medicines patent pool

Generic CAB-LA for PrEP development and access

MPP briefing to LA PrEP Coalition Civil Society Caucus

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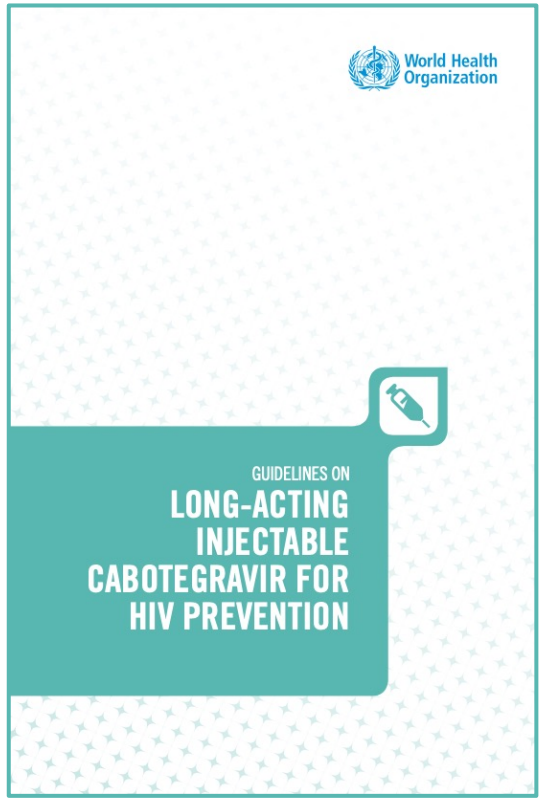
24 May 2024

CAB-LA as one more HIV prevention option

"CAB-LA should be delivered as an additional choice alongside other PrEP options, including oral PrEP and the DVR, as part of a comprehensive HIV prevention approach."



Prevention

- Oral PrEP (TDF/XTC)
  - ***Patents expired***
- Dapivirine vaginal ring
  - ***Population Council***
- **CAB-LA**
  - ***MPP licence***

CAB-LA for PrEP is

- ✓ Recommended by WHO
- ✓ Approved in several countries
- ✓ Effective, well tolerated, safe
- ✓ Taken as an injection every 2 months
- ✓ Patented until 2031 but licensed to MPP – *thanks in large parts to community advocacy efforts!*

More at: *https://medicinespatentpool.org/licence-post/cabotegravir-long-acting-la-for-hiv-pre-exposure-prophylaxis-prep*
https://www.who.int/publications/i/item/9789240054097

MPP-ViiV licence for CAB-LA for PrEP

- The licence enables the **development and supply of generic versions** of CAB-LA for PrEP
- There are **three licensed generic manufacturers** developing the product, and transfer of technical knowhow from ViiV Healthcare to these three licensees was completed at the end of 2023
- The **development of generic versions** (until filing with regulatory authorities) will likely take **until late 2026** and availability at the country level will depend on timelines for regulatory review; meanwhile, the only source of CAB-LA will be the originator product from ViiV Healthcare
- As is usual, the licence is **published on the MPP website** in full

News & Publications » News & Press Releases » Press Releases

ViiV Healthcare and the Medicines Patent Pool sign new voluntary licensing agreement to expand access to innovative long-acting HIV prevention medicine

28 July 2022

ViiV Healthcare

News & Publications » News & Press Releases » Press Releases

Medicines Patent Pool signs sublicences with Aurobindo, Cipla and Viatris to produce generic versions of ViiV Healthcare's innovative long-acting HIV prevention medicine

30 March 2023

- ***Licences should enable potentially millions of people living in areas most impacted by HIV to access this innovative prevention medicine through low-cost generic manufacturers***
- ***Announcement includes potential for large scale manufacturing on the continent of Africa***

AUROBINDO Cipla Mylan

More at: https://medicinespatentpool.org/licence-post/cabotegravir-long-acting-la-for-hiv-pre-exposure-prophylaxis-prep

