ARV Buyer Seller Summit 2023: The Power of Partnerships in the Fight against HIV

30 October – 1 November 2023

Maputo, Mozambique

Moderator

Cathal Meere

Manager Pharma Sourcing

The Global Fund

30 October Monday – Day 1:Strategic perspectives and ambitions in our collective fight against HIV		
Time	**Session – Rovuma Room**	**Speakers**
8:30 – 8:40	**Welcome**	Cathal Meere, Manager Pharma Sourcing, the Global Fund *(conference moderator)*
8:40 – 9:00	**Opening remarks**	Hui Yang, Head of Supply Operations, the Global Fund Ambassador Peter Hendrick Vrooman, US Ambassador to Mozambique HE Dr. Armindo Tiago, Mozambique Minister of Health
9:00 – 10:00	**Priorities in the fight against HIV**	***Introductions***: Cathal Meere Mark Edington, Head of Grant Management Division, the Global Fund James Maloney, Deputy Director, Office of HIV/AIDS, Global Health Bureau, PEPFAR Khadija Jamaloodien, Chief Director, Sector Wide Procurement, National Department of Health, Republic of South Africa
10:00 – 10:15	*BREAK*	
10:15 – 11:30	**Panel 1: Challenges in reaching 2030 HIV goals**	***Moderator*:** Kenly Sikwese, Executive Director, Afrocab Treatment Access Partnership ***Key-note speaker:*** Dr. Aleny Couto, Head of STI and HIV/AIDS program at MoH – Mozambique ***Panel:*** Siobhan Crowley, Head of HIV, the Global Fund Dr. Dianna Edgil, Chief, Supply Chain Health Division, USAID Khadija Jamaloodien Dr. Aleny Couto
11:30 – 12:30	**Panel 2: The role of partnership, innovation and south to south collaboration in accelerating progress**	***Moderator:*** Ellie Marsh, Senior Manager, Strategy, Procedure and Innovation, the Global Fund ***Panel:*** Sandra Nobre, Head of Business Development, Medicine Patent Pool Claudia Martínez, Programme Manager, Access to Medicine Uzoma Ezeoke, Executive Director, Emzor Pharmaceutical Industries Ltd Simo Masondo, Vice President, Government Affairs & Trade Development, Cipla Dr. Boitumelo Semete-Makokotlela CEO of SA Health Products Regulator
12:30 – 13:30	*Lunch*	
13:30 – 17:30	**One on One sessions**	Breakout rooms

31 October Tuesday – Day 2: Demand forecasting and planning to maximize partner engagement

Time	Session – Rovuma Room		Speakers
8:30 – 8:35		***Introductions**:* Cathal Meere	
8:35 – 9:15	**Demand & procurement**	***Lessons learned:*** Country experience on demand forecasting & Q&A	Ivandra Libombo, Chief of Planning Department, Central de Medicamentos e Artigos Medicos (CMAM), Mozambique
9:15 – 10:15		***Lessons learned:*** Procurement experience [panel discussion] & Q&A	***Moderator:*** Daniel Kiesa, Market Advisor, Office of HIV/AIDS, USAID ***Panel***: Ivandra Libombo Jordi Balleste, Unit Chief, Strategic Fund Procurement, Procurement and Supply Management – Pan American Health Organization Alan Pringle, Global Supply Chain Director, GHSC-PSM/Chemonics Wesley Kreft, PPM Project Director, Iplus Solutions Ignace Ndekezi, Head of Department, Procurement and Quantification, Rwanda Medical Supply
10:15 – 10:30		***Forward looking**:* 18-month consolidated forecast from big buyers	Shanil Ramlall, Africa Resource Centre
10:30 – 10:45	*BREAK*		
10:45 – 11:15	**Case study:** Approach to strengthen demand forecast and planning		Martin Auton, Head of Planning, Procurement and Transaction Management, the Global Fund
11:15 – 12:00	**Quality Assurance updates**		Deusdedit Mubangizi, Unit Head, Prequalification Unit, Regulation and Prequalification Department, World Health Organization Sandrine Cloëz, Specialist, Pharmaceutical Products Quality Assurance, the Global Fund
12:00 – 12:30	**Closing remarks: Call to action**		***Moderator:*** Cathal Meere Mozambique Ministry of Health South Africa National Department of Health The Global Fund PEPFAR
12:30 – 13:30	*Lunch*		
13:30 – 17:30	**One on One sessions**		Breakout rooms

Opening remarks

Hui Yang
Head of Supply Operations
The Global Fund

Peter Hendrick Vrooman
the United States Ambassador to the Republic of Mozambique

HE Dr. Armindo Tiago
Minister of Health, Mozambique

Priorities in the fight against HIV

Mark Edington
Head of Grant Management
The Global Fund

James Maloney
Deputy Director, Office of HIV/AIDS,
Global Health Bureau, USAID

Khadija Jamaloodien
Chief Director, Sector Wide Procurement, National Department of Health, Republic of South Africa

Global Fund Priorities in the Fight Against HIV

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30th October 2023

Maputo, Mozambique

Progress in the Fight Against HIV

Access the **recently published 2023 Global Fund Results Report** here

$27.8 billion

Total HIV investment by the Global Fund from 2002 through 2022

Key HIV Results in 2022 in Countries where the Global Fund Invests

24.5M

People on antiretroviral therapy for HIV

12.2M

HIV tests taken by priority and key populations

15.3M

People reached with HIV prevention services

710K

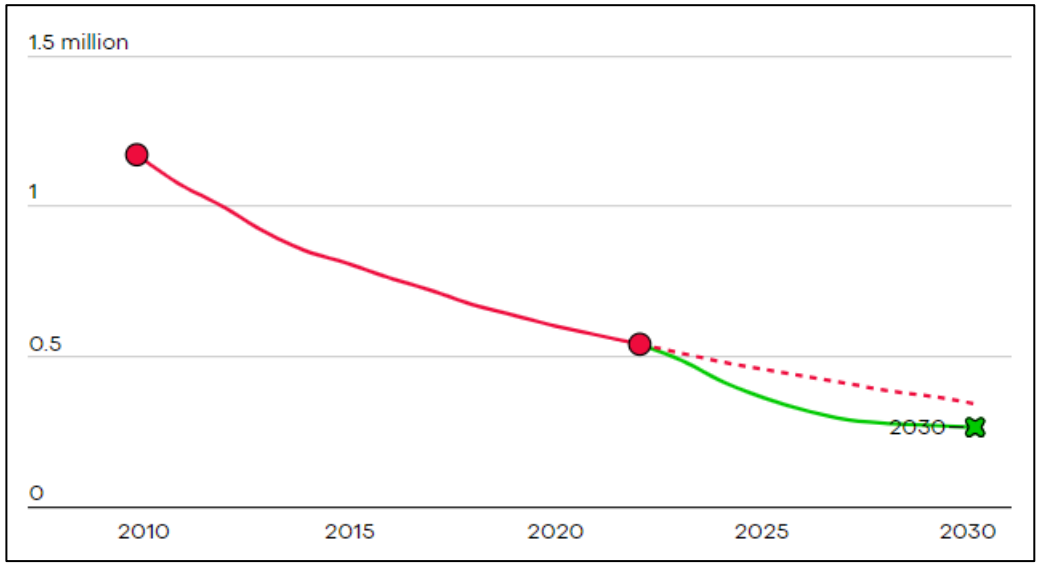
Mothers living with HIV received medicine to keep them alive + prevent transmitting HIV to their babies

The percentage of people in need of antiretroviral therapy who received it where Global Fund invests **has significantly increased in recent years, from 48% in 2015 to 78% in 2022**.

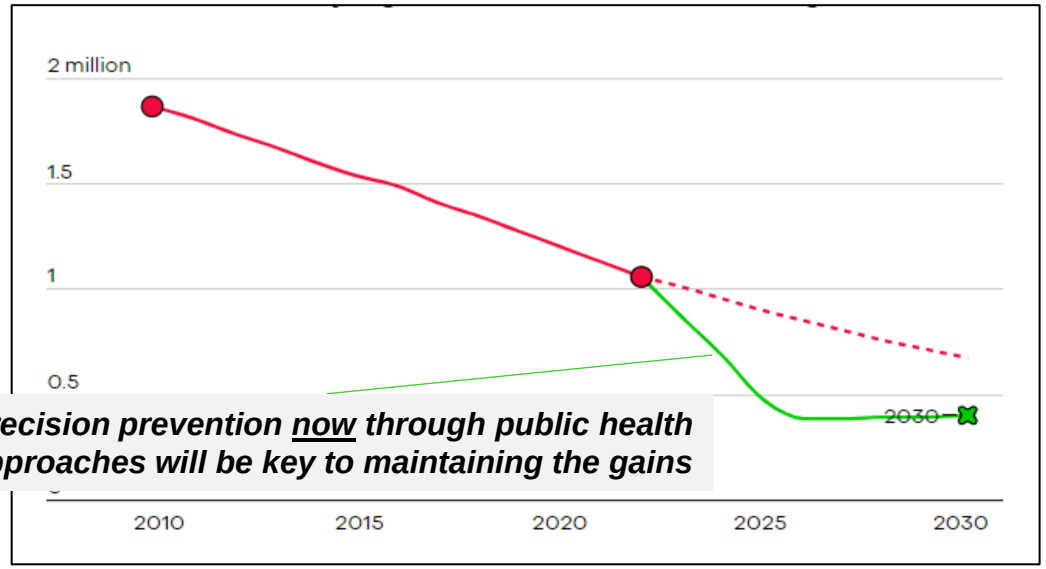
K = thousands; M = millions **Source**: The Global Fund 2023 Results Report Link

Currently Offtrack to Meet 2030 UNAIDS Targets

AIDS-related deaths: Progress towards the UNAIDS target



New HIV infections: progress towards the UNAIDS target



Precision prevention <u>now</u> through public health approaches will be key to maintaining the gains

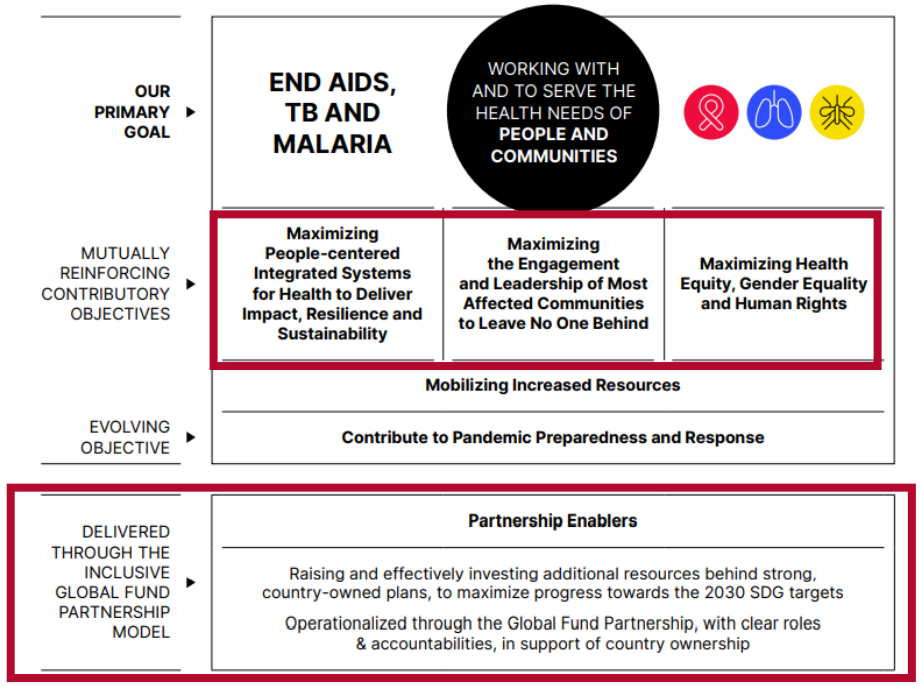
Historical trend | Continuation of recent trend | Global target pathway to 2030 | 2030 target

Macroeconomic conditions, such as **economic recessions, climate change, ongoing recovery from COVID disruptions**, continue to challenge partner governments capacity to reach 2030 UNAIDS targets

Source: The Global Fund 2023 Results Report 2023 Link

Global Fund Strategy (2023-2028)

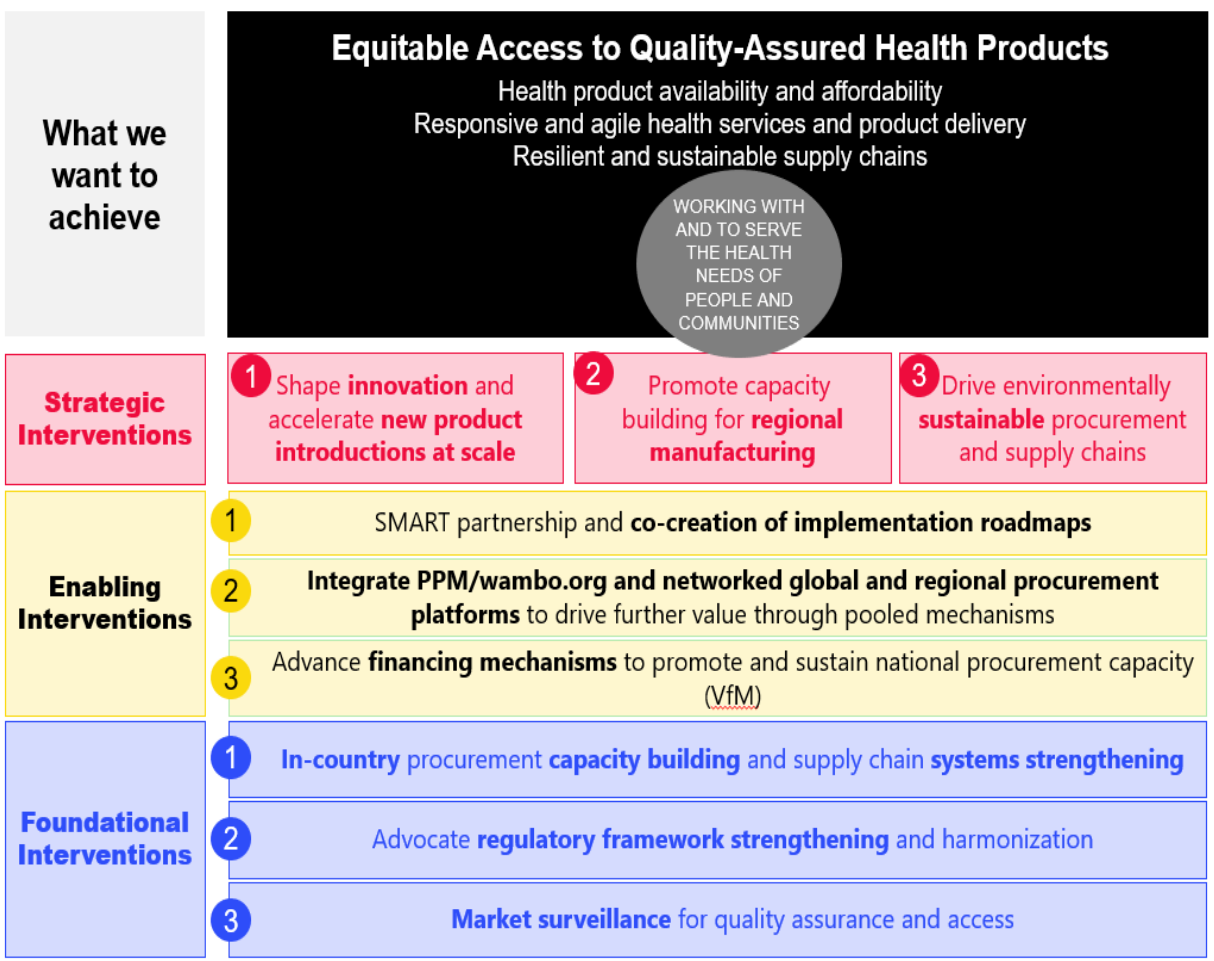
Fighting Pandemics and Building a Healthier and More Equitable World



1. **Across all three diseases, an intensified focus on prevention.** We have made better progress on saving lives than on reducing infections, but to end the pandemics, we have to cut new infections dramatically, including among key and vulnerable populations.
2. **Much more emphasis on integrated, people-centered services,** rising above disease silos to build RSSH that protect people from multiple pathogens, address their holistic needs and underpin health and well-being for all.
3. **A more systematic approach to supporting the development and integration of community systems for health,** recognizing the vital role they play in combatting the three diseases and reinforcing system resilience and sustainability.
4. **A stronger role and voice for communities living with and affected by the diseases,** reinforcing this unique strength of the Global Fund partnership and tackling barriers to effective participation and leadership, to put the most affected communities at the center of everything we do.
5. **Intensified action to address inequities, human rights and gender-related barriers,** scaling up and strengthening current activities, building on our experience, and raising our level of ambition.
6. **Greater emphasis on programmatic and financial sustainability,** to ensure the progress we achieve can withstand shocks and reversals, and that the momentum can be sustained.
7. **Greater focus on accelerating the equitable deployment of and access to innovations,** working with partners to take an end-to-end view to rapidly address bottlenecks to deployment to those most in need.
8. **Much greater emphasis on data-driven decision-making,** by investing in systems and capabilities to enable the rapid generation, analysis and use of high-quality, disaggregated data.
9. **Explicit recognition of the role the Global Fund partnership can and should play in pandemic preparedness and response,** given the knock-on impact of pandemics on HIV, TB and malaria, the unique positioning of the Global Fund in this arena, and acknowledging the need to define roles and responsibilities in collaboration with our partners.
10. **Clarity on the roles and accountabilities of Global Fund partners across every aspect of the Strategy** to ensure we hold each other mutually accountable in delivering this Strategy.

Two components of the Global Fund's strategy include **ensuring equitable deployment of and access to HIV innovations** as well as **having an intensified focus on prevention.** **Continued, effective partnerships will be necessary to achieve global targets.**

NextGen Market Shaping Approach to support Global Fund Strategy



Global

1. Work with industry and partners to **drive innovation that is accessible** to LMICs
2. Secure supply that is **affordable, available, quality and responsiveness**
3. Foster **South-to-South collaboration**

Regional

1. Leverage PPM / wambo.org procurement mechanism to collaborate with partners to build regional procurement capacities
2. Stimulate and sustain regional manufacturing capacity building

National

1. Use grant investments and country partners to strengthen in-country supply chain systems
2. Ensure quality assured health products will be distributed effectively and efficiently to communities and people we serve

HIV Investment Priorities for Grant Cycle 7

$6.5 billion **Total HIV allocation for the upcoming 3-year grant cycle (known as GC7), which will start in 2024**

Supported Geographies

Countries Receiving GC7 HIV Allocation

Investment Priorities

The Global Fund has **laid out prioritized, evidence-based and rights-based interventions that demonstrate impact for consideration in funding requests**. These include, for the first time, program essentials, which are critical to address the ambitious goals set out in the HIV global strategies. When part of national programs, program essentials will support countries to achieve national targets and can be funded by either the Global Fund or other sources.

ARVs play **a critical role** in helping countries **deliver on program essentials** related to **HIV primary prevention, elimination of vertical transmission, HIV treatment and care, and differentiated service delivery**.

