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"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).