Generic CAB-LA nominal licence territory + *countries without patent for CAB-LA*

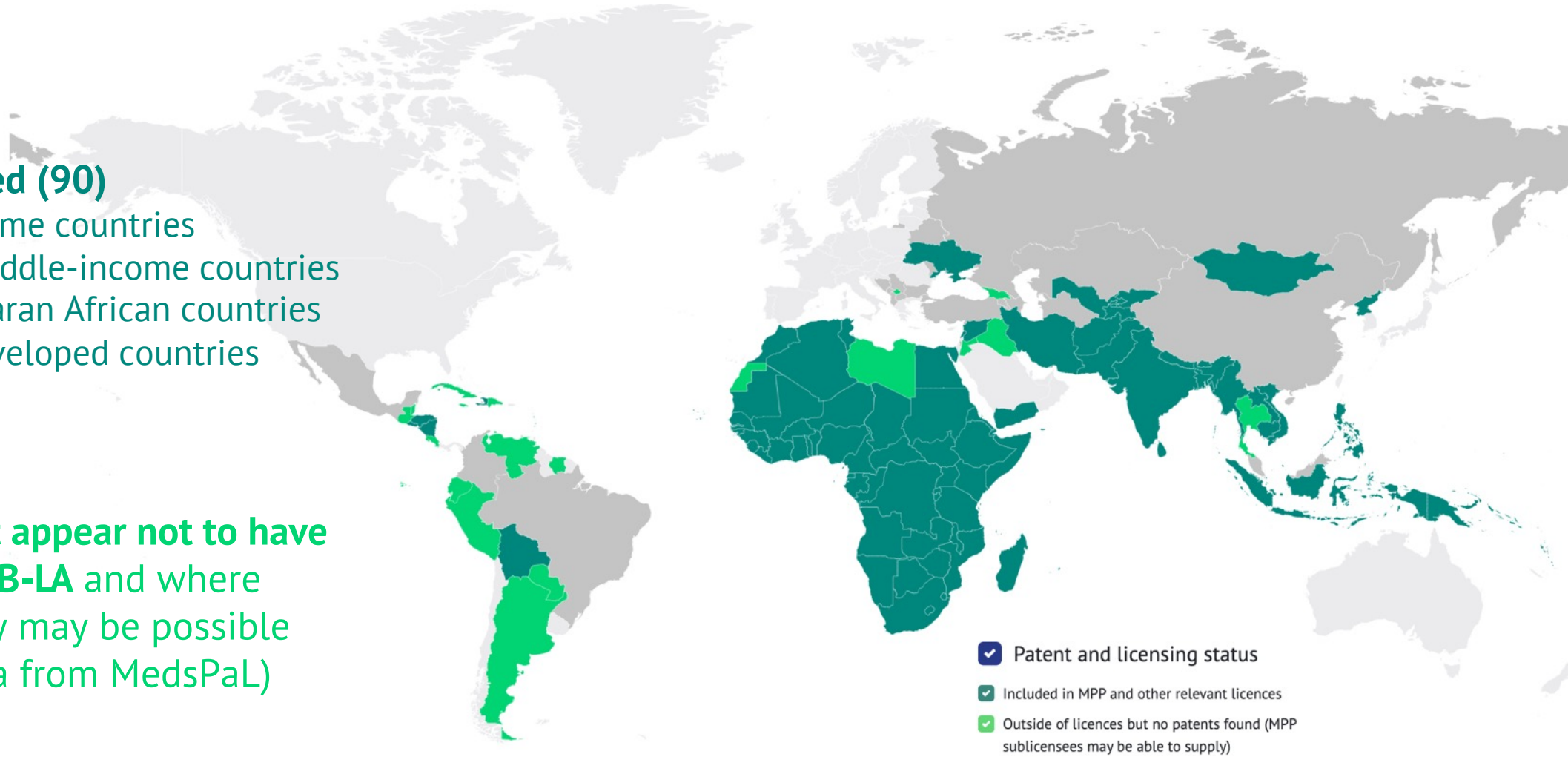
This is what we call the effective territory…

Countries listed (90)

- All low-income countries
- All lower middle-income countries
- All sub-Saharan African countries
- All least-developed countries

+

Countries that appear not to have patents on CAB-LA and where generic supply may be possible (based on data from MedsPaL)



More at: https://medicinespatentpool.org/progress-achievements/access-to-medicines-tracker
https://medicinespatentpool.org/licence-post/cabotegravir-long-acting-la-for-hiv-pre-exposure-prophylaxis-prep

Partnering with generics

Sub-licensee selection process

- MPP invites qualified product developers to **apply for licences** to manufacture and sell licensed medicines in LMICs; this is done **through an Expression of Interest (EOI) process**
- The assessment is rigorous and objective (with **blinded review** for short-listing), and responses are graded using a standardised tool and top-scoring applicants are selected
- The number of licences granted is usually informed by demand forecasts and other information; in the CAB-LA case, **the number of licensees was pre-aligned** with ViiV Healthcare, and included in the license agreement

More at: https://medicinespatentpool.org/partners/how-to-get-or-give-a-licence

By granting multiple sublicences, MPP aims to support adequate supply and competitive pricing

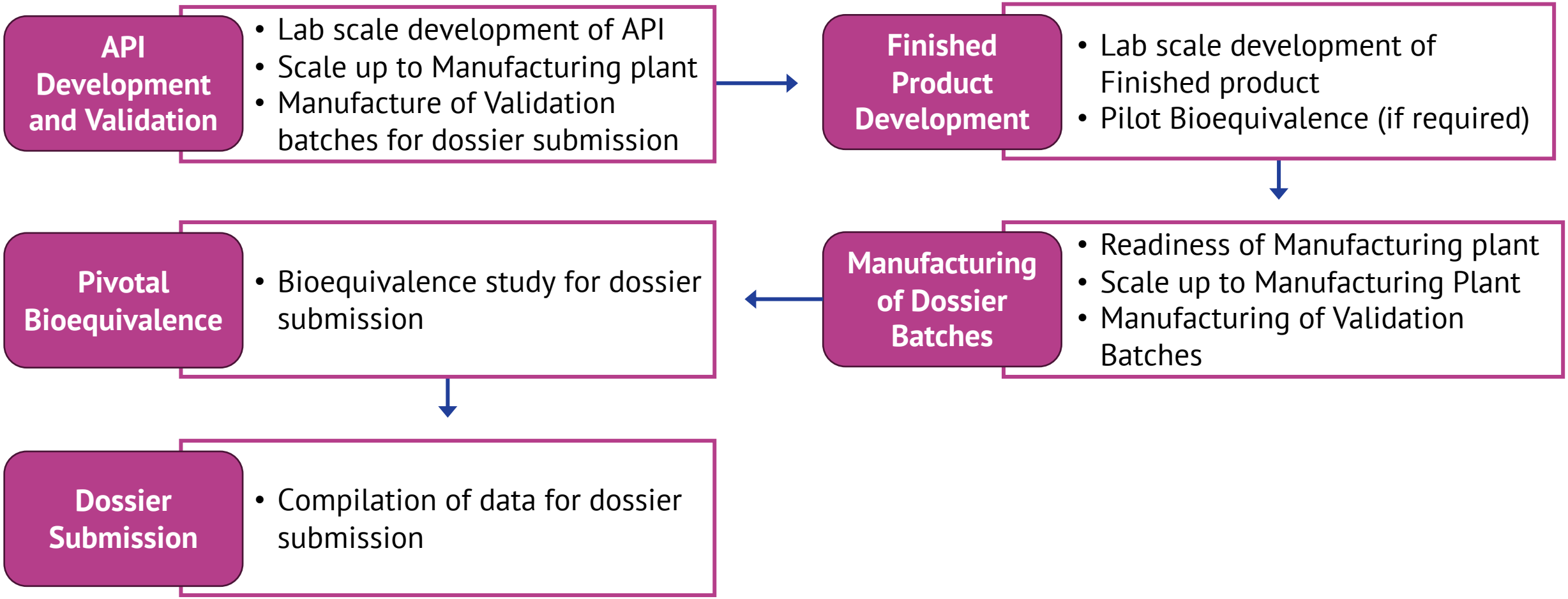
For CAB-LA, there was also an onsite audit of short-listed candidate's manufacturing plant