Source: The Global Fund HIV Information Note for Grant Cycle 7 Link; Global Fund Overview of the 2023-2025 Allocations Link

Prioritized Products for Introduction & Scale-up in GC7

Product Area	Objective	Products
Diagnostics/ screening *HIV*	**Improve case finding, accelerate self-care and prevention**	• HIV self-testing[2] • Early infant diagnosis (EID), including at point of care
Diagnostics/ screening *Coinfections and comorbidities*	**Accelerate rapid diagnosis of important coinfections and comorbidities**	• Diagnostics for advanced HIV disease, especially fungal and next generation lateral flow urine lipoarabinomannan assay (LF-LAM) • Dual HIV/Syphilis rapid diagnostic tests (RDT) • Multi-disease RDTs: sexually transmitted infections (STI)/HIV/Hepatitis • Multi-disease molecular testing: TB/Hepatitis/HIV/drug resistance • Human papillomavirus (HPV) nucleic acid amplification tests (NAATs) for screening • Hepatitis C self-tests
Prevention *HIV*	**Expand choice, accelerate self-care, enable people-centered services**	• Pre-exposure prophylaxis (PrEP) – dapivirine vaginal ring and long-acting injectable cabotegravir • Long-acting opioid substitution therapy (OST)
Management *HIV treatment and care*	**Achieve early and sustained viral suppression**	• Dolutegravir-based regimens, including 10mg dolutegravir for children • Point of care (POC) technologies for viral load measurement, including early infant diagnosis (EID) • Point of care CD4 count testing (Visitect)
Prevention and management *Coinfections and comorbidities*	**Optimize HIV management to reduce morbidity and mortality**	• TB preventive therapy: 3HP (weekly isoniazid and rifapentine for 3 months) • Hepatitis B and C antiviral drugs • Liposomal amphotericin B (single high dose) for Cryptococcal infection
Devices/ technology	**Accelerate differentiation and digital and virtual service delivery** for people-centered services	• Use of virtual interventions, including the use of both telephone and internet-based platforms to reach and engage clients in HIV testing, prevention, and treatment.
	Enhance public health surveillance and response	• Rapid survey tools • Geo-mapping (mapping using geospatial data)

The Global Fund has clearly outlined products that principal recipients (PRs) should consider to **prioritize for introduction and scale-up in the upcoming cycle,** including **optimal ARVs for HIV treatment and prevention (both pre- and post-exposure prophylaxis)**.

Global Fund is **working closely with suppliers and partners to support access to these innovations** to accelerate introduction at scale.

Given tight fiscal envelopes, the Global Fund is **strongly urging PRs to consider cost-effective approaches to drive budget efficiencies and ensure value for money**.

Source: The Global Fund HIV Information Note for Grant Cycle 7 Link

ARV Market Overview

The Global Fund **benefits significantly from the work of** governments, affected communities, suppliers, donors, technical agencies, procurement agents, and other partners to **create a healthy, sustainable ARV market**.

US$1.8B

2021 ARV market size in generic accessible low- & middle-income countries (CHAI estimate)

US$430M

Average annual value of ARVs ordered through PPM from 2020-2022

THE GLOBAL FUND

The Global Fund manages ~25% of the orders for the ARV market through the Pooled Procurement Mechanism (PPM). Some Principal Recipients (PRs) use Global Fund funding to directly procure commodities.

Source: Adapted graphic from CHAI HIV Market Report 2022 (Link); PPM ARV procurement data from 2020-2022

Power of Partnerships: TLD Case Study

$75 TLD PRICE → **<$45**

Breakthrough annual price for generic TLD announced by partner coalition in 2017

Reduced annual price announced by the Global Fund in 2023

Ministries of Health, affected communities, suppliers, donors, technical agencies, procurement agents, and other partners have played an instrumental role in driving the TLD introduction since 2017.

<100K DTG ACCESS → **>19M**

PLHIV taking TLD (or other DTG-based regimens) in LMICs in 2017

PLHIV taking TLD (or other DTG-based regimens) in LMICs today

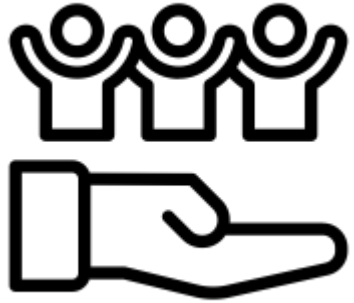
K = thousands; M = millions; LMICs = low- and middle-income countries; DTG = dolutegravir; PLHIV = people living with HIV; **Source**: UNAIDS Press Release, 21 09 2017 Link; Global Fund Press Release, 30 August 2023 Link; CHAI 2023 HIV Mid-Year Market Memo Link; CHAI 2017 HIV Market Report 2018 Link

Call to Action

Continue to drive **product innovation**, and **accelerate equitable access** to quality assured products

Foster **south-south collaboration** to bring supply close to high volume demand

Drive advances across the supply chain to **reduce environmental footprint**



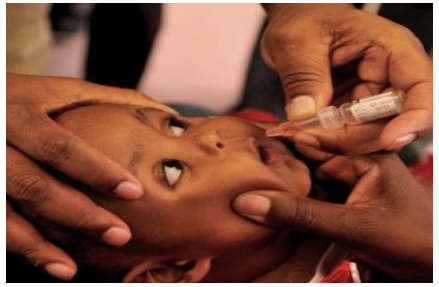
Establish public-private partnerships to **reach underserved communities and the most vulnerable**

Priorities in the fight against HIV

Mark Edington
Head of Grant Management
The Global Fund

James Maloney
Deputy Director, Office of HIV/AIDS,
Global Health Bureau, USAID

Khadija Jamaloodien
Chief Director, Sector Wide Procurement, National Department of Health, Republic of South Africa



Priorities for South Africa in the fight against HIV

Khadija Jamaloodien
Chief Director: Sector Wide Procurement
National Department of Health: South Africa

30 October 2023

SOUTH AFRICAN CONTEXT

62 million population of South Africa

R 260 billion public health medicine budget

84% of the population dependent on public health

8,5% of GDP spent on health care

+4,500 health establishments in the public sector

70,000 pediatric patients receiving ART treatment

5,8 million Patients receiving treatment for HIV

7,8 million Population living with HIV

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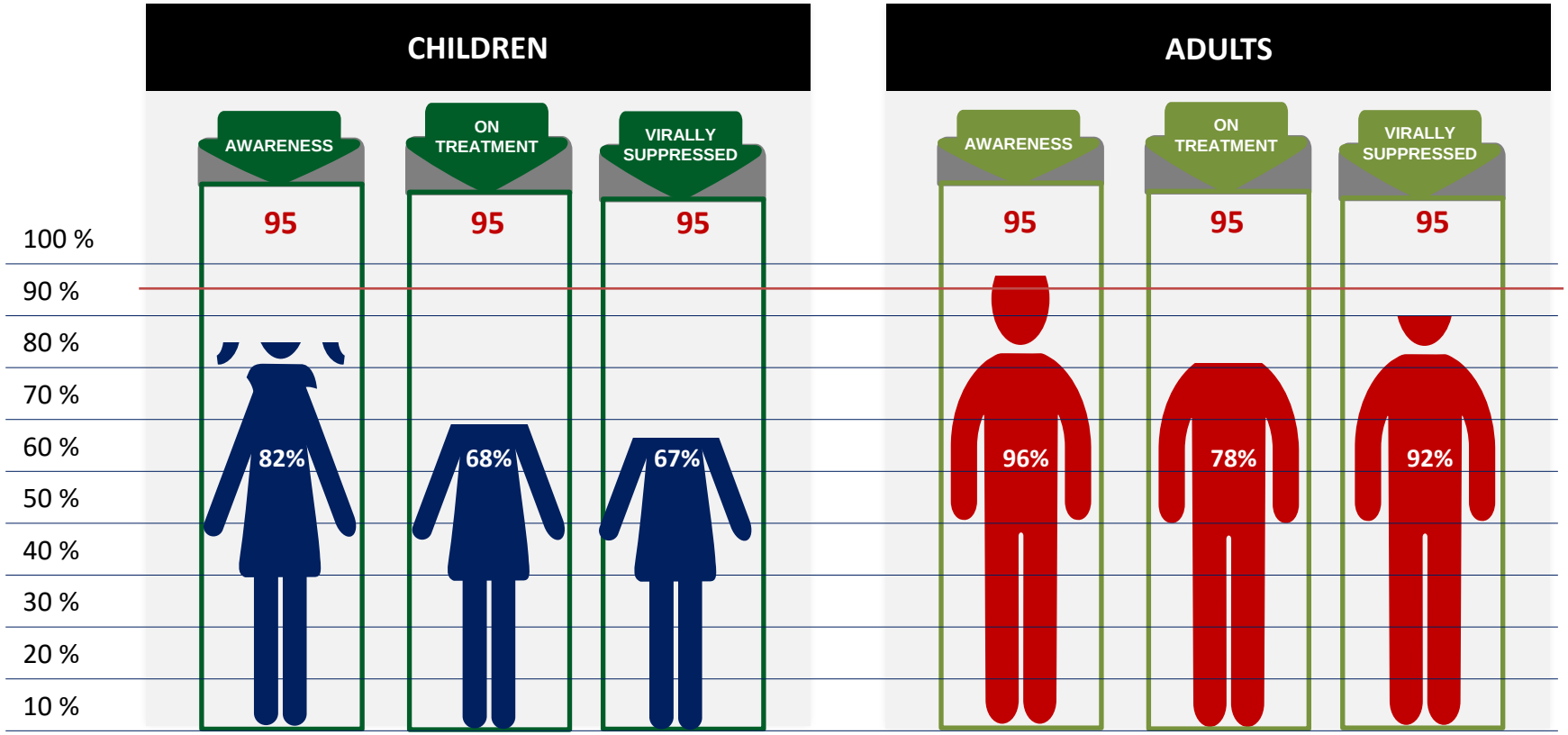
STRATEGY TO DRIVE IMPROVEMENT IN 95-95-95 CASCADE

95-95-95 Target vs Actual (Public & Private sector) March 22 -August 2023



AWARENESS:

- Status is strong as 1st 95 target was achieved

ON TREATMENT:

- The number of PLHIV has increased by 119,000
- The number of PLHIV on ART has increased by 190,485
- The number of PLHIV virally suppressed has increased by 481,436

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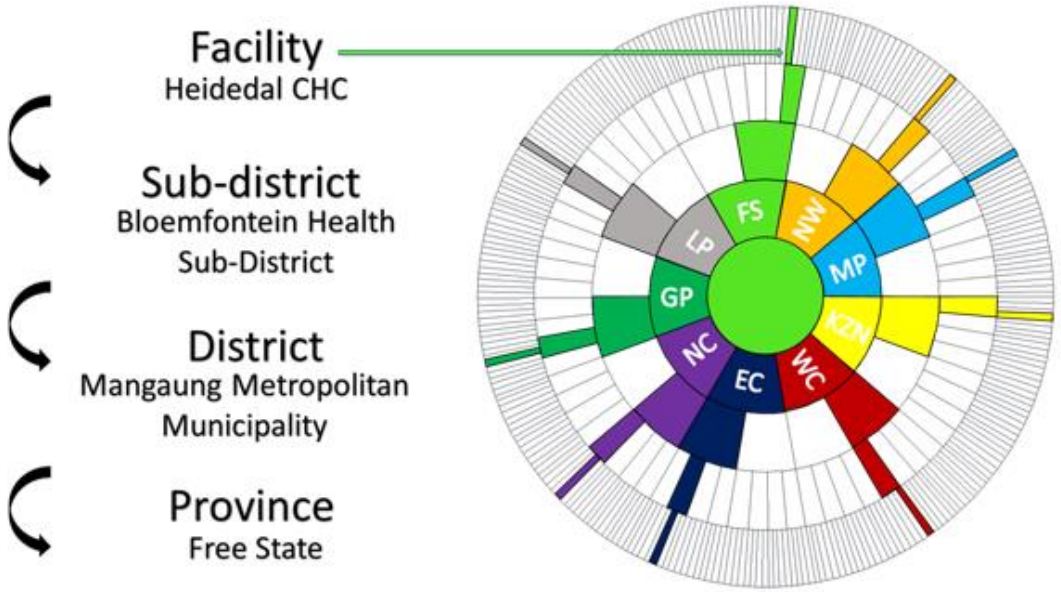
STRATEGY TO DRIVE IMPROVEMENT IN 95-95-95 CASCADE

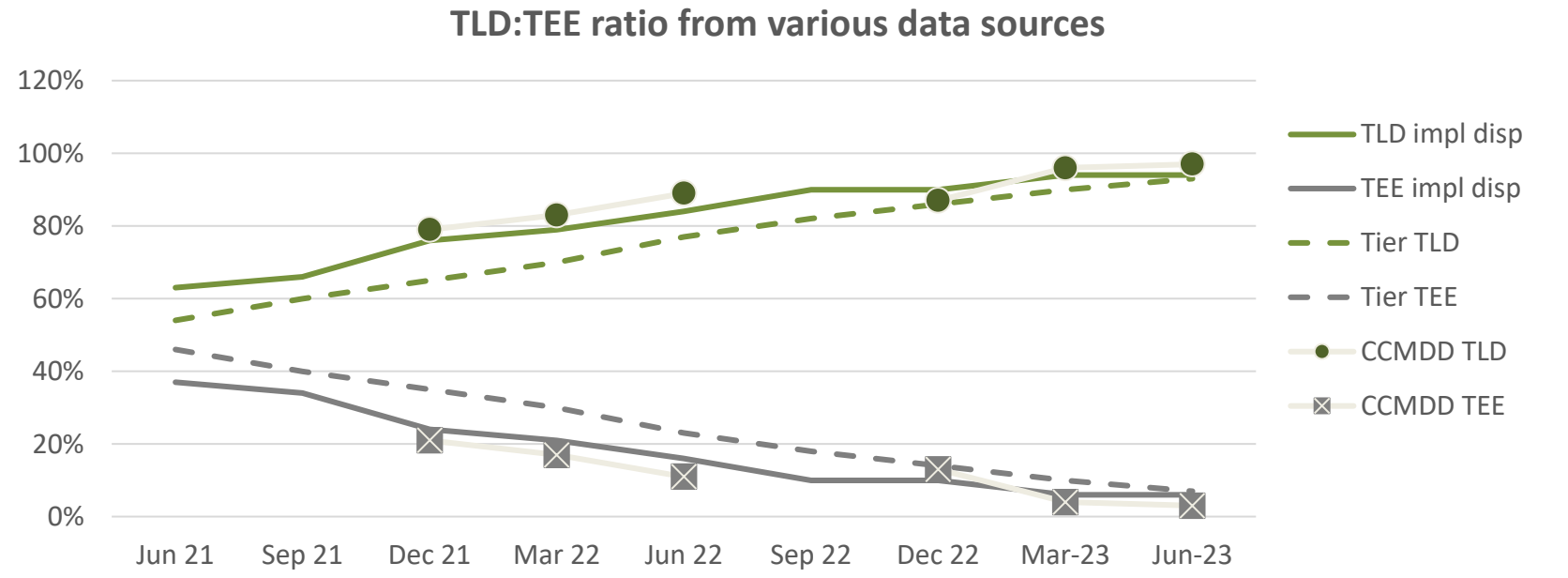
- Adopt the Nerve Centre Approach to strengthen Nerve Centres across the country and create a culture of improvement.
- Prioritise activities of Nerve Centres to focus on 2nd 95
- Prioritise 100 facilities across all provinces to anchor the Approach and scale best practices

100 facilities, 17 districts, 9 provinces

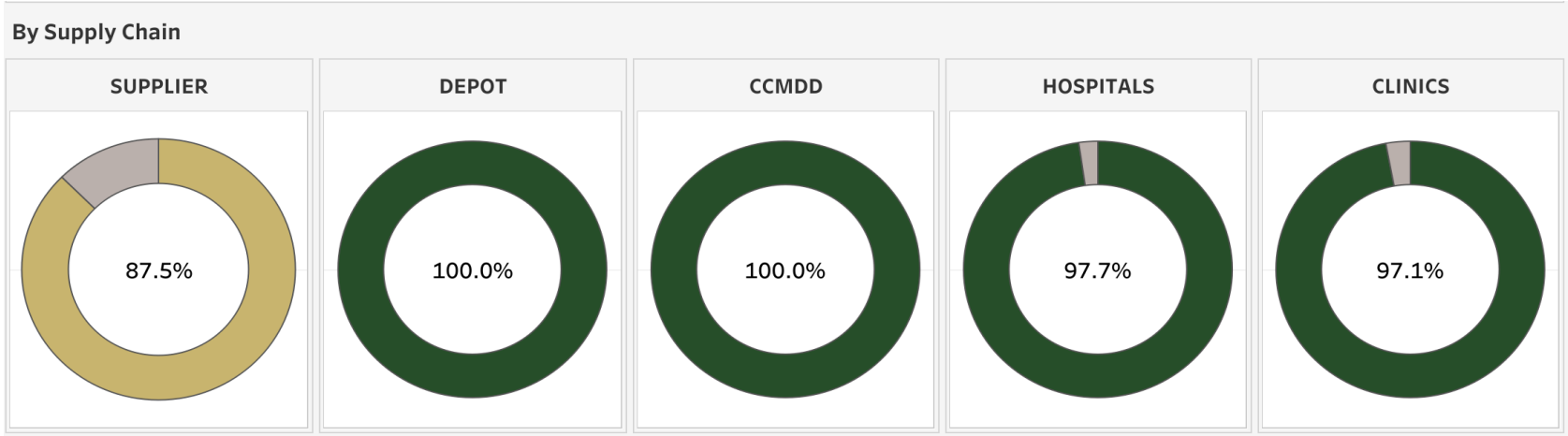


TLD TRANSITION - ALL DATA POINTS INDICATING GOOD PROGRESS

ACHIEVING 93:7 TLD:TEE RATIO AS OF JUNE 2023, 1ST LINE ART AVAILABILITY >90%



- CCMDD is our chronic medicines distribution that serves ~2m clients on ARV
- Implied dispensing based on stock movement in provinces and amount supplied from suppliers
- TIER data is facility-level data at patient level



MEDICINE AVAILABILITY

- 1st Line ARV availability maintained at over 90% nationally

RECENT DEVELOPMENTS

ARV GUIDELINES

- The 2023 ART Clinical Guidelines was published in April 2023
- Training in progress
- pDTG & 4-in-1 (ABC/3TC/LPV/r) included in Guidelines
- TLD preferred regimen for all cohorts

MULTI-MONTH DISPENSING

- Already offered Nationally
- Nationally 55% of Patients are receiving 3MMD via CCMDD
- Use of 84/90s has increased to 400K per month
- Increase 84/90s uptake resulted in Supplementary Tender

CHANGES TO THE 1ST LINE ART REGIMENS
CHANGES IN THE 2023 ART GUIDANCE FOR CLHIV

Age & Weight	Current Regimen	New Regimen
Birth to 4 weeks and up to 2.9kg	AZT + 3TC + NVP	AZT + 3TC + NVP
Over 4 weeks and 3 kg to 19.9kg	ABC + 3TC + LPV/r	ABC + 3TC + DTG
20 to 29.9kg	ABC + 3TC + DTG	ABC + 3TC + DTG
30 to 34.9kg	ABC + 3TC + DTG	TDF + 3TC + DTG
Over 35kg	TDF + 3TC + DTG	TDF + 3TC + DTG

TDF: ≥ 30kg; DTG 10mg: ≥3kg and ≥4 weeks old

DTG should be part of the preferred first line ART regimen for all adults, adolescents, children and infants living with HIV, including women of child-bearing potential but excluding neonates.

