 11% (YW in SA and Zimbabwe) vs 20% (YW in SA and Kenya) vs >50% (W in SA) vs 61% (Adults, AGYW, FSW in SA).
  - ◊ Product formulation is consistently the second most important attribute.
    - * LAIs are frequently the most preferred form; Daily oral pills are frequently the least preferred form.
  - ◊ Dosing frequency is more challenging to interpret (Often combined with the product form).
    - * Mixed preferences. Longer acting is generally better, but some populations did not prefer the longest dosing interval (e.g., AGYW in SA prefer Q3M vs Q6M).
    - * **People have a variety of needs.**
  - ◊ Pregnancy prevention is important.
    - * A majority across studies prefer a dual-indication product over a single-indication product.
- Significant data gaps.
  - ◊ Preference data on prevention are extremely limited outside of E and S Africa and among men and key populations (i.e., Hardest to reach).
  - ◊ Patient preferences on HIV treatment formulations is hugely understudied, especially in LMICs and key populations (i.e., Women, children, MSM, and sex workers).

Plugs remaining gaps

Ministries want products that fill gaps in their HIV response.

- HIV treatment: Significant progress toward global targets, but high-level reporting masks unequal progress among various groups and geographies.
  - ◊ Treatment access: 89% who know their HIV status are on ART.
    - * Men and key populations (context-dependent) are less likely to be on ART.
    - * Geographic inequalities.
    - * Subnational differences in ART coverage.
    - * Inconvenient care leading to significant cycling in and out of care (20-50% of ART initiates in SSA are "re-initiations"); Current delivery models are not meeting people's unique needs.
    - * Poor data systems.
  - ◊ Viral suppression: 93% on ART have suppressed viral load.
    - * Regional inequalities.
    - * Gender gaps.
    - * Poor failure management (People remain on failed regimens).
    - * Adherence issues (Poor mental health; Persistent stigma; Burden of QD dosing; Suboptimal ART).
- HIV prevention: Global progress toward new infection targets is off-track and huge inequalities remain.
  - ◊ 2020 UNAIDS target was missed by 1M infections.
    - * New HIV infections declined by 4.5% per year from 2015 to 2021; Will need a 35% per year decline to reach the 2025 target (Innovations are needed to close the gap).
    - * 6 of 7 new infections in SSA are among young girls (15-19y).
    - * Globally, key populations and their partners contributed 70% of all new HIV infections in 2021.

"Ministries seek products that fill their specific gaps and are affordable, meet the needs of their population, and are at least as good as what we have."

Francois Venter Executive Director, Reproductive health and HIV institute at University of Witwatersrand

"The clinician's perspective"

"I feel a mounting sense of anxiety about how much work there is to do to get [LAI ARVs] into the people who [need them]"

Mass treatment in the early 2000s

We had an imperfect drug, but we made it work.

- d4T (AZT) + 3TC + EFV or NVP. 3 tablets am and 2 tablets pm.
- Various forms of rationing. Balancing toxicity vs cost vs level of immunosuppression (CD4); Based on adherence visits or systems barriers.
- We started building the delivery system as we went.

Takeaways.

- We had drug to test the system.
- Many of the things we feared never happened. Mass resistance never became a programmatic issue – It informed the next round of drugs.

Cycle of ARV introduction in the LA era

A new product must offer a big step forward.

- **LAIs offer a huge advancement in terms of dosing.**

Then, negotiations:

- Price. Is it reasonable to replace what we currently have?
- Co-formulations in the first line. **This falls aways with the current LAIs.**

Specific considerations are different than in the past.

- TB drug interaction should not be a barrier for first-line therapies.
  - ◊ TB affects <1% PLWH at ARV initiation, and incidence falls on ART, even without IPT.
  - ◊ EFV- and DTG-based regimens work perfectly well for the few months ATT is needed.
- HBV coverage should not be required to advance a LA product.
  - ◊ Moving into the LA era, we will need to discuss what to do when HIV therapies stop covering HBV (i.e., No ramivudine- or TFV-based regimens in the mix).
- **Pregnancy and breastfeeding becomes central.**
  - ◊ Due to the sheer number of women who are vulnerable to infection and are presenting with new or re-infection.
  - ◊ The litmus test for new regimens should be if they can be used among women of child-bearing potential (LEN, CAB, and TLD have an evidence base; ISL and other drugs do not).
- Alignment with children and adolescents is desirable.
- Aging and comorbidities are increasingly important
  - ◊ Diabetes mellitus and frailty (i.e., Not the classic HIV co-morbidities).
- Resistance warrants engagement but is a less pressing issue.