Sub-licensee selection criteria

- **Capacity, capabilities and track-record** for manufacturing quality-assured medicines (including experience developing, manufacturing and/or marketing other products)
- **R&D, financials, and regulatory compliance** (including around required quality standards)
- **Specific plans** for the licensed product (regarding development, manufacturing, regulatory plan, distribution, and projected investments – viability of those plans, especially in case of projects requiring specific capital expenditure or investments)
- **Readiness with needed formulation technologies** (in the CAB-LA case, this included long-acting injectables and nano-milling technology)
- **Past experience and performance as MPP licensee**

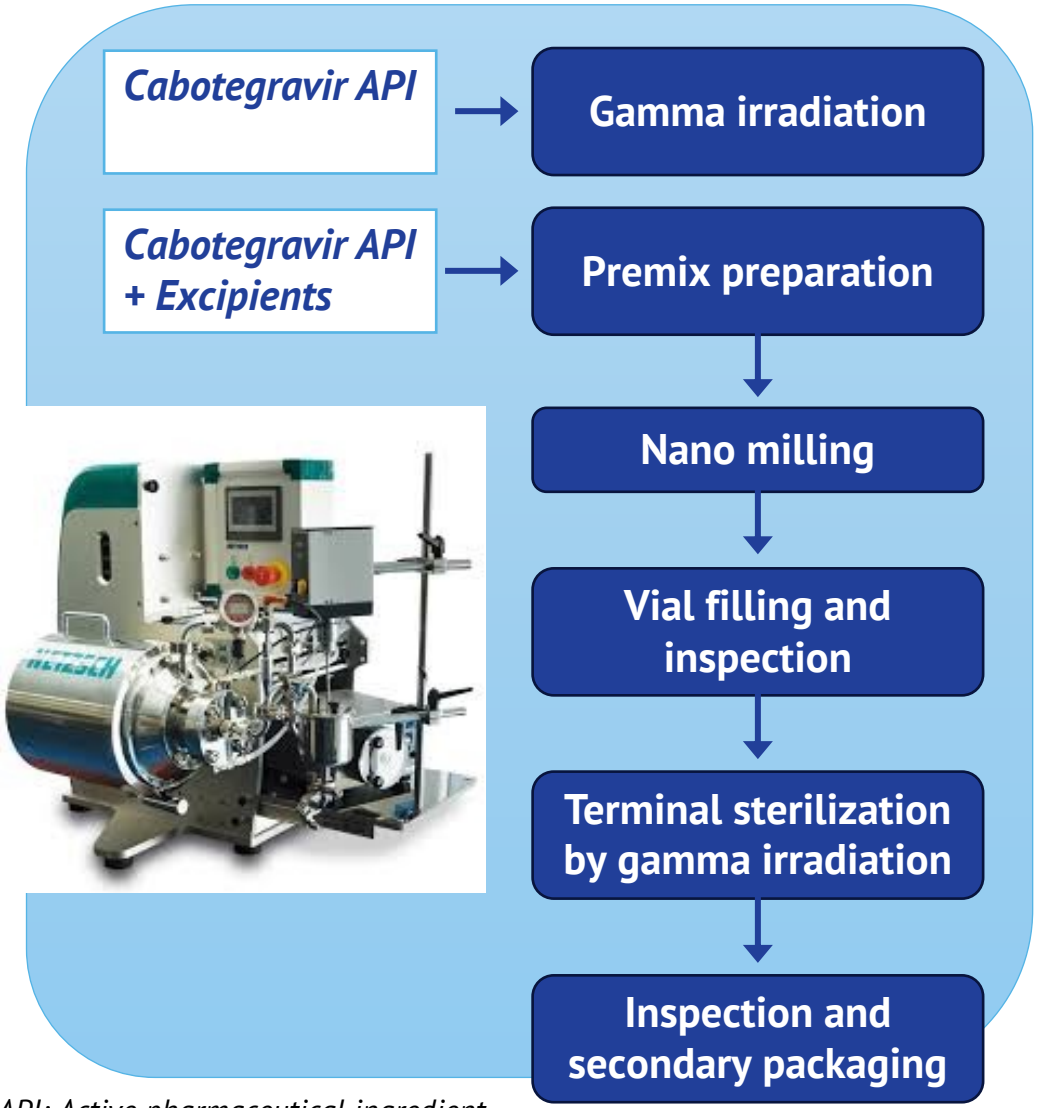
Cabotegravir product development

Process flow for CAB-LA product development and registration



- *API: Active pharmaceutical ingredient*
- *LAI: Long-acting injection*

Cabotegravir LAI manufacturing : Critical aspects



- *API: Active pharmaceutical ingredient*
- *LAI: Long-acting injection*

1 Gamma Irradiation

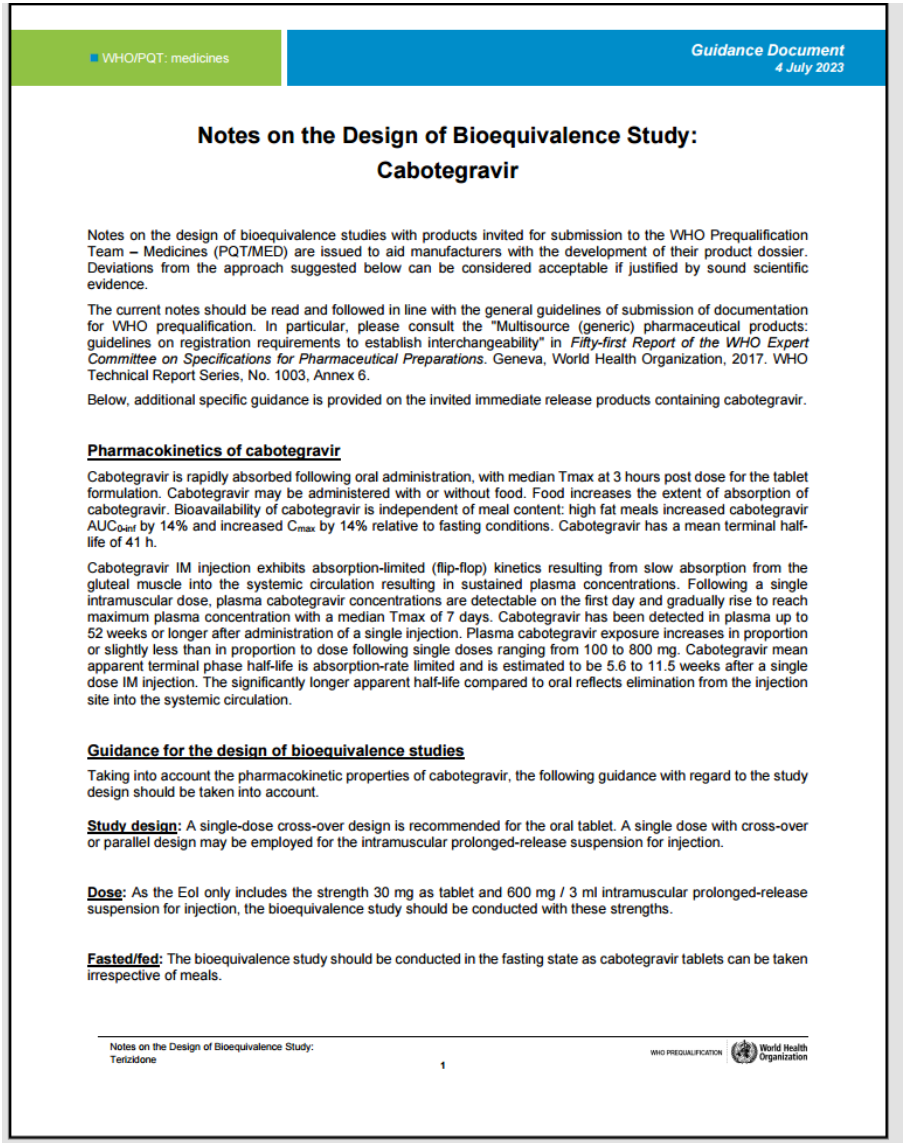
- Non-standard process for terminal sterilization
- Generics do not have in house facility, will have to outsource
- Challenges in validation of gamma irradiation for ensuring sterility
- Stability of product after gamma irradiation
- Transportation and handling challenges

2 Nano milling

- Non-standard process for particle size reduction
- Requires special equipment and manufacturing line, capex involved
- Expertise in installation, handling and running of the equipment
- Challenges in optimization of process parameters
- Challenges in product physicochemical stability
- Batch size restriction : limited by mill volume and milling time

Cabotegravir LAI bioequivalence : Critical aspects