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PAEDIATRIC ARV PRODUCT OPTIMISATION:

ALL CHILDREN SHOULD BE SWITCHED TO OPTIMAL FORMULATIONS TO ENHANCE ADHERENCE, CLINICAL EFFICACY, ADMINISTRATION, PALATABILITY AND TO REDUCE SIDE EFFECTS

PRODUCT	OPTIMAL PRODUCT	ELIGIBILITY
Abacavir 20mg/ml oral solution	Abacavir 120mg, Lamivudine 60mg dispersible tablet	Weight 3 -24.9kg
Abacavir 60mg dispersible/crushable tablet	Abacavir 120mg, Lamivudine 60mg dispersible tablet	Weight 3 -24.9kg
Lamivudine 10mg/ml oral solution	Abacavir 120mg, Lamivudine 60mg dispersible tablet	Weight 3 -24.9kg
Abacavir 600mg and Lamivudine 300mg tablet	Abacavir 600mg, Lamivudine 300mg, Dolutegravir 50mg tablet	If on Dolutegravir 50mg tablet
Lopinavir 40mg, Ritonavir 10mg capsule	Dolutegravir 10mg dispersible tablet	Weight 3 -19.9kg
Lopinavir 80mg, Ritonavir 20mg/ml oral solution	Dolutegravir 10mg dispersible tablet	Weight 3 -19.9kg
Lopinavir 100mg and Ritonavir 25mg film coated	Dolutegravir 10mg dispersible tablet	Weight 3 -19.9kg
Lopinavir 200mg, Ritonavir 50mg film coated tablet	Dolutegravir 10mg dispersible tablet	Weight 14-19.9kg
Lopinavir 200mg, Ritonavir 50mg film coated tablet	Dolutegravir 50mg tablet	Weight >=20kg

Initiate the process of switching

All Children above the age of 10 years and over 30kgs should be switched if eligible to TLD: Tenofovir 300mg, Lamivudine 300mg, Dolutegravir 50mg tablet

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PAEDIATRIC REGIMENS UPDATE - 2023

Switching REGARDLESS of viral load

CURRENT REGIMEN	CRITERIA FOR SWITCH	REGIMEN IF CHANGE INDICATED
TEE ABC/3TC/EFV or NVP AZT/3TC/EFV or NVP AZT/3TC/DTG LPV/r or ATV/r regimen for < 2 years	Switch all to DTG irrespective of VL	Best first option: TLD* *no renal dysfunction *≥ 10 years old *≥ 30kg If patient does not qualify for TDF ABC/3TC/DTG If patient has ABC hypersensitivity AZT/3TC/DTG

ADULT REGIMENS UPDATE - 2023

Switching DEPENDANT on viral load

PREFERRED REGIMEN

1st line in adults, including pregnant women and adolescents (> 30kg and > 10 years of age)

TLD

Concomitant TB:

If on a rifampicin-containing regimen:

- Double up the DTG by giving it 12 hours after TLD
- Continue this boosting dose until 2 weeks after stopping rifampicin

ALL COHORTS - REGIMENS UPDATE - 2023

Switching DEPENDANT on viral load

VL CONSIDERATIONS	CURRENT REGIMEN	CRITERIA FOR SWITCH	REGIMEN IF CHANGE INDICATED
<1000	Any LPV/r or ATV/r for > 2 years	Switch all to DTG-containing regimen	TLD*
Adult / Adolescent			
2 or more VLs > 1000 taken 2 or more years after starting PI	On LPV/r or ATV/r Adherence less than 80%	Switch all to DTG-containing regimen Don't do HIVDRT	TLD*
	On LPV/r or ATV/r Adherence of 80% or more	Don't qualify for same day switch May require HIVDRT	Individualised treatment may be required
Children < 10 years OR < 30 kg			
	On LPV/r or ATV/r	Don't qualify for same day switch May require HIVDRT	May need 4-in-1 (ABC/3TC/LPV/r) OR ABC/3TC/DTG OR individualised treatment

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*no renal dysfunction
*≥ 10 years old
*≥ 30kg

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DTG RESISTANCE AND DRUG RESISTANCE TESTING

Adult / Adolescent

Patients on DTG-containing regimens:

Two or more VL > 1000

On TLD for less than 2 years

Maintain adherence and repeat VL at 6 months

Children < 10 years OR < 30 kg

On TLD for at least 2 years

Adherence > 80%

Discuss with expert

May need INSTI HIVDR

Gatekeeping instituted

NOVEL ART FORMULATIONS

DAPIVIRINE RING

- Reviewed by the South African National Essential Medicines List Committee (NEMLC)
- Indication:
  - Preventing HIV acquisition in women
- Main comments:
  - Currently no evidence comparing Dapivirine to the current Standard of Care (TE)
- Future plans:
  - Study being done that may provide evidence for future reviews by NEMLC

NOVEL ART FORMULATIONS

CAB-LA

(LONG ACTING CABOTEGRAVIR)

Reviewed by NEMLC:

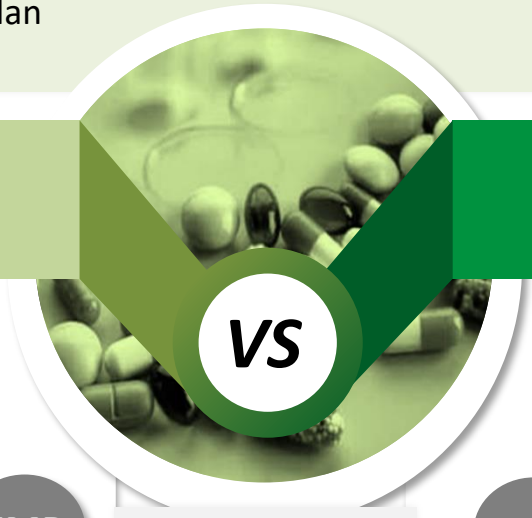
- High certainty of efficacy from the evidence, however several factors had to be considered before being approved:
  - Registration with SAHPRA
  - Evidence of efficacy in regimens not requiring oral lead-in doses
  - Cost information needs to be available

Notes:

- Innovator product has been licensed. Sublicences for cheaper drug production have been issued to 3 companies
- Affordability in the context of shrinking budgets is a concern. It is unlikely that generically produced versions will be available before the next ARV tender

HIV AND TUBERCULOSIS (TB)- NOVEL BPAL-L REGIMEN

- The HIV co-infection rate among notified TB cases in South Africa was 59% (2019)
- The 9-month RR-TB regimen has been replaced by a 6-month treatment regimen
- The 6-month regimen is part of the TB Recovery Plan
- Can be used in PLHIV



OLD REGIMEN		BPaL-L
BDQ, LZD, LFX, CFZ, INH HD, PZA, EMB	Formulation	BDQ, LZD, LFX, Pa
9 Months	Duration	6 Months
3488	Pill Burden	908

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CONCLUSION

- **Shift in focus from treatment to prevention**, which informs our cascade.
- **New and optimal** products available for children which are more effective, more palatable and easier to administer.
- **New supplementary tender** contains specifications for new paediatric formulations and increased uptake in TLD 84's/90's.
- **Accurate information on patient numbers** per regimen remains a challenge, but we will work with suppliers to ensure availability.

THANK YOU

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Break

Panel 1: Challenges in reaching 2030 ARV goals

Kenly Sikwese
Executive Director, Afrocab
Treatment Access Partnership

Dr. Aleny Couto
Head of STI and HIV/AIDS program,
Mozambique Ministry of Health

Siobhan Crowley
Head of HIV, the Global Fund

Dr. Dianna Edgil
Chief, Supply Chain Health
Division, USAID

Khadija Jamaloodien
Chief Director, Sector Wide Procurement,
National Department of Health
Republic of South Africa



ARV Buyer Seller Summit 2023:

The Power of Partnerships in the Fight against HIV

30th October 2023

Maputo, Moçambique











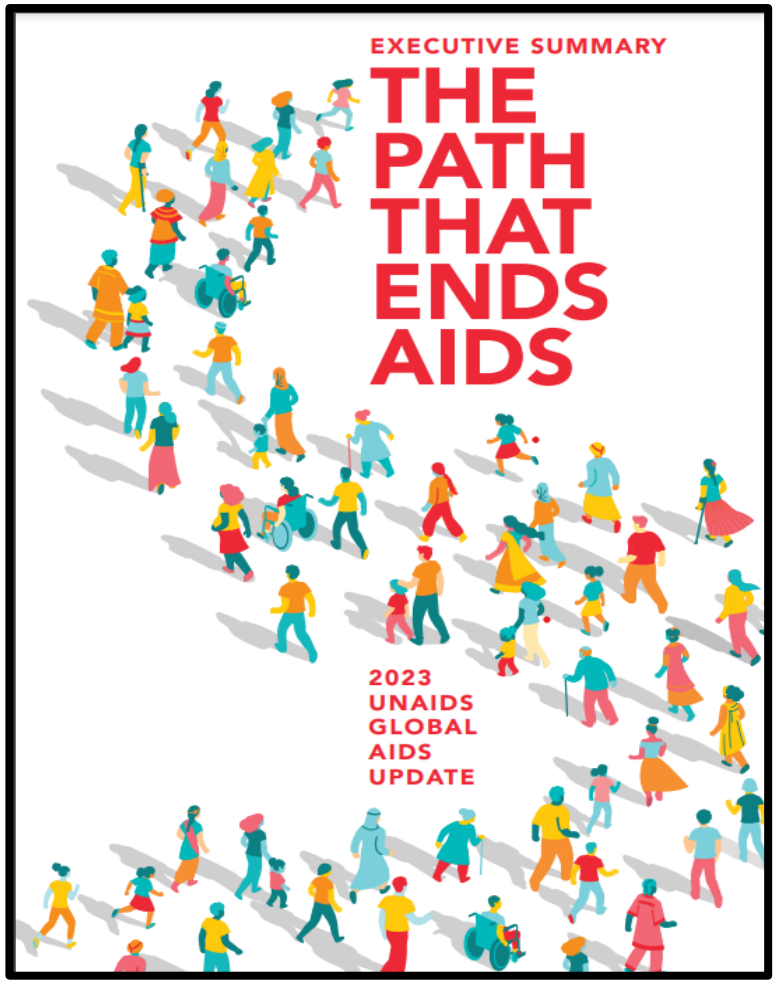
Challenges in reaching 2030 goals

REPÚBLICA DE MOÇAMBIQUE

Where are we ?

Context

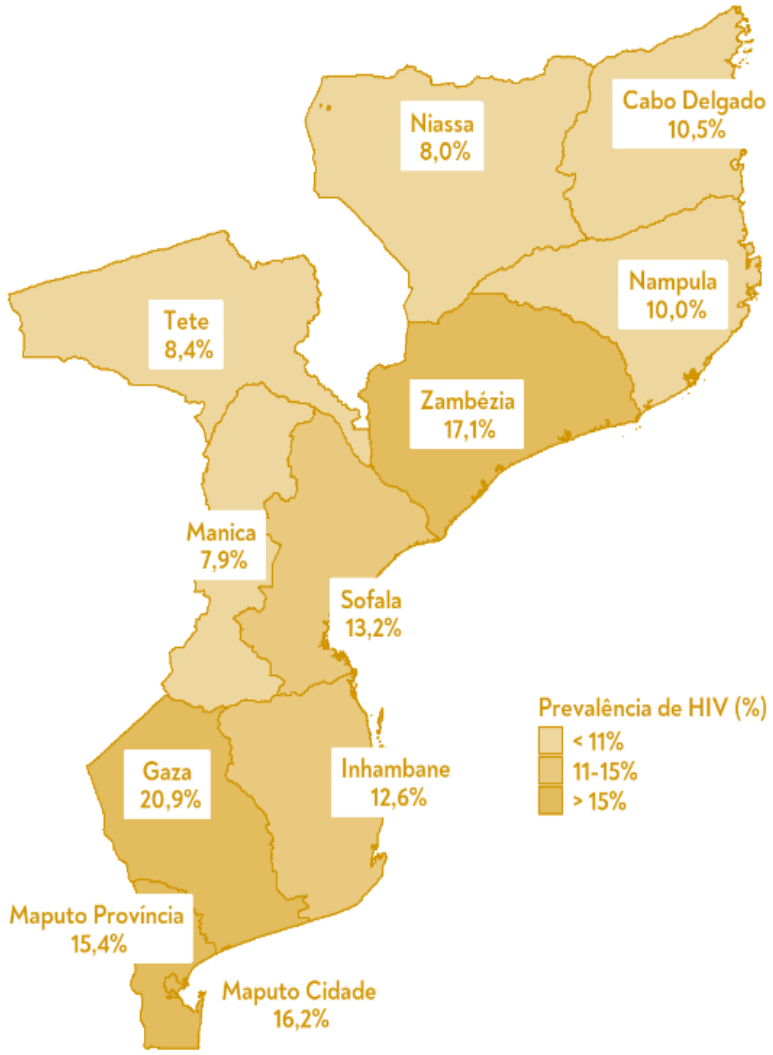
- Actually Globally 38.4 milion [33.9 –43.8] people are living with HIV
- UNAIDS data show that today, 29.8 million of the 39 million [33.1 million–45.7 million] people living with HIV globally are receiving life-saving treatment.
- An additional 1.6 million people received HIV treatment in each of 2020, 2021 and 2022



FAST-TRACK
ENDING THE AIDS EPIDEMIC BY 2030

Country Context

- Mozambique has the sixth highest HIV prevalence in the world
- And is in the fourth position in terms of new HIV infections, behind South Africa, Nigeria and Russia and in the second position in relation to the countries of the Southern African region;
- Adolescent girls and young women, as well as other vulnerable populations and key populations, continue to be the most affected by the epidemic

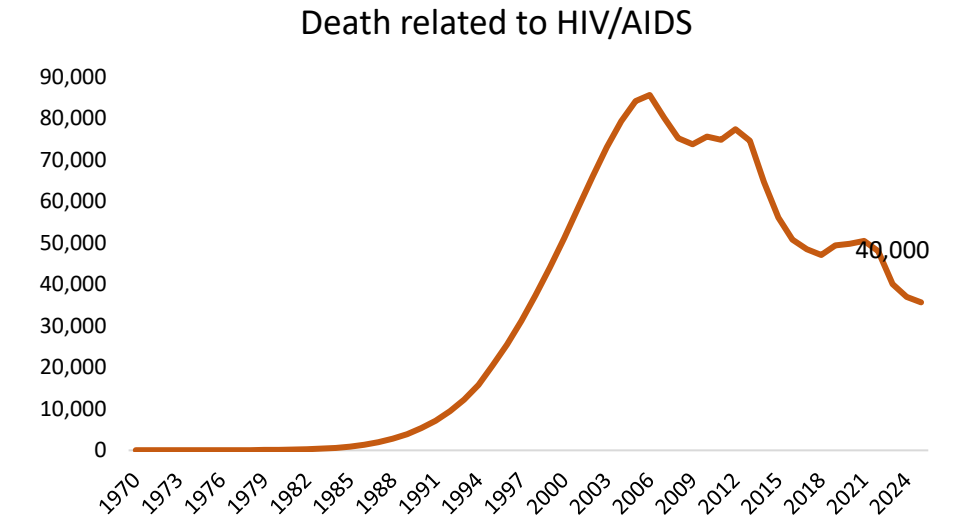


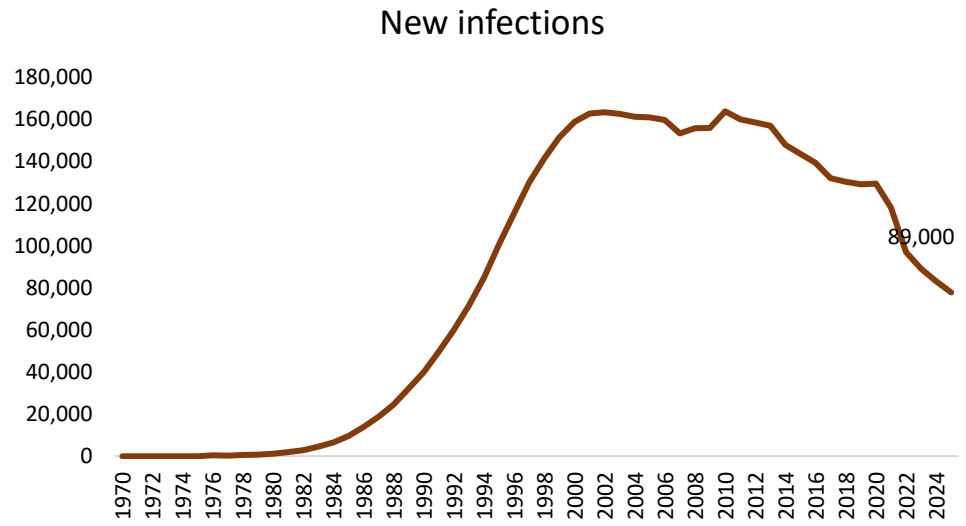
HIV Prevalence : 12.5% (INSIDA 2021

Epidemiology

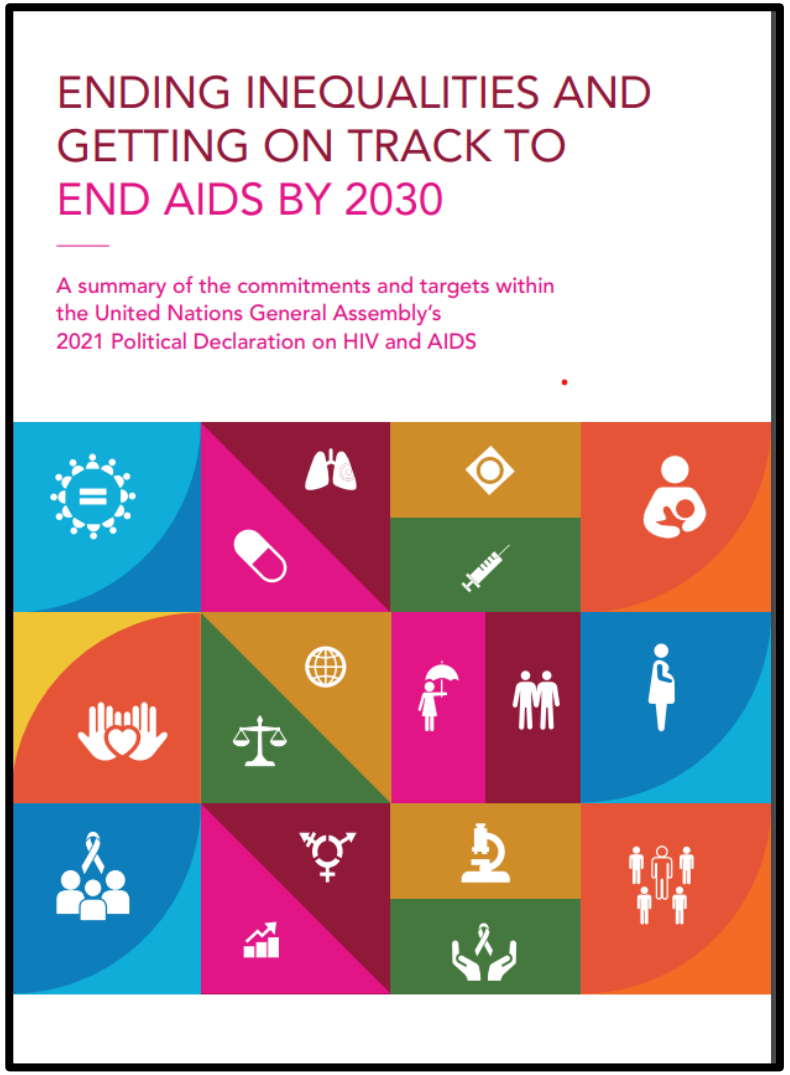
Mozambique, 2023	Total	Percentage PLHIV National	Confidence Interval
N° PLHIV	2 465 000		2.29-2.67
N° Adults 15+ LHIV	2 315 000	94%	2.15-2.51
N° Men 15+ LHIV	825 000	33%	760,000-900,000
N° Women 15+ LHIV	1 490 000	60%	1.38-1.62
N° Pregnant Women HIV+	123 000		92,000 - 164,000
N° Children LHIV	150 000	6%	125,000 - 170,000
New Infections	89 000		74,000 - 112,000
New infections per day	244		
New infection adults	77 000		64,000-96,000
New infections children	12 000		9,000-16,000
Death related to HIV/AIDS	40 000	2%	34,000 - 47,000