Then, the dance around what should happen first.

- Guideline vs recommendation vs generic uptake vs adoption.
  - ◊ Generics will not manufacture a formulation before it is in the guidelines; Then need a volume guarantee, and finally (hopefully) something useful happens.
    - * That is what happened with TLD; TLD now completely dominates the guidelines in LMICs.

Challenges for health systems

LA HIV treatment.

- All current LAIs require HCW administration. Extra tablets for bridging and/or loading add complexity.
- Choice means more than one regimen. Supply lines; HCW prejudice; Switching.
- Reminders, tails, and loss to follow up. Once PEPFAR hands over a program, health systems (LMICs and high-income settings) are not good at getting people back for clinic visits.

LA HIV PrEP.

- LAI PrEP is completely unavailable (No CAB-LA or LEN in the system).
  - ◊ Studies show near 100% efficacy, but no lives have been changed.
- We are not moving quickly enough.
  - ◊ South Africa (SA) is touted as a PrEP success story, but it is a disaster.
    - * 10-20M people are eligible for PrEP.
    - * Product registrations: Oral TDF/xTC (2015); CAB-LA (2022); DPV ring (2022).
    - * 1.3M on PrEP (~ 50% re-starts); Only 1685 on CAB-LA and 790 on DPV ring (AVAC data as of 9/24).
  - ◊ ***CAB-LA has been licensed in SA for over 2y but is not available for purchase.***

Plan for LAI HIV PrEP

CAB-LA.

- Cannot be purchased from ViiV for treatment, prevention, or research. Very few, highly regulated implementation projects via donated CAB.
- Small volumes will trickle into the market via three generics at a unknown price in 2027. More than 7y after efficacy shown.

LEN

- Gilead access statement is totally vague beyond a willingness to work with communities to make LEN available.
- Volume, price point, and plan are unknown. ***Doses for 100M are needed.***

What does this mean?

- LAI PrEP programs cannot be scaled when pharma is gate keeping the two drugs we need.
  - ◊ It is impossible to test CAB-LA at scale with current volumes, even for key populations.
    - * The largest study in South Africa has 2000 participants.
  - ◊ Endless meetings on roll-out of a drug that is unavailable are just wishful thinking.
- Governments will not engage with buying LAIs until a price is set.

Plan for LAI HIV treatment

Context.

- Most people on ARVs want LAIs (not only key populations).
- Very few people initiating ARVs are truly ART-naive (<10%).

LAI CAB/RPV.

- The products are registered with no access from ViiV or Janssen.
  - ◊ The immediate compelling indication is non-adherent populations – We need it yesterday.
    - * The only way to access these life-saving products would be via some compounding mechanism.
  - ◊ Significant challenges: Cold chain; Resistance; Administration; and Cost.
    - * Not likely to replace TLD because the cost of the combination alone is so high.
- There are no other options.
  - ◊ Weekly oral LEN/ISL are the only other products on the horizon (Promising P2 data).
  - ◊ There is total gate keeping by pharma on other obvious combinations (e.g., CAB/LEN).
  - ◊ Each pharmaceutical company has its own issue regarding access.
    - * Janssen has given no indication of a RPV access plan.
    - * Gilead (LEN) will hopefully do the right thing.
    - * ViiV (CAB) has been chaotic from the start.
    - * Merck (ISL) has a pipeline but has not been engaged in terms of access.

What does this mean?