- Long-acting product: **lengthy bioequivalence study (approximately 18-24 M)**
- WHO PQ recommendations suggest **42 weeks sampling time**
- Likely to be **parallel design (wash out 60 weeks)**, increase in variability
- Overall variability is high **(%CV of 55-60%)**: larger number of subjects
- Difficult to screen formulations in **pilot studies**
- USFDA guidance has additional requirements for **drug device combination**



WHO/PQT: medicines

Guidance Document
4 July 2023

Notes on the Design of Bioequivalence Study: Cabotegravir

Notes on the design of bioequivalence studies with products invited for submission to the WHO Prequalification Team – Medicines (PQT/MED) are issued to aid manufacturers with the development of their product dossier. Deviations from the approach suggested below can be considered acceptable if justified by sound scientific evidence.

The current notes should be read and followed in line with the general guidelines of submission of documentation for WHO prequalification. In particular, please consult the "Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability" in *Fifty-first Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva, World Health Organization, 2017. WHO Technical Report Series, No. 1003, Annex 6.

Below, additional specific guidance is provided on the invited immediate release products containing cabotegravir.

Pharmacokinetics of cabotegravir

Cabotegravir is rapidly absorbed following oral administration, with median Tmax at 3 hours post dose for the tablet formulation. Cabotegravir may be administered with or without food. Food increases the extent of absorption of cabotegravir. Bioavailability of cabotegravir is independent of meal content: high fat meals increased cabotegravir $AUC_{0\text{-}inf}$ by 14% and increased C_{max} by 14% relative to fasting conditions. Cabotegravir has a mean terminal half-life of 41 h.