Source: Estimates UNAIDS 2022, Spectrum 6.29



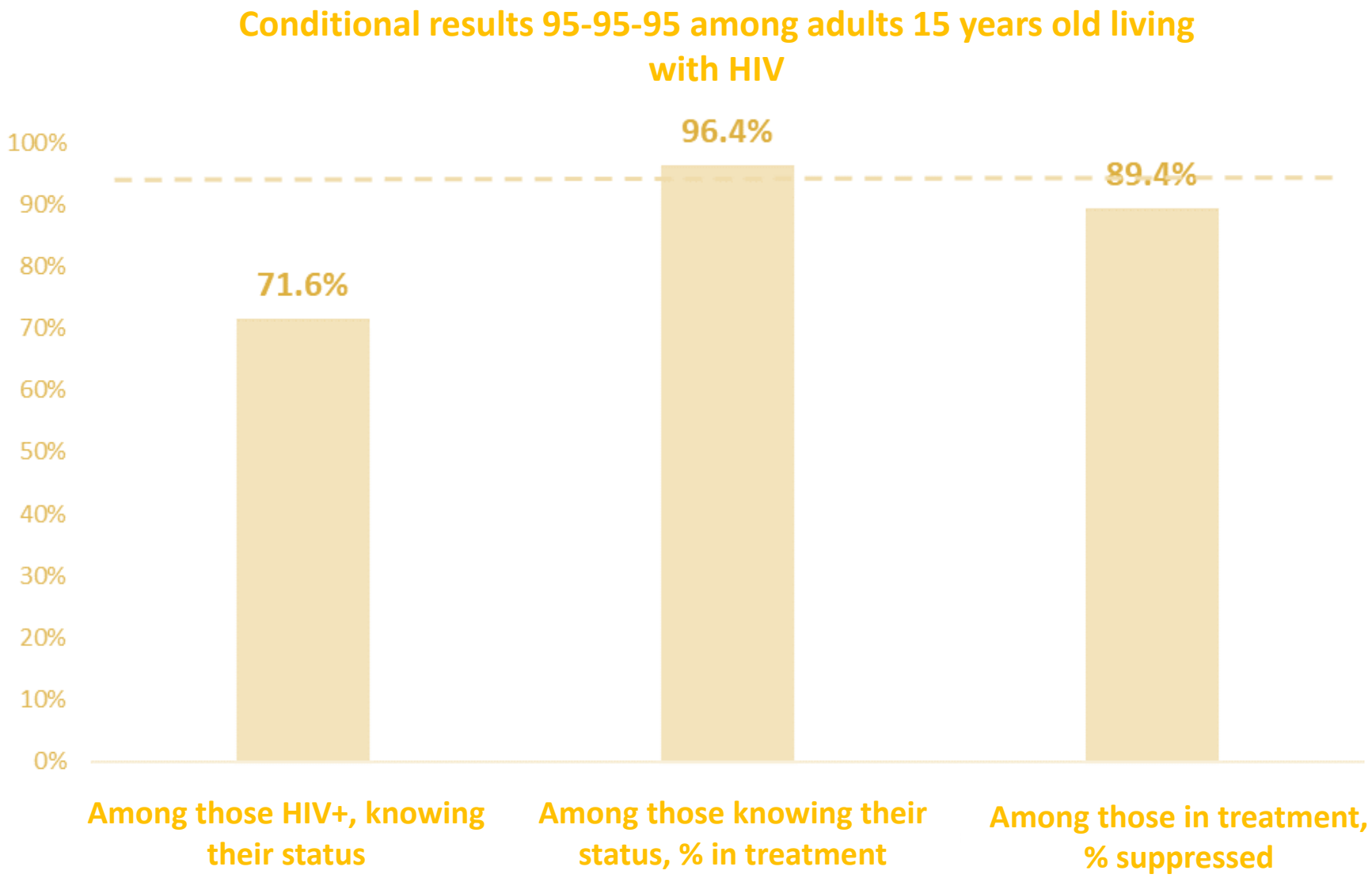


Strategic Framework



1. Reduce new HIV infections
2. Reducing AIDS-related deaths and improving the well-being of PLHIV

HIV Cascade


Conditional results 95-95-95 among adults 15 years old living with HIV
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
71.6%
96.4%
89.4%
Among those HIV+, knowing their status
Among those knowing their status, % in treatment
Among those in treatment, % suppressed

What are the challenges ?

Challenges....!!

Programatic

Systems

Programatic Challenges....!!

- Limited investment in prevention that is not reaching the right population
- High HIV transmission mother to child, leading to high number of CLHIV
- Linkage and retention to care (impact on treatment cascade mainly in viral suppression)
- Service Deliver with limitations and don’t serv to the populations needs
- Identification of new HIV cases

Programatic Challenges....!!

- Hard reach populations (Adolescents, Key Populations and Men)
- Gender inequalities and limited empowerment of PLHIV (women)
- High stigma and discrimination towards Key Populations, Adolescents
- Limited focused approach's due to the innumerous gaps in the system

Systems Challenges....!!

- Weak health systems that supports integration based on efficiencies
- Weak community leadership
- Limited local data and costing studies to support the guidelines
- Limited domestic investment and resources
- Universal health coverage (still not consolidated)

Obrigado – Khanimanbo

Panel 1: Challenges in reaching 2030 ARV goals

Kenly Sikwese
Executive Director, Afrocab
Treatment Access Partnership

Dr. Aleny Couto
Head of STI and HIV/AIDS program,
Mozambique Ministry of Health

Siobhan Crowley
Head of HIV, the Global Fund

Dr. Dianna Edgil
Chief, Supply Chain Health
Division, USAID

Khadija Jamaloodien
Chief Director, Sector Wide Procurement, National
Department of Health
Republic of South Africa

Panel 2: The role of partnership, innovation and South to South collaboration in accelerating progress

Ellie Marsh (Moderator)
Senior Manager, Strategy, Procedure and Innovation, the Global Fund

Sandra Nobre
Head of Business Development, the Medicines Patent Pool

Claudia Martínez
Programme Manager, Access to Medicine Foundation

Uzoma Ezeoke
Executive Director
Emzor Pharmaceutical Industries Ltd

Simo Masondo
Vice President, Government Affairs & Trade Development, Cipla

Boitumelo Semete-Makokotlela
CEO, South African Health Products Regulatory Authority

THE GLOBAL FUND

PEPFAR

USAID
FROM THE AMERICAN PEOPLE

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

MINISTÉRIO DA SAÚDE

Thank You

ARV Buyer Seller Summit 2023: The Power of Partnerships in the Fight against HIV

30 October – 1 November 2023

Maputo, Mozambique

31 October Tuesday – Day 2: Demand forecasting and planning to maximize partner engagement

Time	Session – Rovuma Room		Speakers
8:30 – 8:35		***Introductions**:* Cathal Meere	
8:35 – 9:15	**Demand & procurement**	***Lessons learned:*** Country experience on demand forecasting & Q&A	Ivandra Libombo, Chief of Planning Department, Central de Medicamentos e Artigos Medicos (CMAM), Mozambique
9:15 – 10:15		***Lessons learned:*** Procurement experience [panel discussion] & Q&A	***Moderator:*** Daniel Kiesa, Market Advisor, Office of HIV/AIDS, USAID ***Panel***: Ivandra Libombo Jordi Balleste, Unit Chief, Strategic Fund Procurement, Procurement and Supply Management – Pan American Health Organization Alan Pringle, Global Supply Chain Director, GHSC-PSM/Chemonics Wesley Kreft, PPM Project Director, Iplus Solutions Ignace Ndekezi, Head of Department, Procurement and Quantification, Rwanda Medical Supply
10:15 – 10:30		***Forward looking**:* 18-month consolidated forecast from big buyers	Shanil Ramlall, Africa Resource Centre
10:30 – 10:45	*BREAK*		
10:45 – 11:15	**Case study:** Approach to strengthen demand forecast and planning		Martin Auton, Head of Planning, Procurement and Transaction Management, the Global Fund
11:15 – 12:00	**Quality Assurance updates**		Deusdedit Mubangizi, Unit Head, Prequalification Unit, Regulation and Prequalification Department, World Health Organization Sandrine Cloëz, Specialist, Pharmaceutical Products Quality Assurance, the Global Fund
12:00 – 12:30	**Closing remarks: Call to action**		***Moderator:*** Cathal Meere Mozambique Ministry of Health South Africa National Department of Health The Global Fund PEPFAR
12:30 – 13:30	*Lunch*		
13:30 – 17:30	**One on One sessions**		Breakout rooms

Demand and Forecasting team Mozambique MOH

Ivandra Libombo

Chief of Planning Department, Central de Medicamentos e Artigos Medicos (CMAM), Mozambique

Pharmacist, specialist in public health planning

REPÚBLICA DE MOÇAMBIQUE
MINISTÉRIO DA SAÚDE
Central de Medicamentos e Artigos Médicos, IP

ARVs Technical Working Group

- Quantification
- Demand
- Procurement

Lessons learned with the ART implementation

CMAM
Central de Medicamentos
e Artigos Médicos

Maputo, Mozambique – October 2023

Context

- **Initially**, Mozambique **questioned the sustainability** of HIV treatment due to high costs and limited availability of ARVs, with treatment focused to urban areas.
- The development **of optimized ARVs**, coupled with steady cost reductions, expanded manufacturing capacity and improved safety for patients enabled improved retention during the past years
- The **safety** and **low toxicity** of current formulations lead to the expansion of DSDm, decreasing the frequency of the pickup visits and reaching the most rural populations through community health workers.
- In addition, improvements in pack size and **packaging** have led to a significant **reduction in volume**, benefiting the entire supply chain and operational costs.
- These advances lead Mozambique to **reach over 2.1 million patients** with improved viral suppression and quality of life, resulting in reduction on HIV related mortality and new infections.

ART Optimization over time

Estavudina/Lamivudina Nevirapina 30/40

- Twice a day
- 15 days induction
- High toxicity
- Monthly monitoring
- CD4+ 250 threshold

Zidovudina/Lamivudina/ Nevirapina

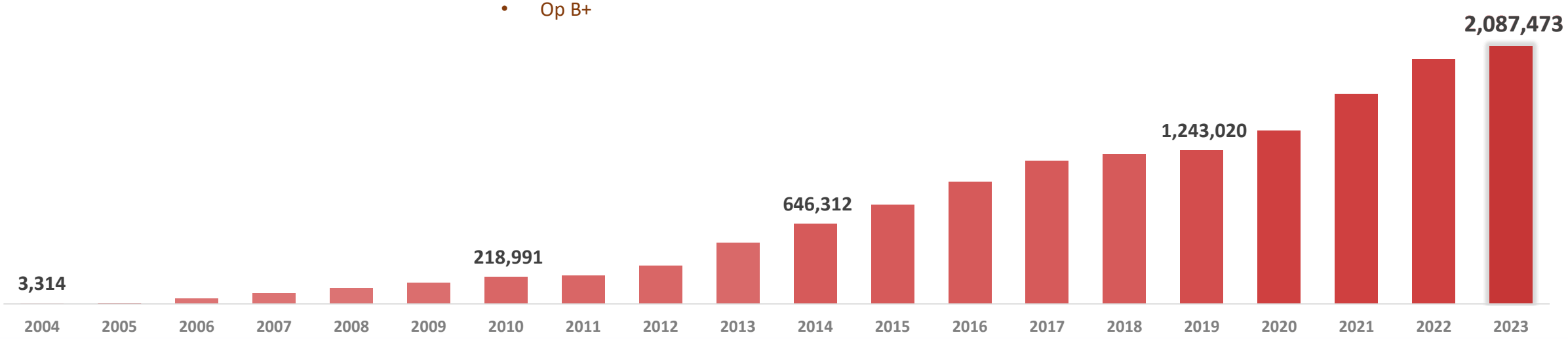
- Twice a day
- 15 days induction
- Anemia risk
- Regular monitoring
- CD4+ 350 threshold
- Op B+

Tenofovir/Lamivudina/ Efavirenz

- Once a day
- Less toxicity
- 3MMD/DSDm
- Spacing clinic visits
- Test and Start

Tenofovir/Lamivudina/ Dolutegravir

- Less toxicity
- 90's Bottles
- 6MMD & DDD community
- 6/12months visits
- Viral Load monitoring



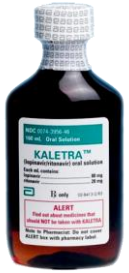
ART Optimization over time

Pediatric formulations consumption

Nevirapine (NVP)

2018

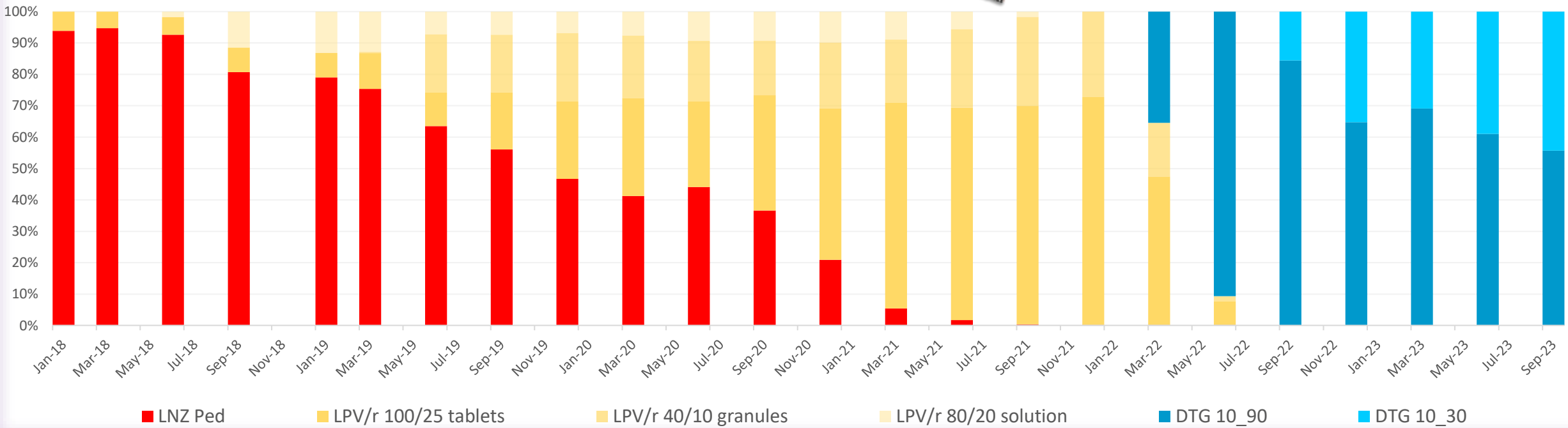
Lopinavir (LPVr Tabs/OS/Pellets/Granules)



2018 - 2022

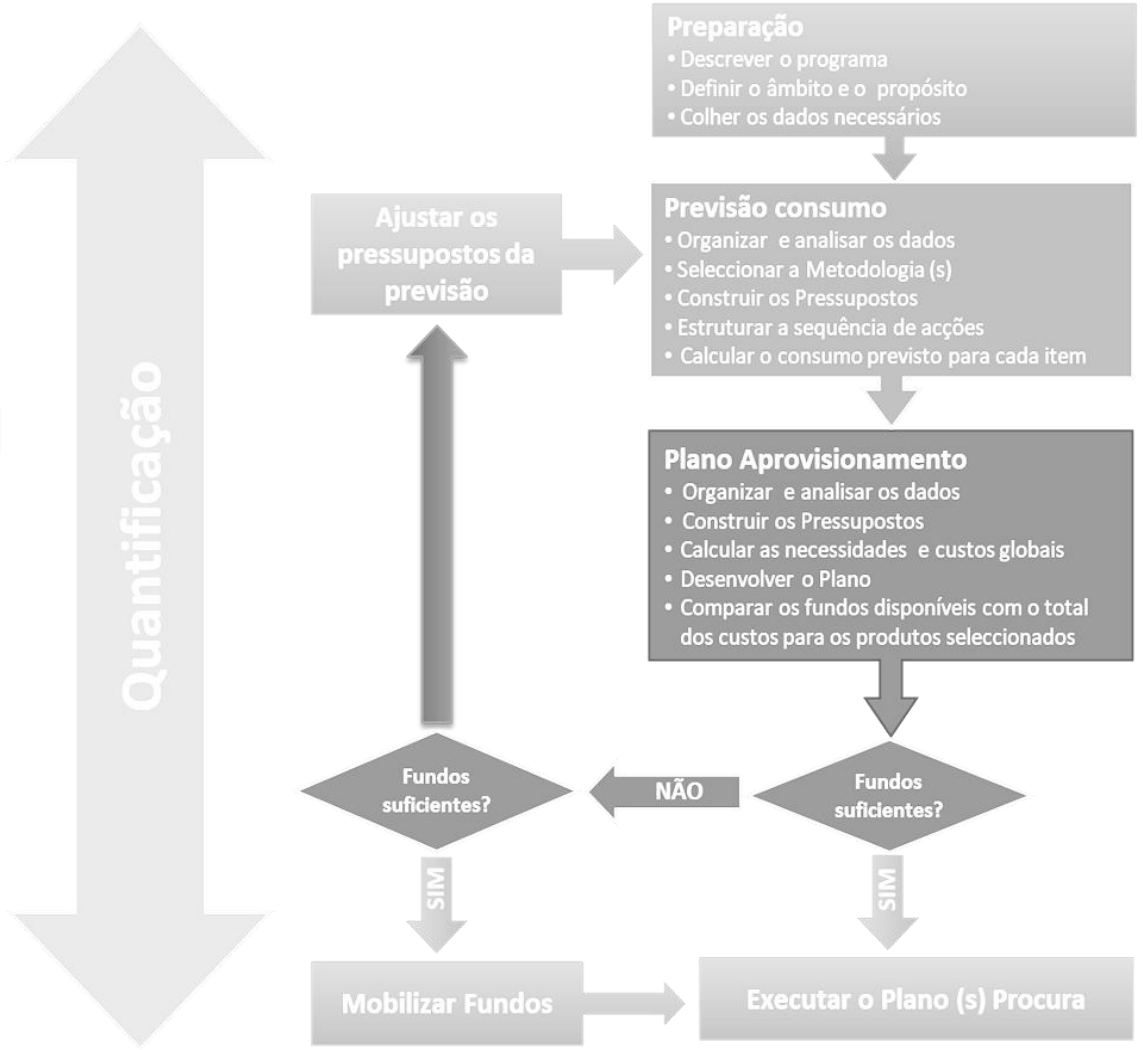
Dolutegravir (pDTG)