- It will likely be >10y before widespread access to LAI treatment.
  - ◊ Even if all companies granted instant access, more studies are needed to persuade WHO, guidelines committees, and governments on use of novel LAI combinations.
    - * Different drug combinations; Switch studies; PK; Naive, unsuppressed, and special population studies.
    - * ADVANCE took 4-5y to get the first results.
  - ◊ Then, we need to work on how to scale it.
- Harmonization of efforts is missing.
  - ◊ TLD introduction was the final success of the OPTIMIZE consortium.
    - * Convened people from every sector; Many parallel projects were conducted (Optimization, Patents, PK studies, Guidelines, etc); and Many projects fell by the wayside.
  - ◊ LEAP is trying to do the right thing on the front end but needs the next steps to get LAI ARVs where they are needed.

Benny Kottiri Office of HIV/AIDS, Bureau for Global Health at USAID

"The payer's perspective: Accelerating LA HIV prevention products from R&D to programs: Opportunities and challenges"

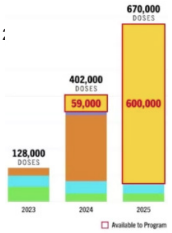
PEPFAR supports a multi-product HIV prevention platform

Programmatic context.

- Choice is encouraged.
  - ◊ QD oral PrEP, QM DPV ring, Q2M CAB-LA (Recent roll out) are currently available.
  - ◊ Q6M LEN is promising (PURPOSE 1 and 2 results).
- There are many challenges, even with choice.
  - ◊ Economic feasibility and licensing are major bottlenecks for LAI introduction in LMICs.
  - ◊ Ministry/government concerns include: Price, Generic licensing, and Local registration.
- USAID and PEPFAR objective.
  - ◊ Convene global stakeholders to set favorable programmatic, policy, regulatory, and market conditions for program roll out of LAIs for HIV.

Long timelines (Approval to programs) in LMICs are unacceptable.

- CAB for PrEP roll out in nine countries.
  - ◊ Choice studies, Pilot projects, and "Real" programs (i.e., Procure & deliver to certain countries).
- **Very limited CAB for program procurement.**
  - ◊ Allocation of non-commercial CAB supply for PrEP in LMICs, 2
    - * 955K of 1.2M doses are for program procurement.
      280K from PEPFAR to date (Orange)
      659K anticipated from ViiV (Yellow).
    - * 245K doses are committed to studies (Green and Blue).
  - ◊ 600K doses in 2025 means ~100K people on CAB-LA.
- **Significant start up delay**.
  - ◊ DCEs indicate LAI preference, but system preparedness takes time (i.e., Transition from QD oral to Q2M injection).



Lessons learned

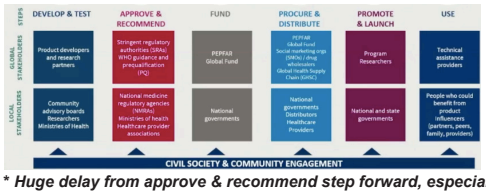
Engage early. Each step from R&D to program implementation has multiple components.

1. Harness research networks to advance R&D.
   Initial work with product developers.
2. Optimize products to meet PEPFAR program needs.
   Ensure product acceptability (Fund DCEs and patient preference studies).
3. Prime enabling environments to accelerate introduction.
   Fund AVAC to work with our community networks; policy and communication programs, and countries.
4. Maximize program integration and impact.
   Program roll out and data collection to assess numbers and impact.
   Impact of HIV prevention is disappointing.

USAID dynamic "end-to-end" model

Coordinated efforts to accelerate the timeline – How?

- Individual parties are doing well, but partnership is needed.
  PEPFAR buying power does not always translate to convening power.



**** Huge delay from approve & recommend step forward, especially for HIV products.***

Product introduction and access program challenges.

- Each element listed is funded.

Policy, Plans, & Costing	Supply Chain & Market Development	Service Delivery	Uptake & Effective Use	Monitoring & Evaluation	Cross-cutting Contributions
Global/national guidance Implementation plans National strategies	Market shaping Demand forecasting Private sector Bottlenecks	Research collabs Implementation research DSD Provider training	End-user engagement Demand generation CQI	Resistance surveillance Routine M&E Data-informed approaches	Evidence/resources Global collabs Capacity building Civil society engagement