Cabotegravir IM injection exhibits absorption-limited (flip-flop) kinetics resulting from slow absorption from the gluteal muscle into the systemic circulation resulting in sustained plasma concentrations. Following a single intramuscular dose, plasma cabotegravir concentrations are detectable on the first day and gradually rise to reach maximum plasma concentration with a median Tmax of 7 days. Cabotegravir has been detected in plasma up to 52 weeks or longer after administration of a single injection. Plasma cabotegravir exposure increases in proportion or slightly less than in proportion to dose following single doses ranging from 100 to 800 mg. Cabotegravir mean apparent terminal phase half-life is absorption-rate limited and is estimated to be 5.6 to 11.5 weeks after a single dose IM injection. The significantly longer apparent half-life compared to oral reflects elimination from the injection site into the systemic circulation.

Guidance for the design of bioequivalence studies

Taking into account the pharmacokinetic properties of cabotegravir, the following guidance with regard to the study design should be taken into account.

Study design: A single-dose cross-over design is recommended for the oral tablet. A single dose with cross-over or parallel design may be employed for the intramuscular prolonged-release suspension for injection.

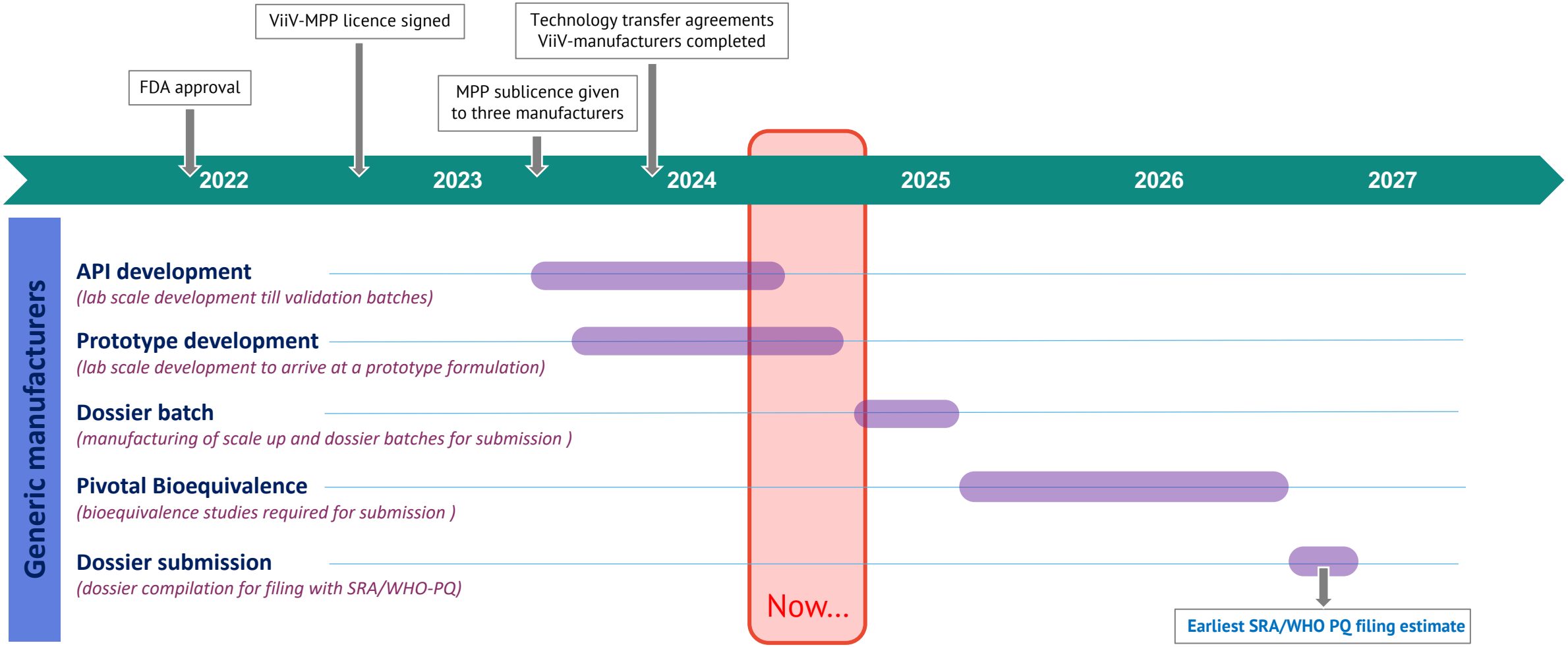
Dose: As the EoI only includes the strength 30 mg as tablet and 600 mg / 3 ml intramuscular prolonged-release suspension for injection, the bioequivalence study should be conducted with these strengths.

Fasted/fed: The bioequivalence study should be conducted in the fasting state as cabotegravir tablets can be taken irrespective of meals.

Notes on the Design of Bioequivalence Study: Terizidone
1
WHO PREQUALIFICATION World Health Organization

- *LAI : Long-acting injection*
- *CV : Coefficient of variation*

Generic CAB-LA for PrEP: Tentative development timeline



- These timelines are not specific to any generic company; these are averages of the timelines required for different activities as shared by MPP licensees.
- The earliest possible timelines for filing is **H2 2026** based on the current estimation by MPP.
- Due to the uncertainty associated with product development, especially for such long-acting products, the timelines quoted here are tentative and can change during development of the product.