2022 – to date



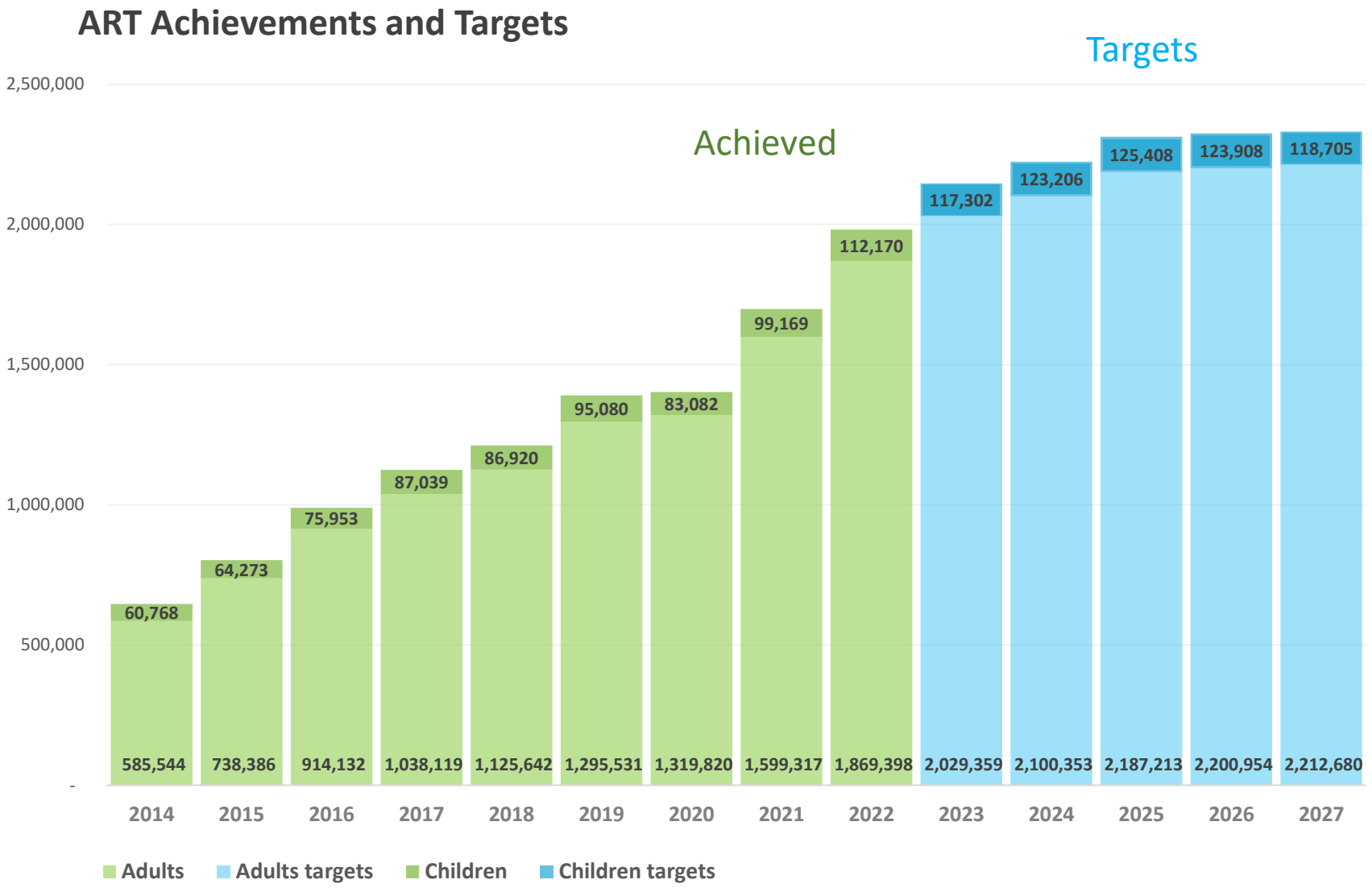
% of the total consumption by formulation

ARVs Quantification



ARVs Quantification

Patient Targets to Medicines



1. Targets

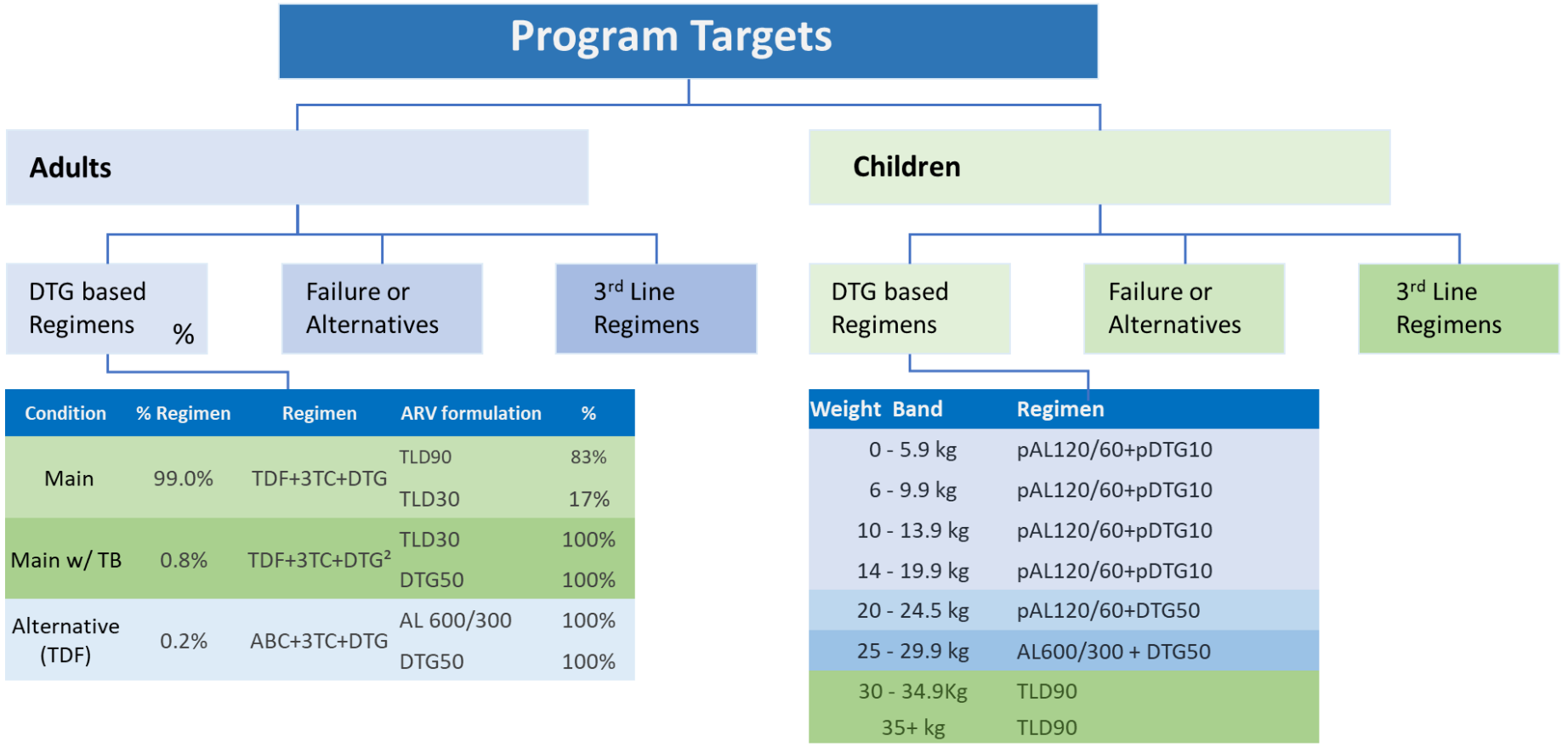
By the National HIV/AIDS Control Program, estimated by year, based in the regular studies (INSIDA 21) and Spectrum outputs.

Considering the adjustment for consumption:

- A percentage of patients skip a tablet per month, over the year represents part of a pack
- Patients that miss the picking during a period (defaulting).
- Patients lost to follow-up (after defaulting services for 2 months).

ARVs Quantification

Forecast Tree - Consumption Estimate



Condition	% Regimen	Regimen	ARV formulation	%
Main	99.0%	TDF+3TC+DTG	TLD90	83%
			TLD30	17%
Main w/ TB	0.8%	TDF+3TC+DTG[2]	TLD30	100%
			DTG50	100%
Alternative (TDF)	0.2%	ABC+3TC+DTG	AL 600/300	100%
			DTG50	100%

Weight Band	Regimen
0 - 5.9 kg	pAL120/60+pDTG10
6 - 9.9 kg	pAL120/60+pDTG10
10 - 13.9 kg	pAL120/60+pDTG10
14 - 19.9 kg	pAL120/60+pDTG10
20 - 24.5 kg	pAL120/60+DTG50
25 - 29.9 kg	AL600/300 + DTG50
30 - 34.9Kg	TLD90
35+ kg	TLD90

3. Forecast Tree

Estimate the consumption for each formulation in Pack:

a) Targets calculate by adults and children per month

X

b) % patients expected in DTG based Regimens (Line)

X

c) % Each regimen

X

d) % Formulations of each regimen

X

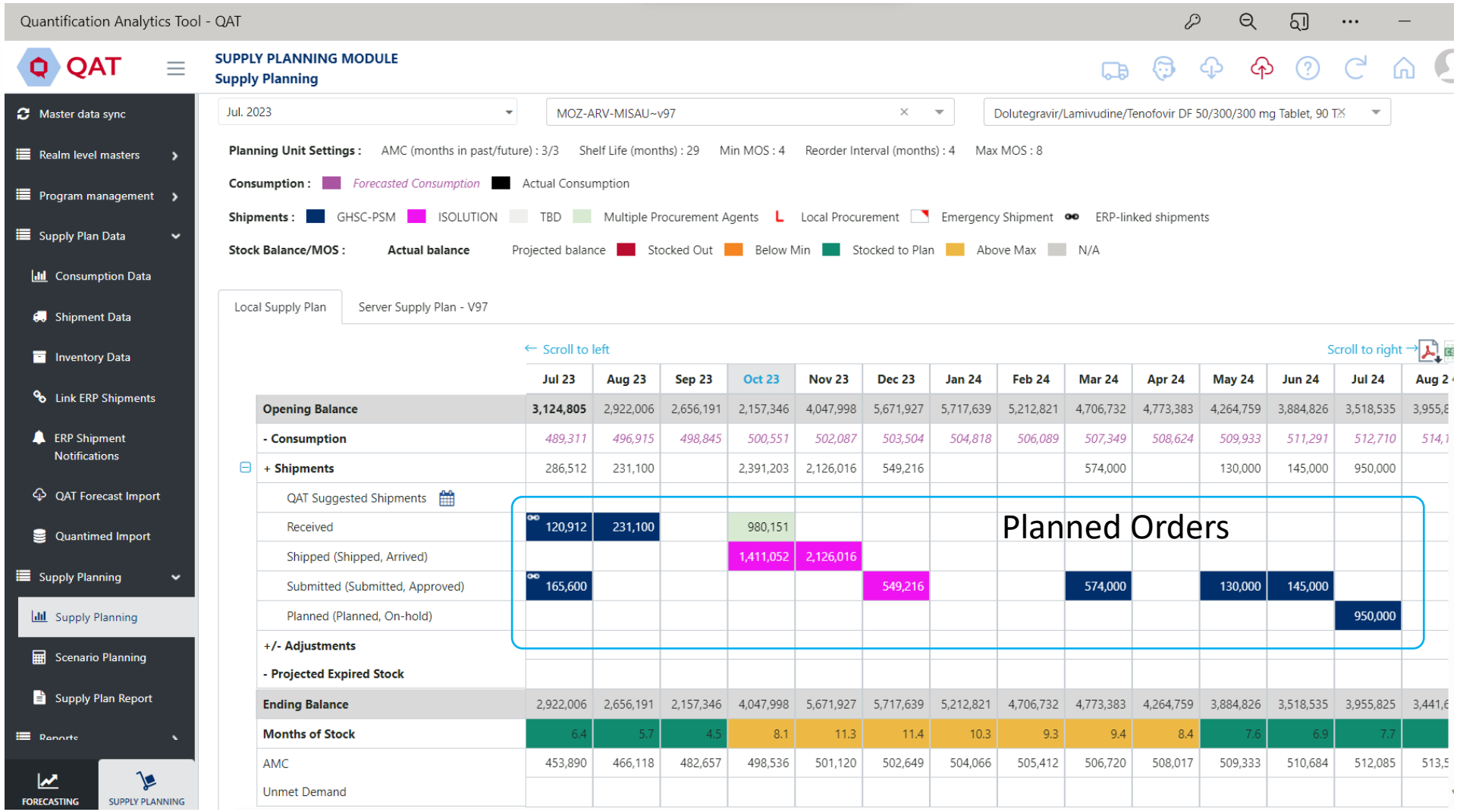
e) Number **pills** per month

/

f) Number of **pills per pack**

ARVs Quantification

Supply Plan and Orders follow up



	Jul 23	Aug 23	Sep 23	Oct 23	Nov 23	Dec 23	Jan 24	Feb 24	Mar 24	Apr 24	May 24	Jun 24	Jul 24	Aug 2
Opening Balance	3,124,805	2,922,006	2,656,191	2,157,346	4,047,998	5,671,927	5,717,639	5,212,821	4,706,732	4,773,383	4,264,759	3,884,826	3,518,535	3,955,8
- Consumption	*489,311*	*496,915*	*498,845*	*500,551*	*502,087*	*503,504*	*504,818*	*506,089*	*507,349*	*508,624*	*509,933*	*511,291*	*512,710*	*514,1*
+ Shipments	286,512	231,100		2,391,203	2,126,016	549,216			574,000		130,000	145,000	950,000	
QAT Suggested Shipments														
Received	120,912	231,100		980,151										
Shipped (Shipped, Arrived)				1,411,052	2,126,016									
Submitted (Submitted, Approved)	165,600					549,216			574,000		130,000	145,000		
Planned (Planned, On-hold)													950,000	
+/- Adjustments														
- Projected Expired Stock														
Ending Balance	2,922,006	2,656,191	2,157,346	4,047,998	5,671,927	5,717,639	5,212,821	4,706,732	4,773,383	4,264,759	3,884,826	3,518,535	3,955,825	3,441,6
Months of Stock	6.4	5.7	4.5	8.1	11.3	11.4	10.3	9.3	9.4	8.4	7.6	6.9	7.7	
AMC	453,890	466,118	482,657	498,536	501,120	502,649	504,066	505,412	506,720	508,017	509,333	510,684	512,085	513,5
Unmet Demand														

4. Supply Plan

Estimate how much is needed to order based:

a) Stocks (expiry dates)

b) Estimated consumption

c) Orders already in process by Supplier and Status (with RO and PO)

d) Adjustments

e) Max and Min of Stock

f) Months of Stock

g) Prices by procurement mechanism.

h) Calculate the needed shipments

ARVs Quantification

Supply Plan and Orders follow up

CMAM Central de Medicamentos e Artigos Médicos

Planned Orders

2 Shipments lines in Supply Plan

Multiple Request Orders (RO) and Purchase Orders (POs), delivered or in transit to different Warehouses in Country

Quantification Analytics Tool - QAT

QAT

SUPPLY PLANNING MODULE
Supply Planning

- Master data sync
- Realm level masters
- Program management
- Supply Plan Data
  - Consumption Data
  - Shipment Data
  - Inventory Data
  - Link ERP Shipments
  - ERP Shipment Notifications
  - QAT Forecast Import
  - Quantimed Import
- Supply Planning
  - Supply Planning
  - Scenario Planning
  - Supply Plan Report
- Reports

FORECASTING | SUPPLY PLANNING

Jul. 2023 | MOZ-ARV-MISAU~v97

Planning Unit Settings : AMC (months in past/future) : 3/3 | Shelf Life (months) : 29 | Min MOS : 4

Consumption : *Forecasted Consumption* | Actual Consumption

Shipments : GHSC-PSM | ISOLUTION | TBD | Multiple Procurement Agents

Stock Balance/MOS : **Actual balance** | Projected balance | Stocked Out | Below Min

Local Supply Plan | Server Supply Plan - V97

← Scroll to left

	Jul 23	Aug 23	Sep 23	Oct 23	Nov
Opening Balance	**3,124,805**	2,922,006	2,656,191	2,157,346	4,047
- Consumption	*489,311*	*496,915*	*498,845*	*500,151*	*502*
+ Shipments	286,512	231,100		2,391,203	2,126
QAT Suggested Shipments					
Received	120,912	231,100		980,151	
Shipped (Shipped, Arrived)				1,411,052	2,126
Submitted (Submitted, Approved)	165,600				
Planned (Planned, On-hold)					
+/- Adjustments					
- Projected Expired Stock					
Ending Balance	2,922,006	2,656,191	2,157,346	4,047,998	5,671
Months of Stock	6.4	5.7	4.5	8.1	
AMC	453,890	466,118	482,657	498,536	501
Unmet Demand					

Shipment Details - Planning Unit - Dolutegravir/Lamivudine/Tenofovir DF 50/300/300 mg Tablet, 90 Tablets

Emergency Shipment | Do not include in projected balance | ERP-linked shipments | Read only Data | Shipment data entry

← Scroll to left | Scroll to right →

	Aug 23	Sep 23	Oct 23	Nov 23	Dec 23	Jan 24	Feb 24
Shipments	231,100		2,391,203	2,126,016	549,216		

Active	ERP flag	QAT Shipment ID	Status *	Receive Date *	Shipment Mode *	Procurement agent *	Local Proc. Agent	Proc. Agent Order No.	Alternate Reporting Unit (ARU) *	Order Quantity (ARU) *
☑	☐	116063	Received	03-OCT-23	Sea	ISOLUTION	☐	RQ20595 PO2300578 RR12859 Zimpeto	Dolutegravir/3TC/TDF 50/300/300 mg Tab, 90 Tab	103,900
☑	☐		Received	05-OCT-23	Sea	GHSC-PSM	☐	RO10173250 PO10025494 RR12871 RR12872 Zimpeto	Dolutegravir/3TC/TDF 50/300/300 mg Tab, 90 Tab	116,251
☑	☐	75941	Received	10-OCT-23	Sea	ISOLUTION	☐	RQ21314 PO12301158 RR1266 RR1269 Beira	Dolutegravir/3TC/TDF 50/300/300 mg Tab, 90 Tab	500,000
☑	☐	135423	Received	25-OCT-23	Sea	ISOLUTION	☐	PO12301969 RR12916 Zimpeto	Dolutegravir/3TC/TDF 50/300/300 mg Tab, 90 Tab	260,000
☑	☐	76177	Shipped	30-OCT-23	Sea	ISOLUTION	☐	RQ21314 PO12301160	Dolutegravir/3TC/TDF 50/300/300 mg Tab, 90 Tab	370,020
			Shipped	30-OCT-23	Sea	ISOLUTION	☐	RQ21314 PO12301159	Dolutegravir/3TC/TDF 50/300/300 mg Tab, 90 Tab	120,000
			Shipped	30-OCT-23	Sea	ISOLUTION	☐	PO12301442 CO12301556	Dolutegravir/3TC/TDF 50/300/300 mg Tab, 90 Tab	491,000
☑	☐	128355	Shipped	30-OCT-23	Sea	ISOLUTION	☐	RQ21314 PO12301495	Dolutegravir/3TC/TDF 50/300/300 mg Tab, 90 Tab	430,032

Received

To be received

ARVs Quantification

Supply Plan coordination during Global Fund grants transition (GC6 21/23 to GC7 24/26)

CMAM Central de Medicamentos e Artigos Médicos

Shipments : GHSC-PSM | ISOLUTION | TBD | Multiple Procurement Agents | Local Procurement | Emergency Shipment | ERP-linked shipments

Stock Balance/MOS : **Actual balance** | Projected balance | Stocked Out | Below Min | Stocked to Plan | Above Max | N/A

Local Supply Plan | Server Supply Plan - V97

CG6 arrivals end by Dec23

GC7 arrivals begin by Jul/Aug23

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Scroll to right →

	Oct 23	Nov 23	Dec 23	Jan 24	Feb 24	Mar 24	Apr 24	May 24	Jun 24	Jul 24	Aug 24	Sep 24	Oct 24	Nov 24	Dec 24
Opening Balance	2,157,346	4,047,998	5,671,927	5,717,639	5,212,821	4,706,732	4,773,383	4,264,759	3,884,826	3,518,535	3,955,825	4,322,839	4,105,873	3,588,491	3,069,415
- Consumption	*500,551*	*502,087*	*503,504*	*504,818*	*506,089*	*507,349*	*508,624*	*509,933*	*511,291*	*512,710*	*514,197*	*515,755*	*517,382*	*519,076*	*520,832*
+ Shipments	2,391,203	2,126,016	549,216			574,000		130,000	145,000	950,000	881,211	298,789			1,560,400
QAT Suggested Shipments															
Received	980,151														
Shipped (Shipped, Arrived)	1,411,052	2,126,016													
Submitted (Submitted, Approved)			549,216			574,000		130,000	145,000						
Planned (Planned, On-hold)										950,000	881,211	298,789			1,560,400
+/- Adjustments															
- Projected Expired Stock															
Ending Balance	4,047,998	5,671,927	5,717,639	5,212,821	4,706,732	4,773,383	4,264,759	3,884,826	3,518,535	3,955,825	4,322,839	4,105,873	3,588,491	3,069,415	4,108,983

Grant bridging Period

Investing in our future — The Global Fund To Fight AIDS, Tuberculosis and Malaria

MOÇAMBICANOS E AMERICANOS JUNTOS NA LUTA CONTRA O HIV/SIDA — PEPFAR

Investing in our future — The Global Fund To Fight AIDS, Tuberculosis and Malaria

Orders arriving with **GC6 Funding Dec23**	Orders arriving with PEPFAR Funding	Orders starting to arrive **with GC7 Funding**

Coordination is critical to ensure a continuous supply of commodities during the Global Fund grant transition period.

