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.