CAB-LA for PrEP beyond generic product development work

Accelerating regulatory approval in India:
Enabling faster access globally

- Accelerating the regulatory approval of CAB-LA in India is important both for the local population and exports globally as MPP-licensed generic manufacturers are based in India
- Efforts are ongoing for the use of fast-track provisions that exist in the Indian regulatory system and that have previously enabled local clinical trial waivers for the regulatory approval of HIV, HCV, and TB medicines
- Various relevant Indian government agencies are being sensitised so that they are supportive during the future regulatory review process
- An option for a pre-submission meeting with the Indian regulator is being assessed

Medicines Patent Pool signs sublicences with Aurobindo, Cipla and Viatris to produce generic versions of ViiV Healthcare's innovative long-acting HIV prevention medicine

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AUROBINDO Cipla Mylan

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CAB-LA for PrEP beyond generic product development work

Engaging stakeholders:

Building demand, anticipation, and momentum

- Stakeholder engagement (like today's session) has been taking place with community leaders, civil society representatives, multilateral organisations, governments, and other technical experts
- MPP has also opened a call for applications for additional community leaders to join its Community Advisory Panel (CAP) and complement the existing pool of community representatives advising MPP, keeping us accountable, and contributing to building demand and expectations

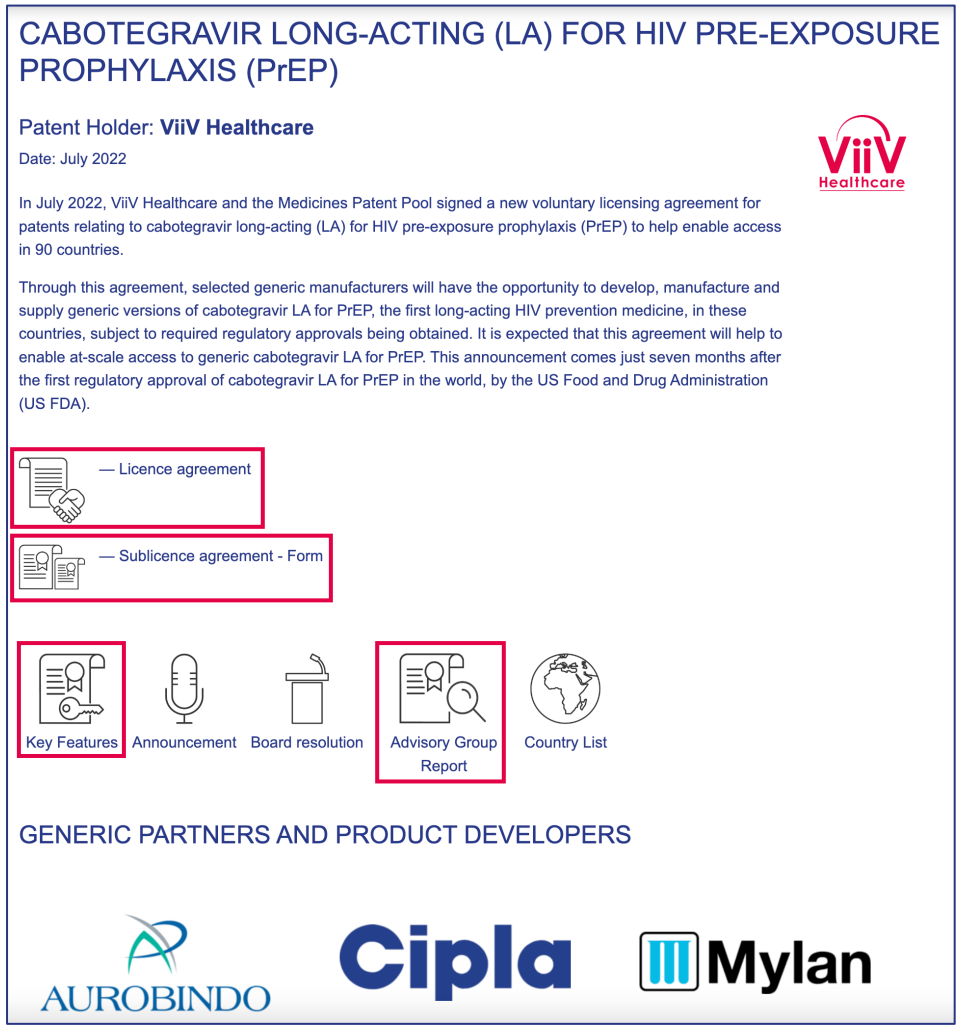
Launching the MPP Community Advisory Panel in 2023

Ongoing recruitment for MPP's CAP

- Latin America
- Francophone sub-Saharan Africa
- Middle East and North Africa
- South Asia (specifically PrEP and HCV)
- People with expertise in pandemic-related products
- People living with/affected by a cardiovascular disease or type 2 diabetes

More at: https://medicinespatentpool.org/who-we-are/career-request-for-proposals/call-for-applications-community-representatives-april24

More information on the licence available online



CABOTEGRAVIR LONG-ACTING (LA) FOR HIV PRE-EXPOSURE PROPHYLAXIS (PrEP)

Patent Holder: **ViiV Healthcare**

Date: July 2022

In July 2022, ViiV Healthcare and the Medicines Patent Pool signed a new voluntary licensing agreement for patents relating to cabotegravir long-acting (LA) for HIV pre-exposure prophylaxis (PrEP) to help enable access in 90 countries.

Through this agreement, selected generic manufacturers will have the opportunity to develop, manufacture and supply generic versions of cabotegravir LA for PrEP, the first long-acting HIV prevention medicine, in these countries, subject to required regulatory approvals being obtained. It is expected that this agreement will help to enable at-scale access to generic cabotegravir LA for PrEP. This announcement comes just seven months after the first regulatory approval of cabotegravir LA for PrEP in the world, by the US Food and Drug Administration (US FDA).