ARVs Future Needs

Orders in process and Planned

	Ordered	Planned for the next 18-24 months			
ARVs	**Process**	**2024 1º Semester**	**2024 2º Semester**	**2025 1º Semester**	**2025 2º Semester**
Pediatric					
Abacavir/Lamivudine 120/60 mg Scored Dispersible Tablet 30 Tablets	264,577	-	191,358	243,000	246,000
Abacavir/Lamivudine 120/60 mg Scored Dispersible Tablet 60 Tablets	524,365	118,000	336,000	340,000	344,000
Darunavir 150 mg Tablet 240 Tablets	75	-	188	174	205
Dolutegravir 10 mg Scored Dispersible Tablet 30 Tablets	260,000	-	-	-	8,000
Dolutegravir 10 mg Scored Dispersible Tablet 90 Tablets	178,400	-	226,620	165,500	165,830
Lamivudine/Zidovudine 30/60 mg Dispersible Tablet 60 Tablets	1,490	910	1,200	1,200	1,200
Lopinavir/Ritonavir 100/25 mg Tablet 60 Tablets	-	-	-	900	700
Lopinavir/Ritonavir 40/10 mg Granule 120 Sachets	-	400	600	600	600
Total	1,228,907	119,310	755,966	751,374	766,535
Adult					
Abacavir/Lamivudine 600/300 mg Tablet 30 Tablets	290,122	48,000	157,000	161,000	168,000
Atazanavir/Ritonavir 300/100 mg Tablet 30 Tablets	98,328	75,443	100,500	106,500	111,300
Darunavir 600 mg Tablet 60 Tablets	1,538	1,530	2,070	2,380	2,660
Dolutegravir 50 mg Tablet 30 Tablets	707,048	-	315,000	330,893	337,235
Dolutegravir/Lamivudine/Tenofovir DF 50/300/300 mg Tablet 30 Tablets	1,995,582	1,200,000	2,169,800	2,084,433	2,142,520
Dolutegravir/Lamivudine/Tenofovir DF 50/300/300 mg Tablet 90 Tablets	5,311,535	-	3,690,400	3,270,000	3,300,000
Lamivudine/Tenofovir DF 300/300 mg Tablet 30 Tablets	751,649	10,000	627,884	731,923	851,312
Lamivudine/Zidovudine 150/300 mg Tablet 60 Tablets	-	-	-	21,000	38,500
Ritonavir [Norvir] 100 mg Film-Coated Tablet 60 Tablets	1,410	1,072	2,370	2,376	2,639
Lopinavir/Ritonavir 200/50 mg Tablet 120 Tablets	-	-	-	4,000	-
Total	9,157,212	1,336,045	7,065,024	6,714,505	6,954,166
Prophylaxis					
Nevirapine 10 mg/mL Suspension w/ Syringe 240 mL	76,600	-	141,000	100,000	102,000
Zidovudine 10 mg/mL Solution w/ Syringe 240 mL	74,080	-	118,300	77,000	78,500
Total	150,680	-	259,300	177,000	180,500

Quantities in Process
2023/2024 are already on order and/or in production by the suppliers.

Quantities Planned
Quantities planned to be ordered in the coming semesters.

The plan is reviewed quarterly (stocks, consumption, deliveries & prices) and new orders are committed quarterly or semi-annually.

Less than 12 months planned for orders

More than 12 months planned for funding advocacy.

1st semester 2024, Global Fund grant transition - GC6 to GC7.

Pediatric ARVs to be reviewed as new formulations become available.

TLD90 – is the main ARV cost driver

ARV Supply Chain

Warehousing and Distribution

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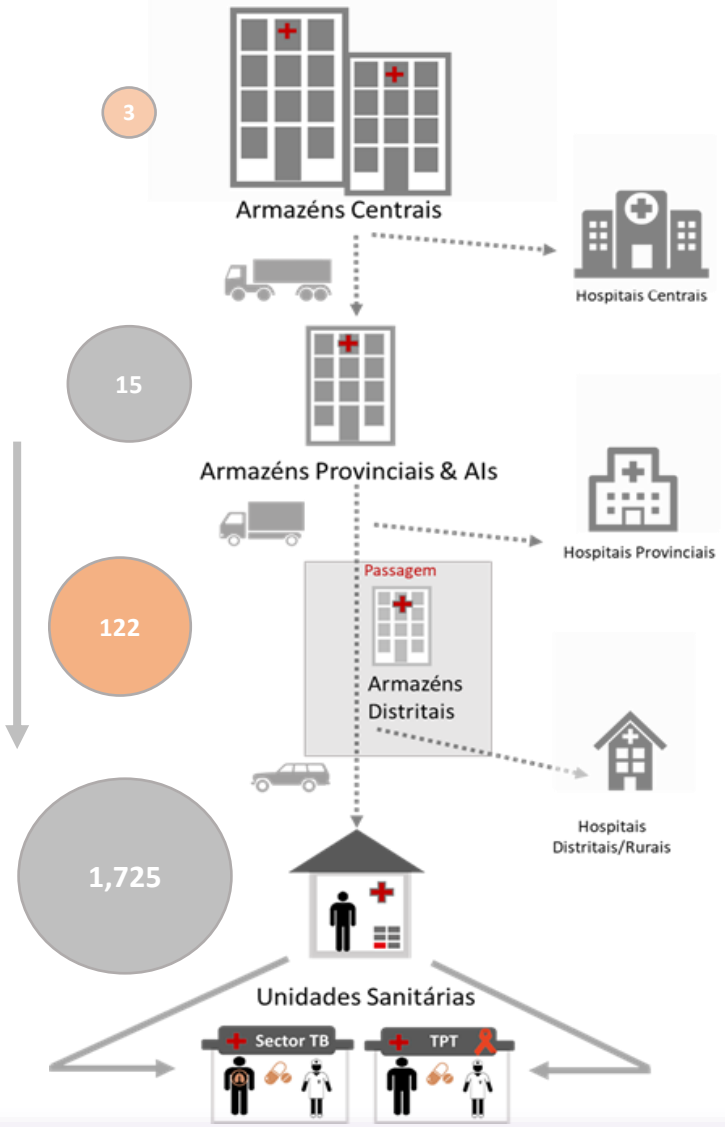
e Artigos Médicos

ARV Supply Chain

Warehousing and Distribution

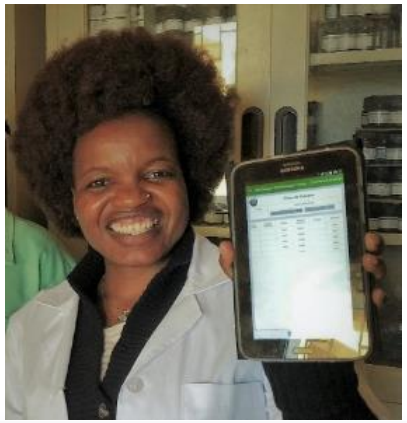


1. **Central Warehouses: 3 Central Warehouses** – operational
   - 2 locations in Maputo (Machava e Zimpeto)
   - 1 Beira
   - 1 Nampula
2. **Provincial & Intermediary Warehouses:** 10 Provincial Warehouses and 5 Intermediate Warehouses.
3. **District Warehouses :** 122 - to be deactivated
4. **Health Facilities:** 1,725 providing ARVs and increasing gradually
5. **Community Health Workers:** with 8,300

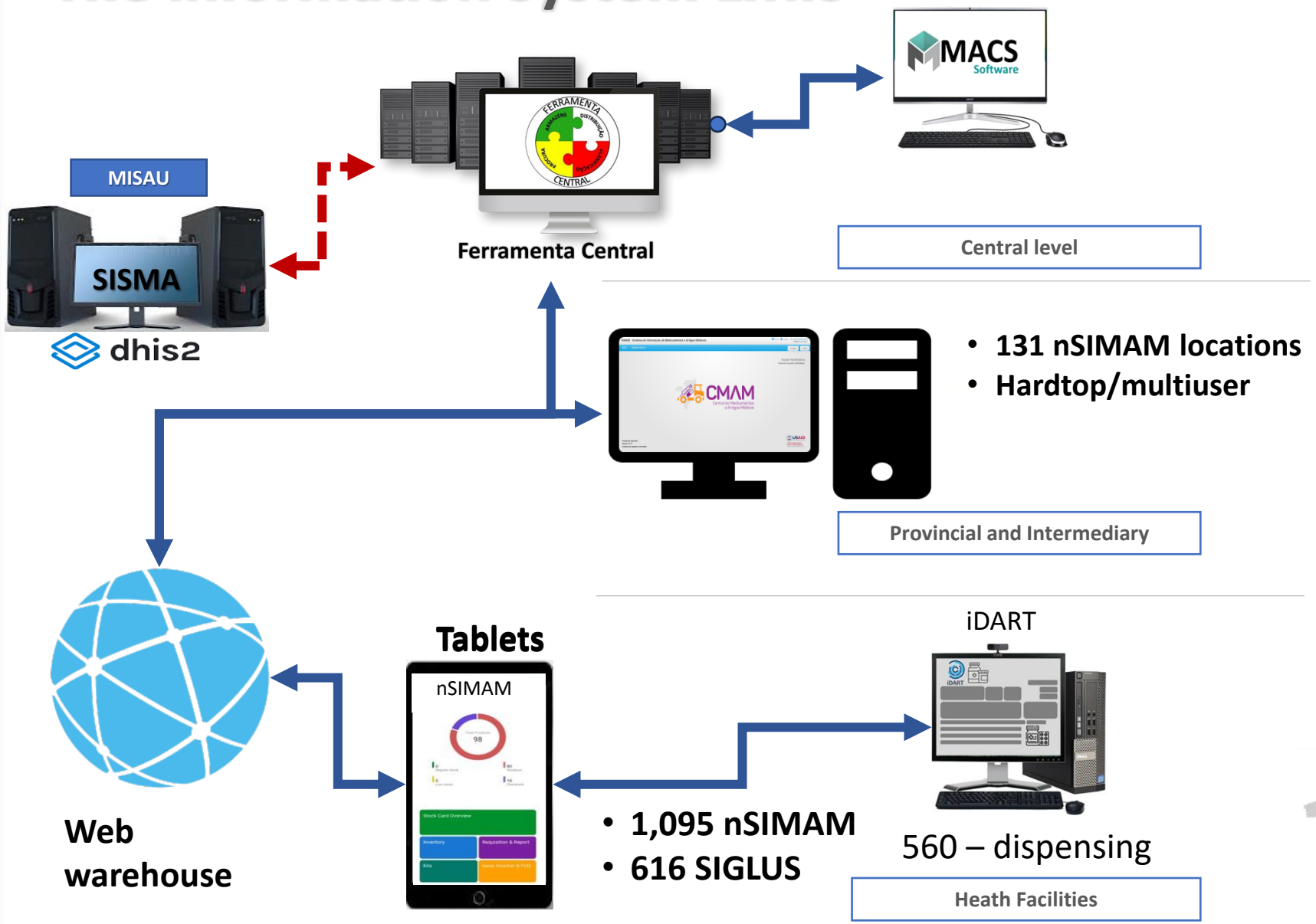
Systems

LMIS – Data driven decision making process

- Support the Quantification
- Supply plan updates & monitoring
- Distribution and re-supply decision
- Stocks visibility, reconciliation and accountability
- Interoperability with Health Information Systems
- Strategic planning



The Information System LMIS

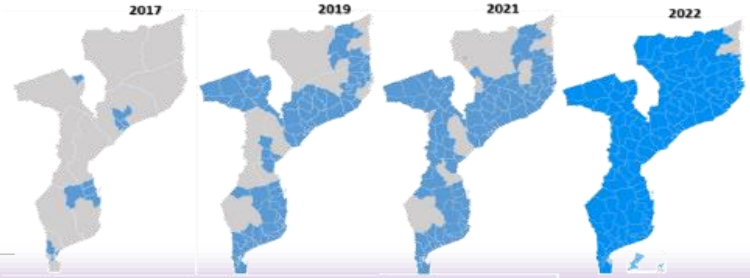


1. **ERP SAP/Bio – Finances & Procurement**
   Financial management and cost accounting and links to service and product procurement processes
2. **QAT – Planning**
   Estimating consumption, supply planning, monitoring orders and analyzing product gaps
3. **Ferramenta Central**
   Mother tables, data storage, distribution plans, KPIs and M&A, data visibility

   Interoperability with SISMA (HMIS)
4. **MACS**
   Storage cube management - central warehouses
5. **nSIMAM (SIGLUS/SIMAM)**
   Inventory management, requisitions and reports for Health Units and storage points.

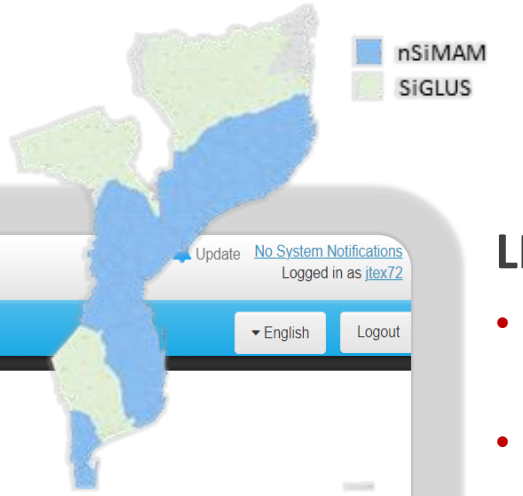
Implementation:

- System Simplification (1 system Prov/HF)
- Automate transactions between warehouses
- End-to-end visibility



The Information System LMIS

nSIMAM Webpage visibility



SIMAM - Sistema de Informação de Medicamentos e Artigos Médicos

Update No System Notifications
Logged in as jtex72

Home | Analytics Reports | English | Logout

Home / Analytics Reports / Stock Status Report

Relatório do estado de stock

Programa: TARV | Código do produto | Nome do produto: Tenofovir+Lamivudina+Dolutegravir; 300+300+50mg 90 Comp; Comp | Estado de stock | Província | Distrito | Nome da instalação | Última atualização

Informação do estado de stock

Província	Distrito	Nome da instalação	Programa	Código do produto	Nome do produto	Total do stock existente	Valor total	Estado de sto
MANICA	MACATE	Armazém Intermediário de Chimoio	TARV	08S18WI	Tenofovir+Lamivudina+Dolutegravir; 300+300+50mg 90 Comp; Comp	34,774	432,240.82	Stock regular
ZAMBEZIA	ILE	Armazém Intermediário de Ile	TARV	08S18WI	Tenofovir+Lamivudina+Dolutegravir; 300+300+50mg 90 Comp; Comp	26,228	326,014.04	Stock acumulad
ZAMBEZIA	MOCUBA	Armazém Intermediário de Mocuba	TARV	08S18WI	Tenofovir+Lamivudina+Dolutegravir; 300+300+50mg 90 Comp; Comp	18,155	225,666.65	Eminência de ro
ZAMBEZIA	MOPEIA	Armazém Intermediário de Mopeia	TARV	08S18WI	Tenofovir+Lamivudina+Dolutegravir; 300+300+50mg 90 Comp; Comp	34,347	426,933.21	Stock acumulad
INHAMBANE	VILANKULO	Armazém Intermediário de Vilankulo	TARV	08S18WI	Tenofovir+Lamivudina+Dolutegravir; 300+300+50mg 90 Comp; Comp	61,736	767,378.48	Stock acumulad
SOFALA	MARINGUE	Centero de Saude de Senga-Senga	TARV	08S18WI	Tenofovir+Lamivudina+Dolutegravir; 300+300+50mg 90 Comp; Comp	119	1,479.17	Stock acumulad
MANICA	MOSSURIZE	Centro Chitsama	TARV	08S18WI	Tenofovir+Lamivudina+Dolutegravir; 300+300+50mg 90 Comp; Comp	19	236.17	Stock regular
SOFALA	DONDO	CENTRO DE SADE DE NHAMPOEPUA	TARV	08S18WI	Tenofovir+Lamivudina+Dolutegravir; 300+300+50mg 90 Comp; Comp	98	1,218.14	Stock acumulad
MAPUTO PROVINCIA	MANHICA	Centro de Saude 25 de Setembro/Chihenhisse	TARV	08S18WI	Tenofovir+Lamivudina+Dolutegravir; 300+300+50mg 90 Comp; Comp	9	111.87	Stock regular
MAPUTO PROVINCIA	MANHICA	Centro de Saúde 3 de Fevereiro	TARV	08S18WI	Tenofovir+Lamivudina+Dolutegravir; 300+300+50mg 90 Comp; Comp	2,832	35,201.76	Stock acumulad