- We are investigating various service delivery channels for LAIs.
  - ◊ ***There is government push back on pharmacy & CHW options***, even for testing.
  - ◊ Our experience with medical male circumcision program roll out (i.e., Government negotiation & staff shifting) may help overcome ministry-level/policy constraints.
- Acceptability; Feasibility & deliverability; Affordability; & Sustainability.
  - ◊ Developing a product that stays in the market goes beyond safety & efficacy.
  - ◊ Special emphasis on sustainability and capacity building. PEPFAR aims to hand over programs.
  - ◊ Our framework to support R&D is based on 20y of experience.
    - * Technology Accelerator hub. Support new R&D/Prioritize products.
    - * Design 2 Delivery (D2D) hub. Incorporate stakeholder and end-user feedback.
    - * Capacity strengthening engagement and mentorship(CaSE) hub. Build research partnerships and use R&D capacity in Africa for sustainability.
    - * Business market dynamics and commercialization hub (BACH). Develop the business case for program success.
    - * Clinical trials hub. Design and conduct early clinical trials (P0-P3) in US and Africa.

How to work with industry partners on new products.

- Touch points from R&D to roll out. Gilead and LEN example.

R&D (Research demand; Equity; Establish value proposition)	• Engaged with Gilead on product affordability 3y ago. • Helped prepare clinical trial sites (Community engagement, policy, etc). • Funded a qualitative sub-study on end-user preferences.
Manufacturing (Early engagement; Design for scalability; Local links)	• Identified potential manufacturers with the capability before clinical trials.
Price negotiation & demand estimation (Demand vs need; Real cost vs innovator margin)	• ***We have not coordinated on this at all.***
Pre-market regulatory approvals (National/International; TA to expedite approval)	• Capacity strengthening around local registration.
Facilitate generic access (Early agreement; Support policy to expedite transition; TA/capacity building to meet quality standards)	• PEPFAR is planning to put a lot of investment in this area.
Financial support for the transition (Incentives to originators for generic licensing; Fund initiatives to lower scaling costs for generics)	• We have a history of financing the initial manufacturing for generics (Family planning space), especially when they don't have volume numbers.
Policy & advocacy (Policy negotiation with governments to facilitate market entry; Advocate for regulatory harmonization)	• Engage directly and indirectly with industry and ministry partners.

Towards a high-level donor commitment model.

- Potential market shaping interventions to support product roll out.
  - ◊ Timeline. Engage stakeholders for a 1-2y timeline for increased demand.
  - ◊ Procurement. Provide a volume guarantee.
  - ◊ Supplier Engagement. Identify suppliers and finance equipment &/or regulatory fees.
  - ◊ Demand Forecasting. Own/lead continuous forecasting analysis to reduce supplier risk.
  - ◊ Demand Generation. Promote/subsidize adoption & wide-scale demand generation to increase uptake.
  - ◊ Market Information. Generate additional reporting requirements and systems for participating countries.
- Firm donor commitment is often a political decision.
  - ◊ Leadership changes introduce complexity.
  - ◊ Ministry decisions are based on total program cost, not simply COGs vs price.

Success is possible with concerted efforts.

- Global ARV demand pooling (PEPFAR, Global Fund, and SA) resulted in a 47% reduction in TLD cost over 5y.
- DTG generic licensing. Timeline to reach LMICs <4y. 2013 FDA approval; 2014 Generic licensing (ViiV/MPP); 2016 Tentative FDA approval of first generic version; 2017 First shipment to LMIC.
- Optimize Consortium is a good overall model. We need global partnership; One agency, funder, or country cannot do it alone.

Takeaways

- LA ARVs are a promising opportunity, but past timelines are too long.
- Early engagement with private sector partners with recurring opportunities for R&D of new technologies can accelerate program implementation.
- Originator vs generic perspective. Originators bear significant R&D, regulatory, and SG&A costs, whereas COGs is the dominant force for generics.
- COGs is one component of product price. COGs and price are highly sensitive to product volume and location of manufacture.
- Facilitators for LA PrEP introduction: Reliable & sustainable supply; Steady demand increase; Balanced procurement price; Regulatory policy; Program timelines.
- Donor-driven economic motivations can stimulate private sector innovations and potential investments in generic manufacturing.
- LA ARVs are viable product options if programmed at large scale.

Long-Acting/Extended Release
Antiretroviral Research Resource Program