— Licence agreement

— Sublicence agreement - Form

Key Features | Announcement | Board resolution | Advisory Group Report | Country List

GENERIC PARTNERS AND PRODUCT DEVELOPERS

AUROBINDO Cipla Mylan

Gaayeb L et al. *Journal of the International AIDS Society* 2023, **26**(S2):e26092
http://onlinelibrary.wiley.com/doi/10.1002/jia2.26092/full | https://doi.org/10.1002/jia2.26092

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

COMMENTARY

Voluntary licensing of long-acting HIV prevention and treatment regimens: using a proven collaboration- and competition-based mechanism to rapidly expand at-scale, sustainable, quality-assured and affordable supplies in LMICs

Lobna Gaayeb[1], Aditi Das[2], Ike James[1], Rajesh Murthy[2], Sandra Nobre[1], Esteban Burrone[1] and Sébastien Morin[1,§]

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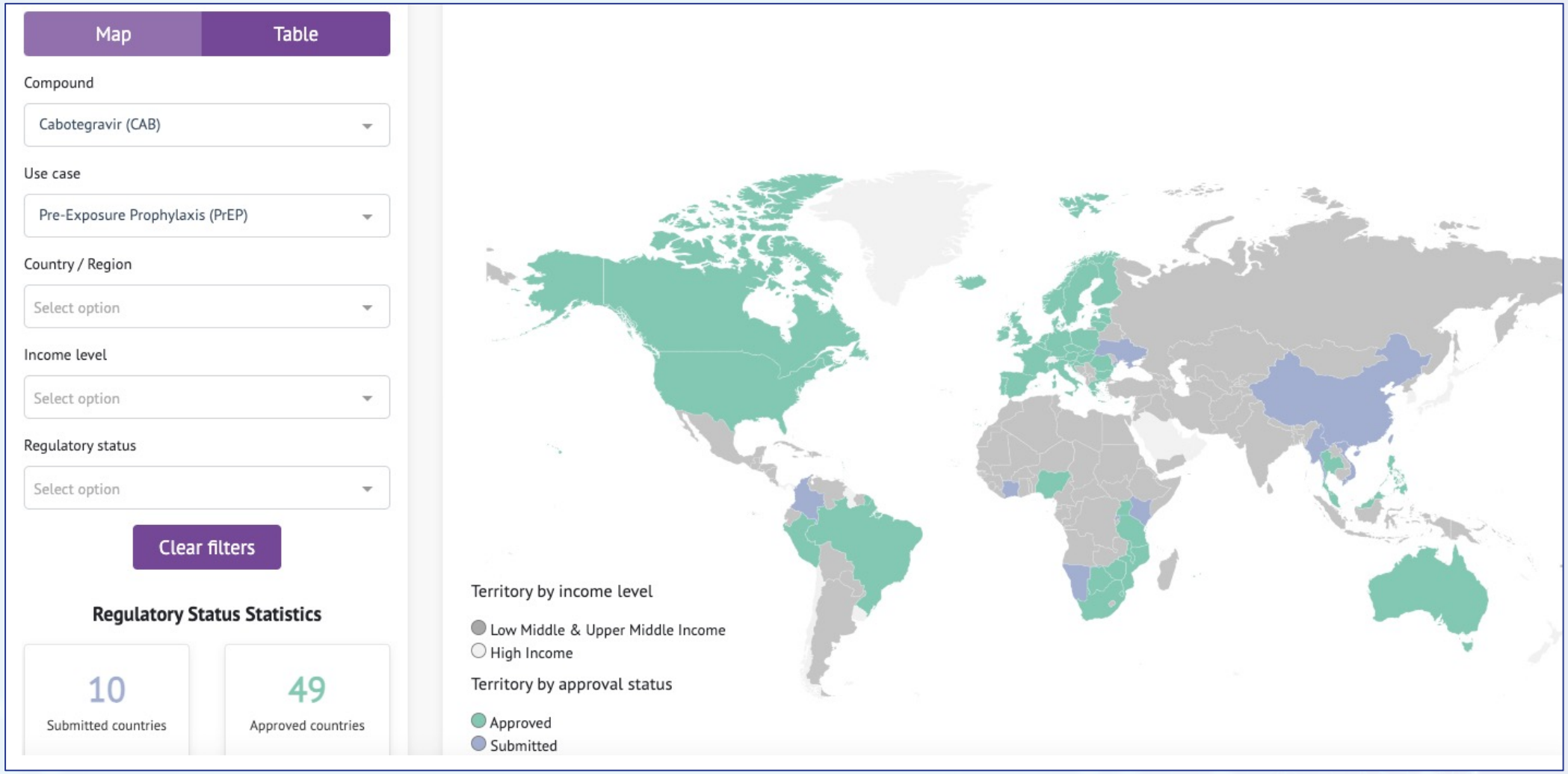
Journal of the International AIDS Society, 2023

https://doi.org/10.1002/jia2.26092

https://www.youtube.com/watch?v=h57gXs4aQtg

More at: https://medicinespatentpool.org/licence-post/cabotegravir-long-acting-la-for-hiv-pre-exposure-prophylaxis-prep
https://medicinespatentpool.org/progress-achievements/prioritisation