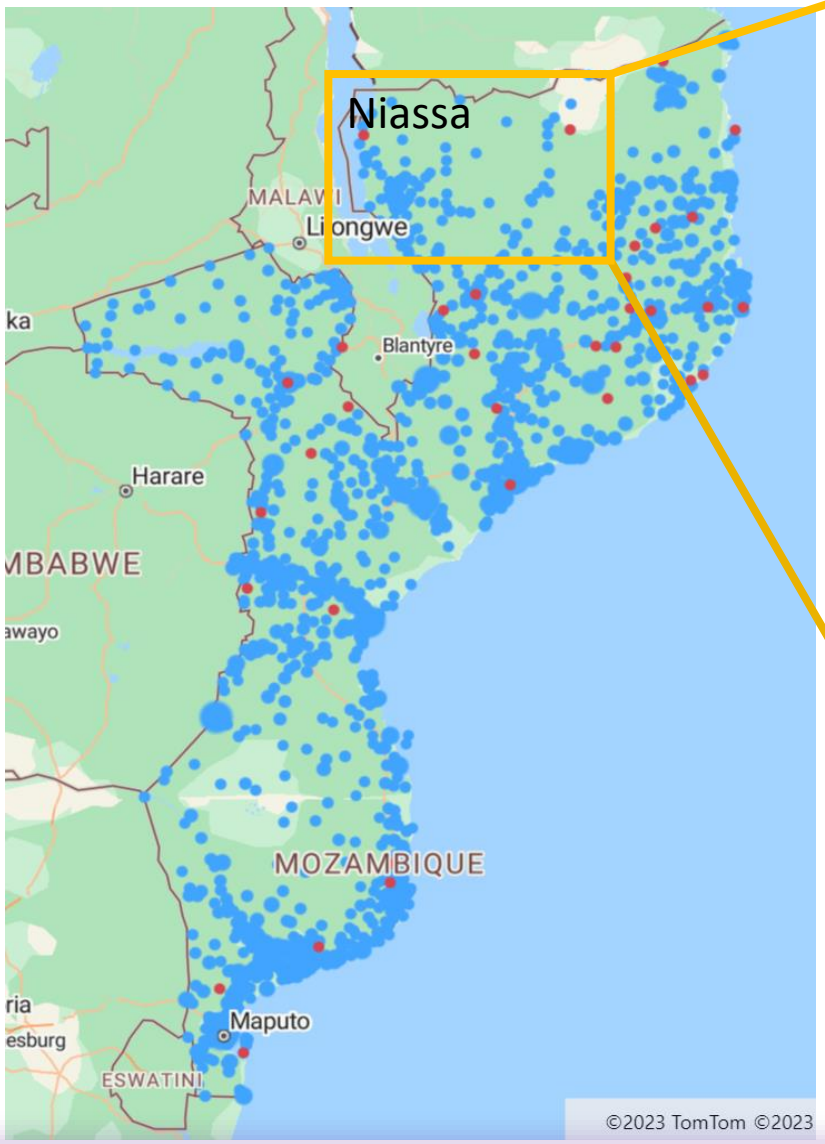
Linhas 1-10 de 1073

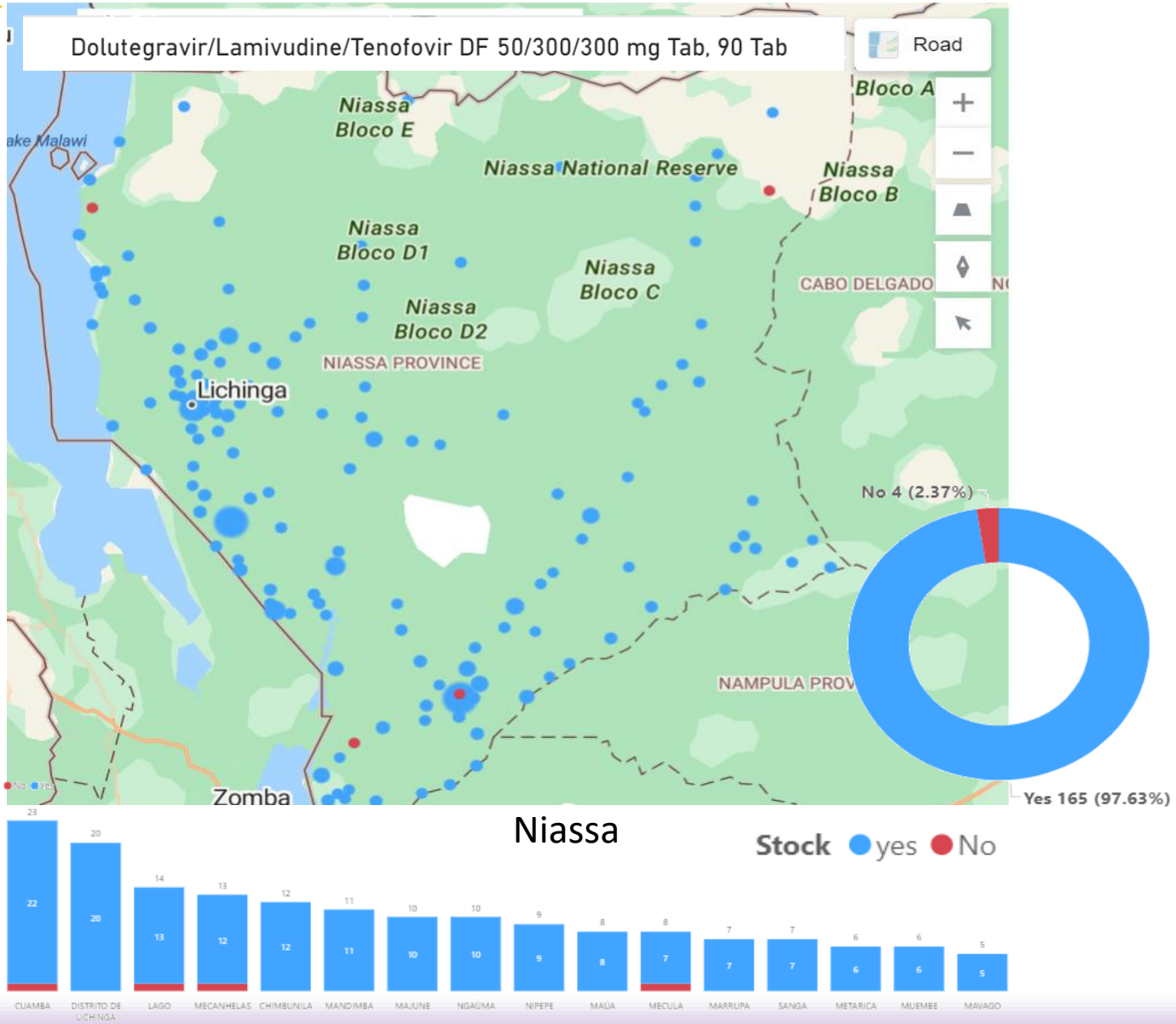
LMIS nSIMAM

- Data by Health Facility and stocking point
- **nSIMAM OpenLMIS 3.0** - server and network (multi-user) & tablet/android (phone)
- Upgrading **SiGLUS OpenLMIS V2.0** Health Facilities only
- **Webpage** - Managers at all levels
- Health Facility/Warehouse automation
- Delivery orders sent electronically.
- Already being implemented Maputo Province and City, Manica, Zambezia and Nampula, Inhambane, Sofala
- nSIMAM full national coverage by March 24

The Information System LMIS

ARVs Stock information visibility





Challenges

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Transitions

- Challenging and unpredictability, new formulations not always well accepted
  - Educating and training Patients, Caregivers, Care providers
  - Supply availability to meet the demand
  - Capacity to cancel orders if needed

Data

- Data entry & data quality
- Internet/air-time at Heath Facility
- Tablets/hardware (continuous replenishment of the aging equipment)

Pediatric formulations

- Quantification, plan the distribution and register in the LMIS
- Very similar packs for different formulations (packs 30's, 60's, 90's) leads to confusion
- Number of packs (up to 25Kg)

Packs

- Patients complaining TLD90 packs rattling during the transport, after the pickup, leading to stigma.

Complexity – impact in a fully stretched supply chain.

Interactions with Suppliers

pALD

- Production capacity to ensure and sustain the transition
- Expiry dates for the first batches (very short shelf life in past transitions)
- Ability to expand the number of manufacturers to provide security
- Production of pDTG and pAL may decrease significantly but will be key for children up to 6kg and the pDTG doubles the dose during TB treatment with rifampicin-containing regimens.
- Will be adjusted the pDTG to 5mg and pAL to 60/30mg to be aligned with pALD?.

ALD

- As the price of the 30 pack is significantly high ($20) and has been stable for a number of years, do you expect it to drop, to allow the triple fixed dose combination across all pediatric weight bands?

Prophylaxis

- After several delays in the availability of AZT or NVP in recent years (following the withdrawal of LZN from treatment). Will we continue to face supply challenges?

PrEP (TL)

- Blistered and different pill color

ARVs (TLD)

- Avoid to change pill color

Muito Obrigada!

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Day 2 Panel: Lessons learned: Procurement experience

Daniel Kiesa (Moderator)
Market Advisor, Office of HIV/AIDS, USAID

Ivandra Libombo
Chief of Planning Department, Central de Medicamentos e Artigos Medicos (CMAM), Mozambique

Jordi Balleste
Unit Chief, Strategic Fund Procurement, Procurement and Supply Management – Pan American Health Organization

Wesley Kraft
PPM Project Director, Iplus Solutions

Alan Pringle
Global Supply Chain Director, GHSC-PSM/Chemonics

Ignace Ndekezi
Head of Department, Procurement and Quantification
Rwanda Medical Supply Ltd

Forward looking: 18-month consolidated forecast from big buyers

Shanil Ramlall
Consultant, Africa Resource Centre

2023 ANNUAL ARV BUYER SELLER SUMMIT

18 MONTH CONSOLIDATED FORECAST

Oct 2023

PEPFAR

USAID FROM THE AMERICAN PEOPLE

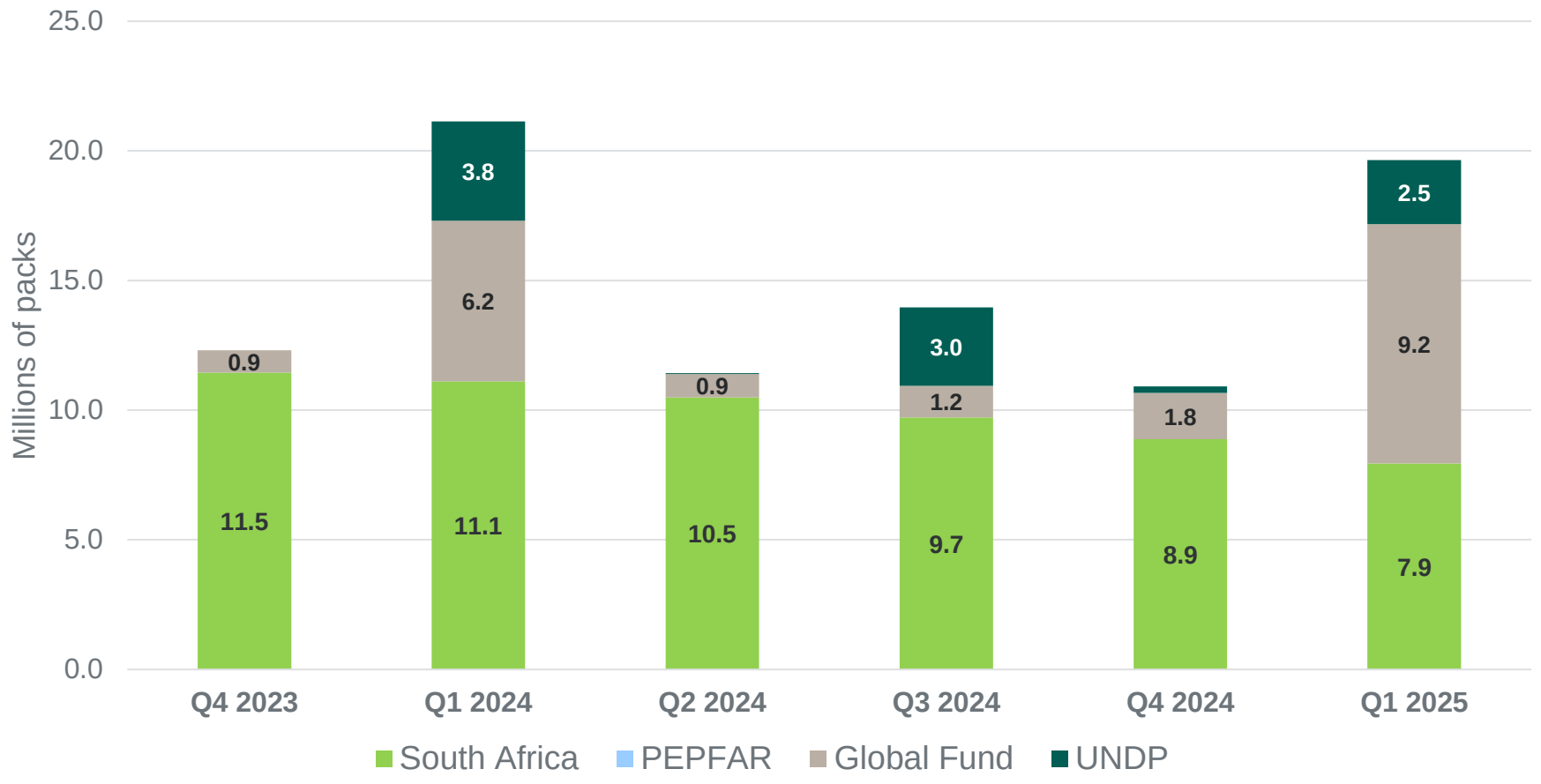
THE GLOBAL FUND

Republic of South Africa

CAVEATS AND LIMITATIONS TO THE CURRENT FORECAST

- **Estimates** based on a combination of currently confirmed orders, firm demand & demand forecasts
- Prepared based on **data currently available** to the various buyers
  - No demand from Kenya and Ethiopia submitted
- **Preliminary estimates for discussion and planning –** not final purchase commitments
- **May not yet fully capture lead times** between order placement at manufacturer and in-country delivery

TLD 28-30 TABLETS; SOUTH AFRICA REMAINS THE MAIN MARKET

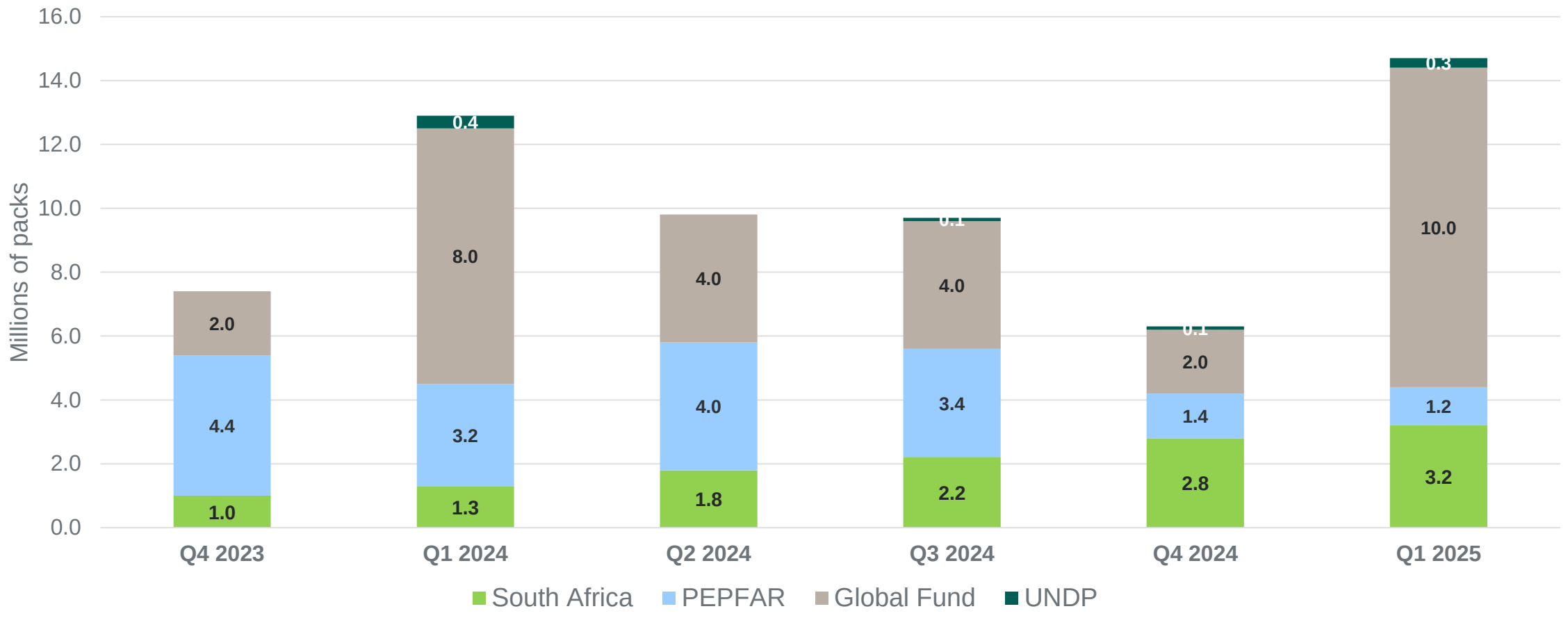


- South Africa estimated usage of 28s reduces over the period due to expected increased usage of 84/90s

❑ Volumes estimates of 84/90s for South Africa is growing resulting in supplementary tender being advertised.

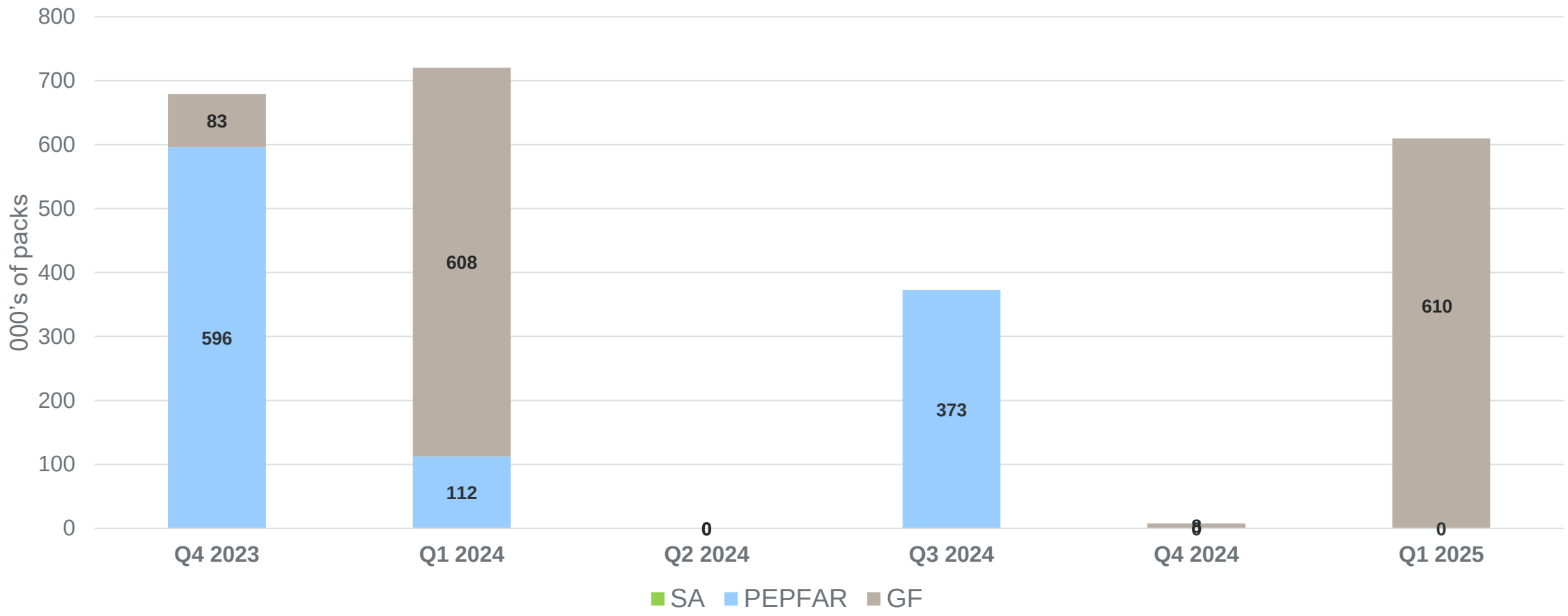
Source: Submissions from GHSC-PSM, Global Fund, South Africa, UNDP

TLD 84-90 TABLETS; FLUCTUATIONS PER QUARTER



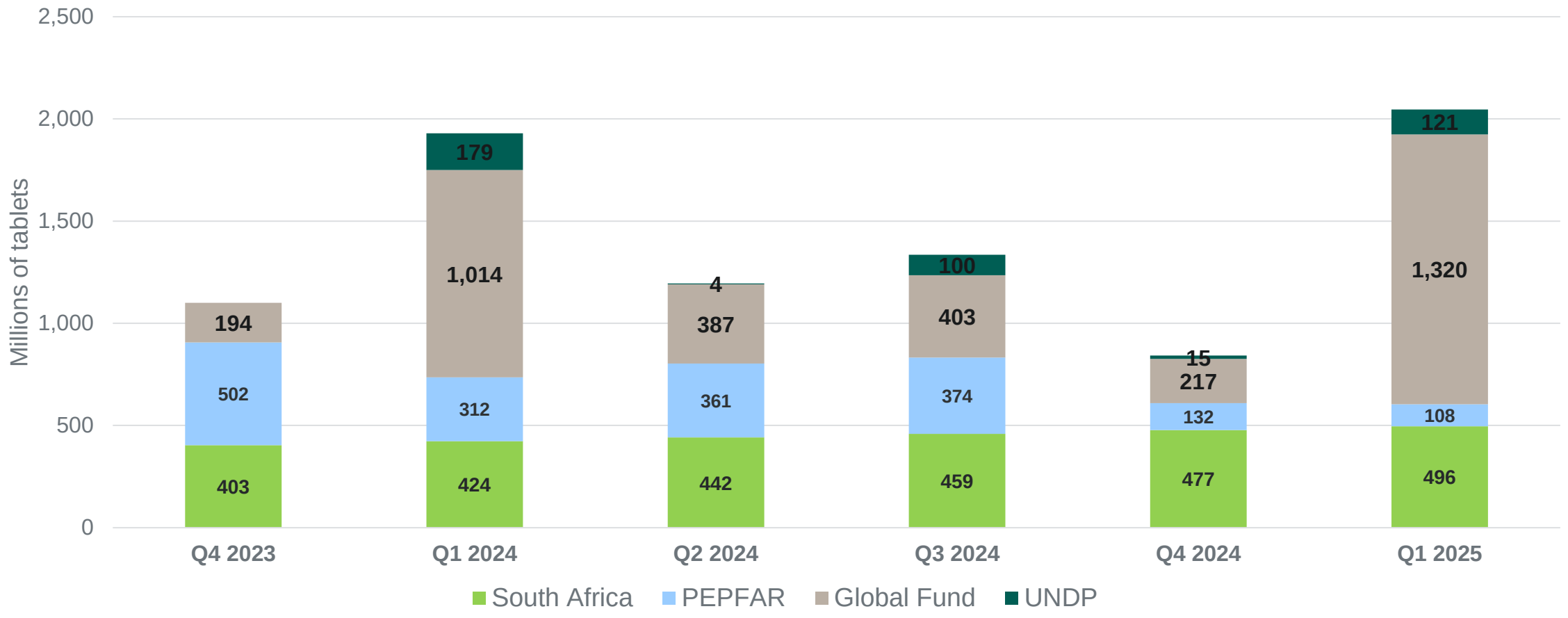
Source: Submissions from GHSC-PSM, Global Fund, South Africa, UNDP
Notes: SA volumes limited to current 2022 ARV tender award