Originator product registration to date

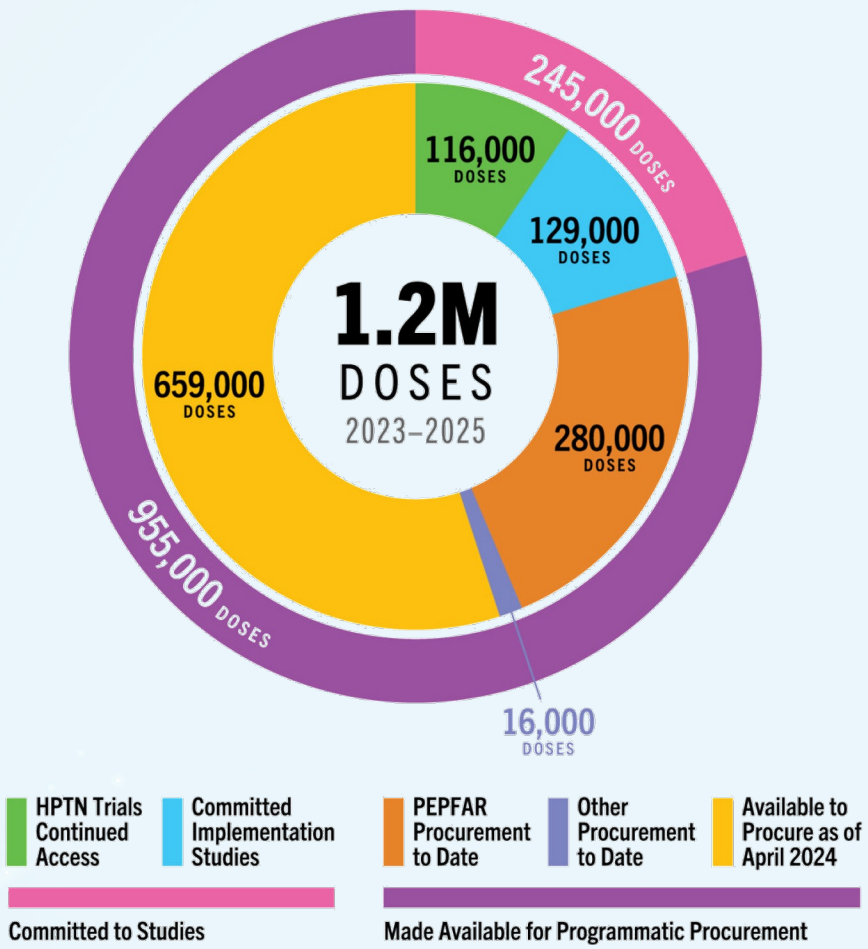


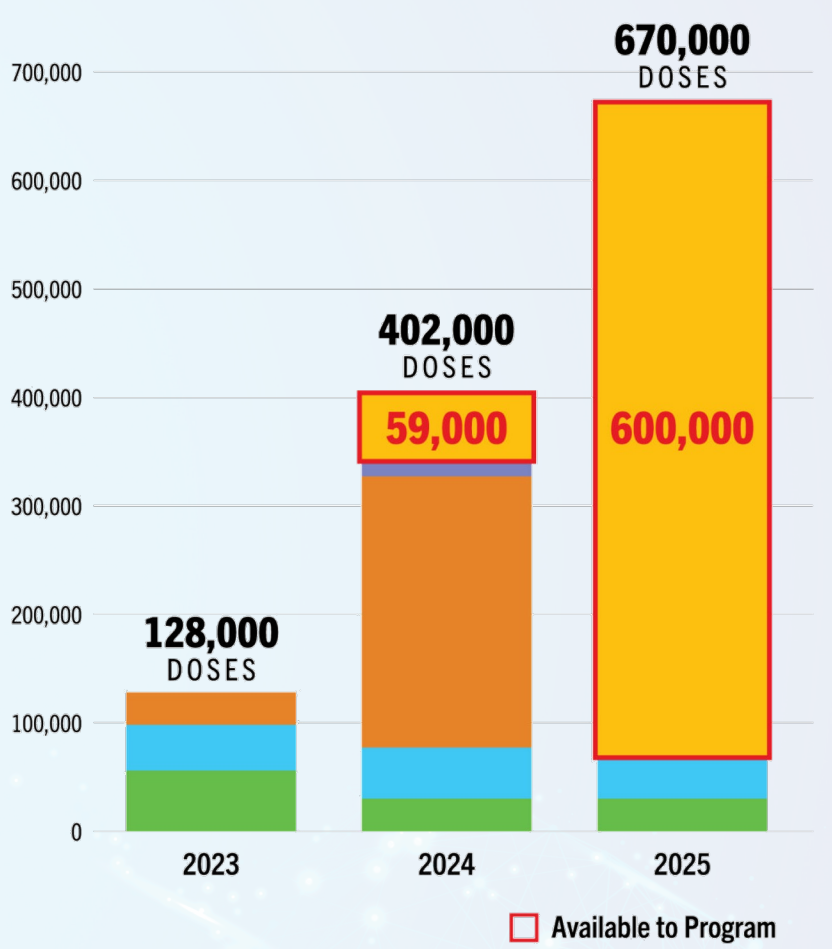
This information is shared as a courtesy. MPP is not involved in originator product rollout.

More at: https://viivhealthcare.com/ending-hiv/viiv-improve-access-to-hiv-medicines
https://lapal.medicinespatentpool.org/landscape

Originator CAB-LA for PrEP non-commercial allocation for LMICs

This information is shared as a courtesy. MPP is not involved in originator product rollout.





April 2024 *www.avac.org*

AVAC Advocacy. Access. Equity.

More at: https://avac.org/resource/allocation-cab-for-prep-2023-2025

medicines patent pool

Thanks for your attention and collective contributions to broad access to PrEP!

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