TLD 180 TABLETS; PEPFAR AND GLOBAL FUND DRIVING DEMAND



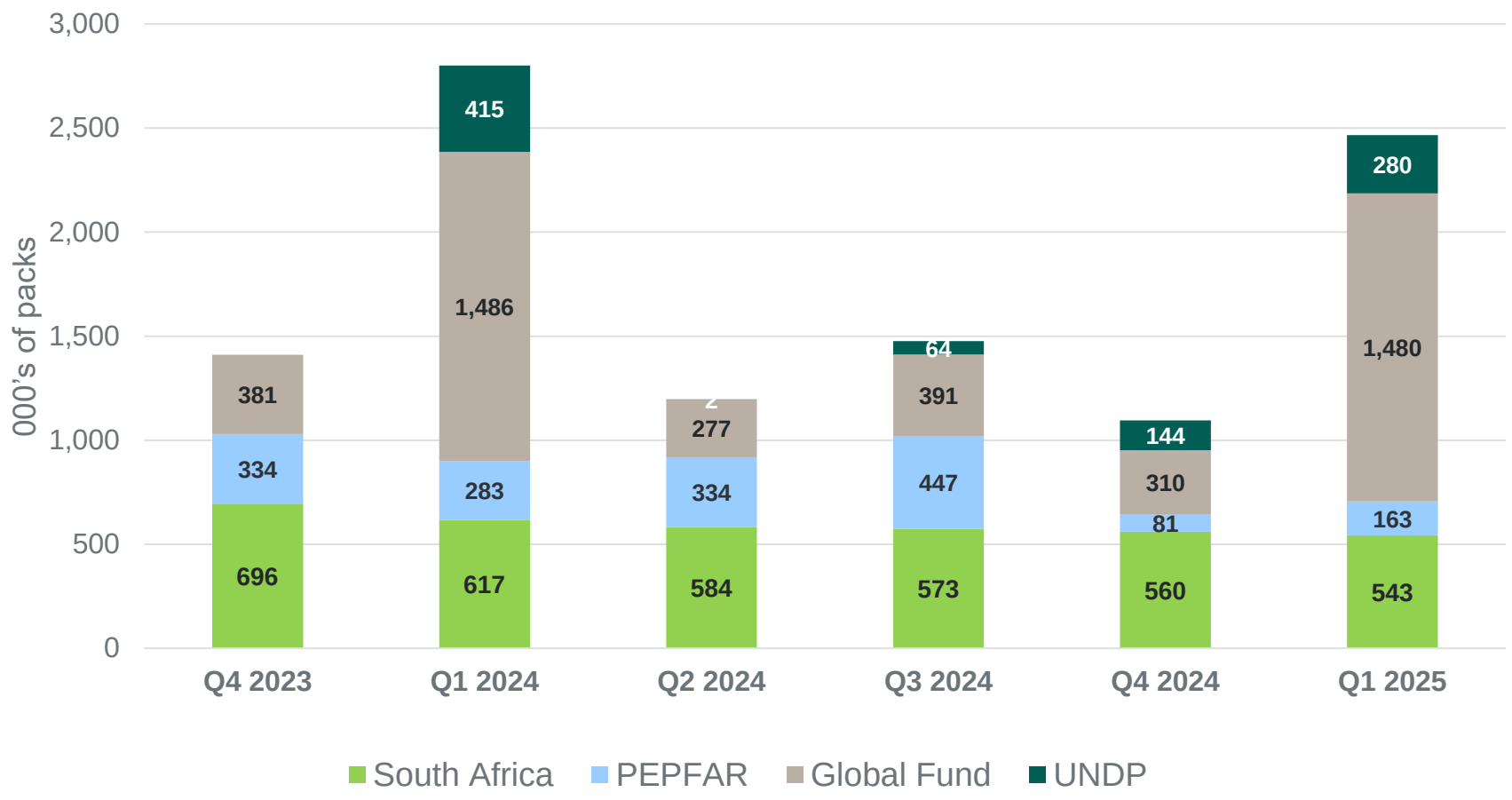
Source: Submissions from GHSC-PSM, Global Fund, South Africa, UNDP

TLD TABLETS (ALL PACK SIZES)



Source: Submissions from GHSC-PSM, Global Fund, South Africa, UNDP
Notes: Note the switch from packs to millions of tablets for this graph.

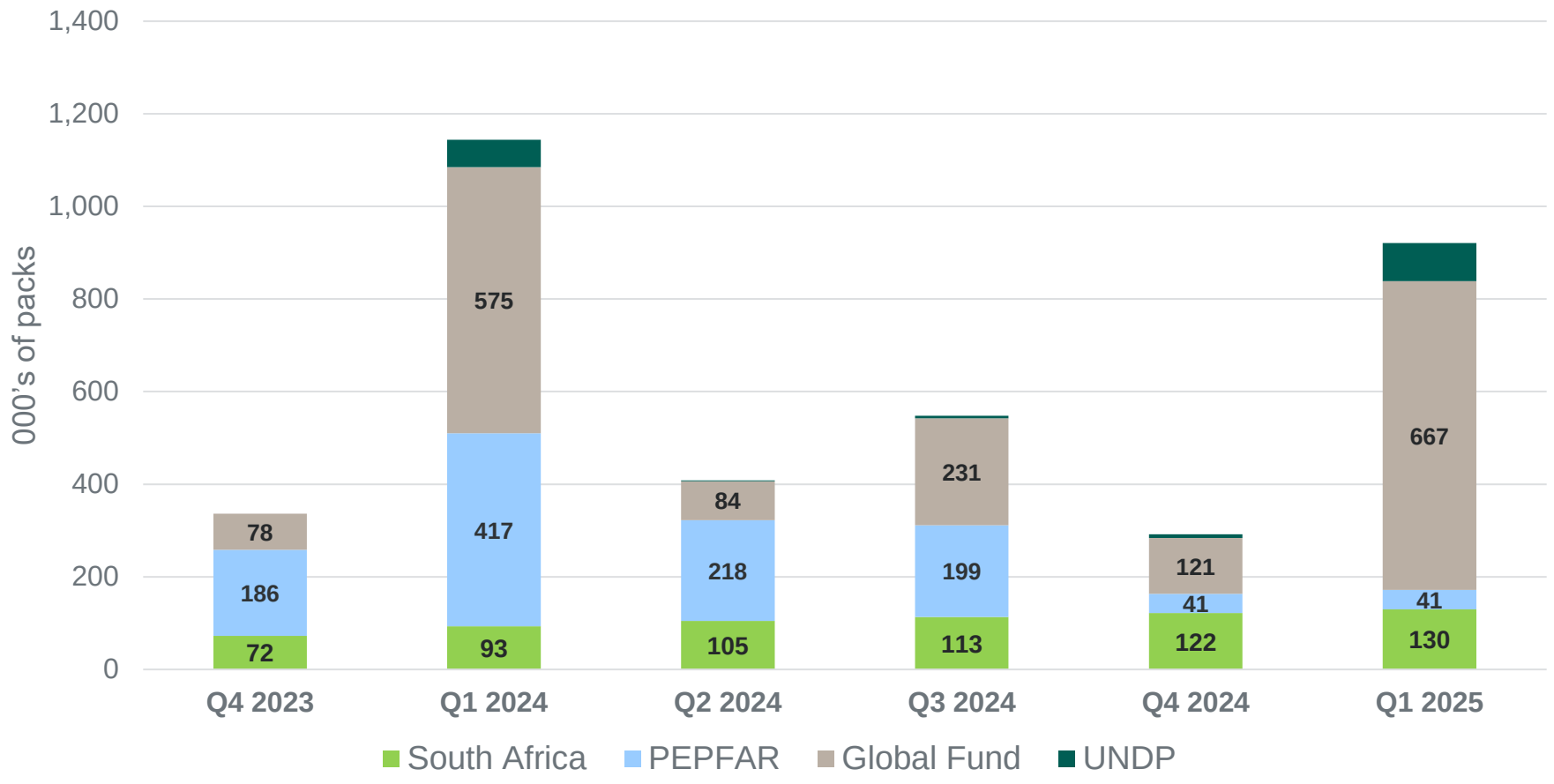
DTG 50 MG, 30 TABLETS



- Little or no demand expressed for 90's packs

Source: Submissions from GHSC-PSM, Global Fund, South Africa, UNDP

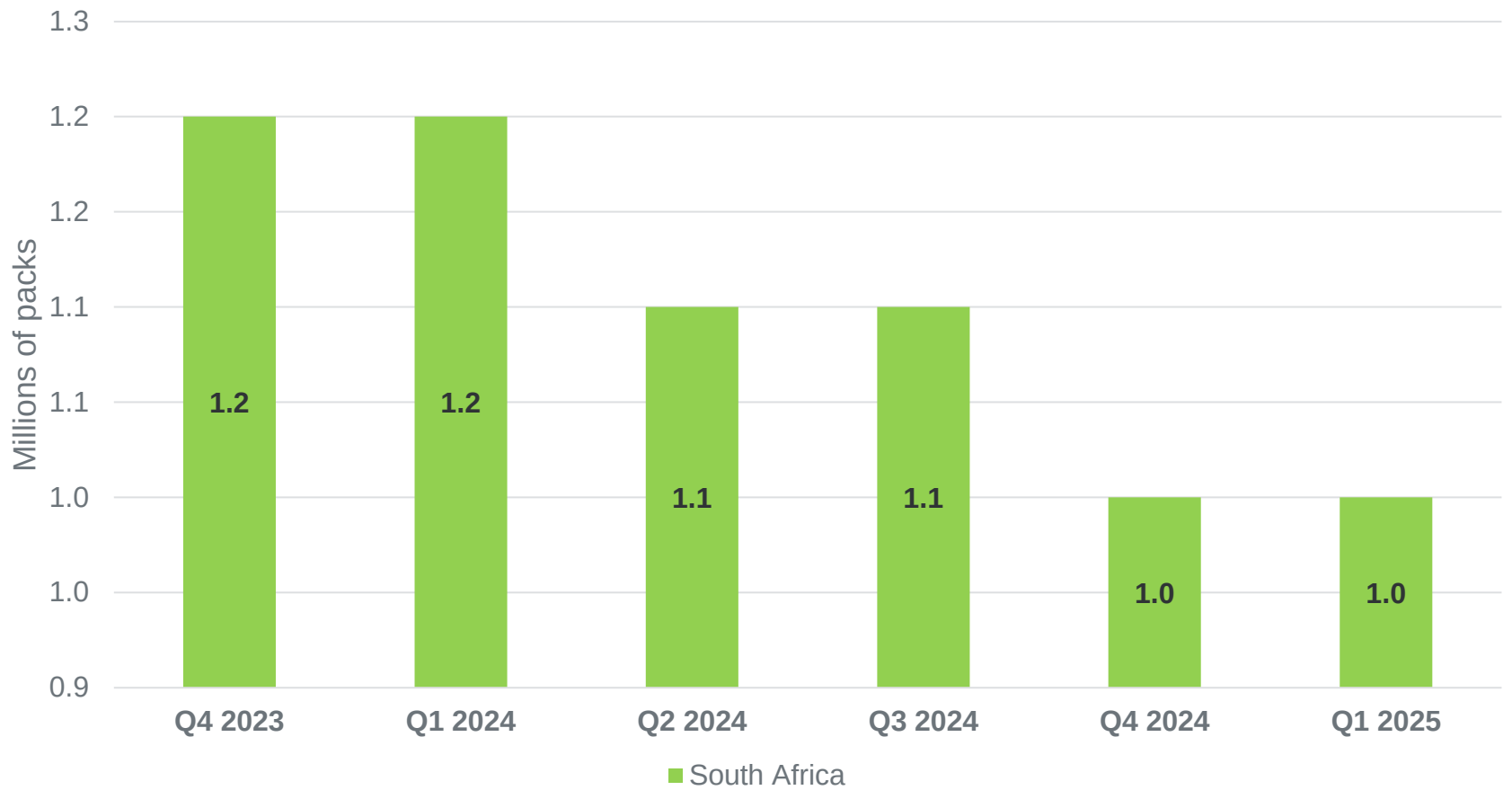
DTG 10 MG, 90 SCORED, DISPERSIBLE TABLETS



- South Africa - Supplementary tender has been advertised for this pack.

Source: Submissions from GHSC-PSM, Global Fund, South Africa, UNDP

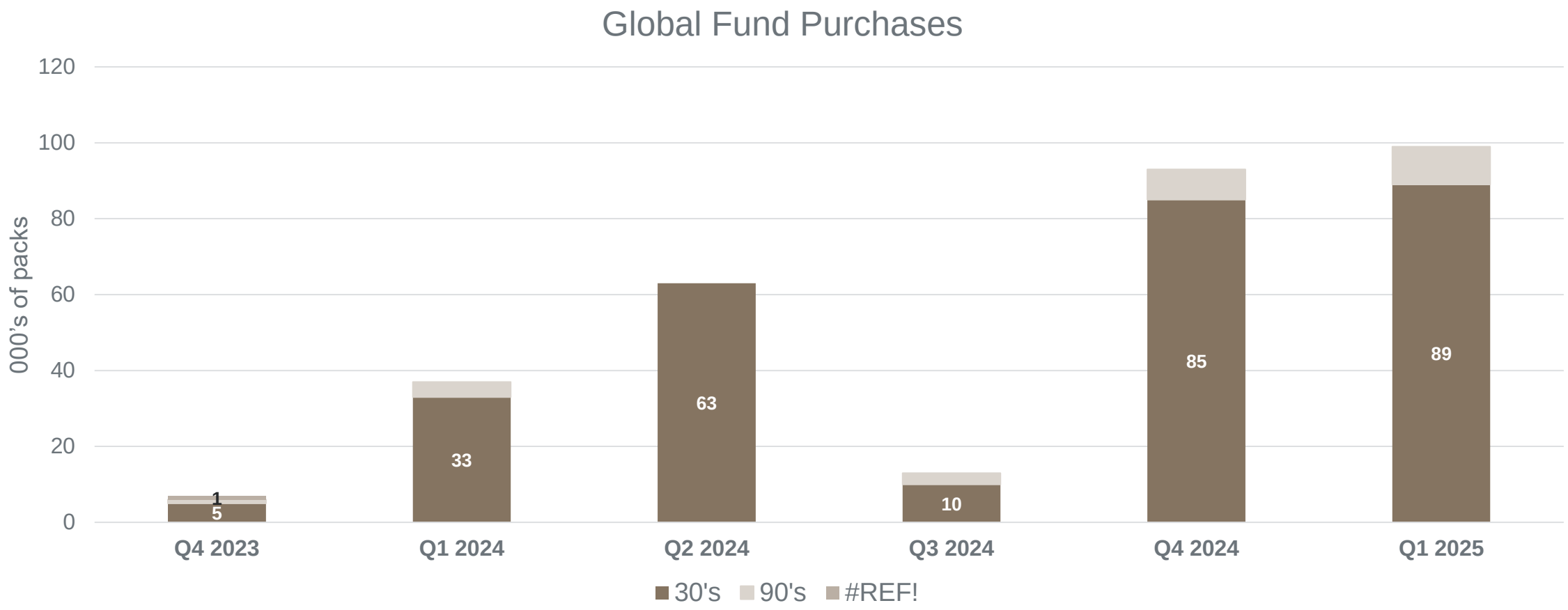
TEE, 28 TABLETS; SOUTH AFRICA IS THE MAIN MARKET



- Volumes may shift downwards depending on how aggressively the country moves past 93:7, TLD:TEE

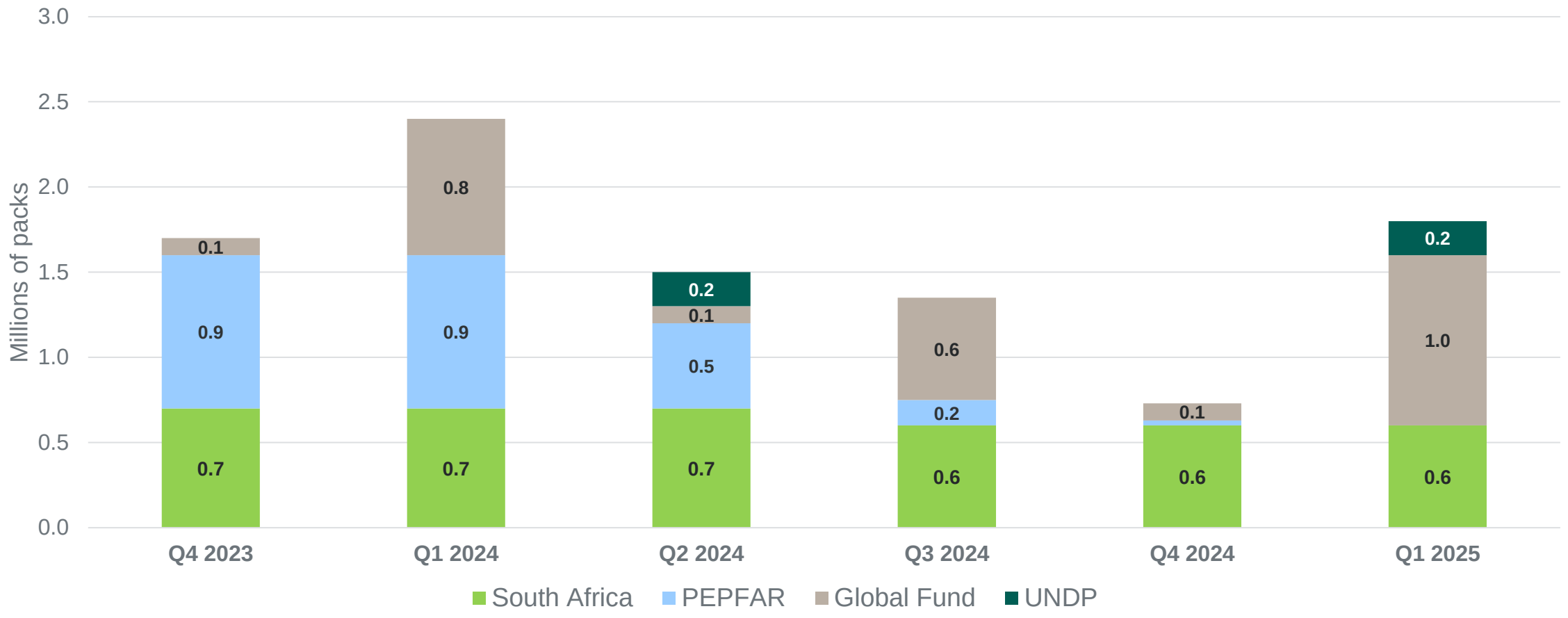
Source: Submissions from GHSC-PSM, Global Fund, South Africa, UNDP

TLE 400 MG; GLOBAL FUND IS THE KEY PURCHASER



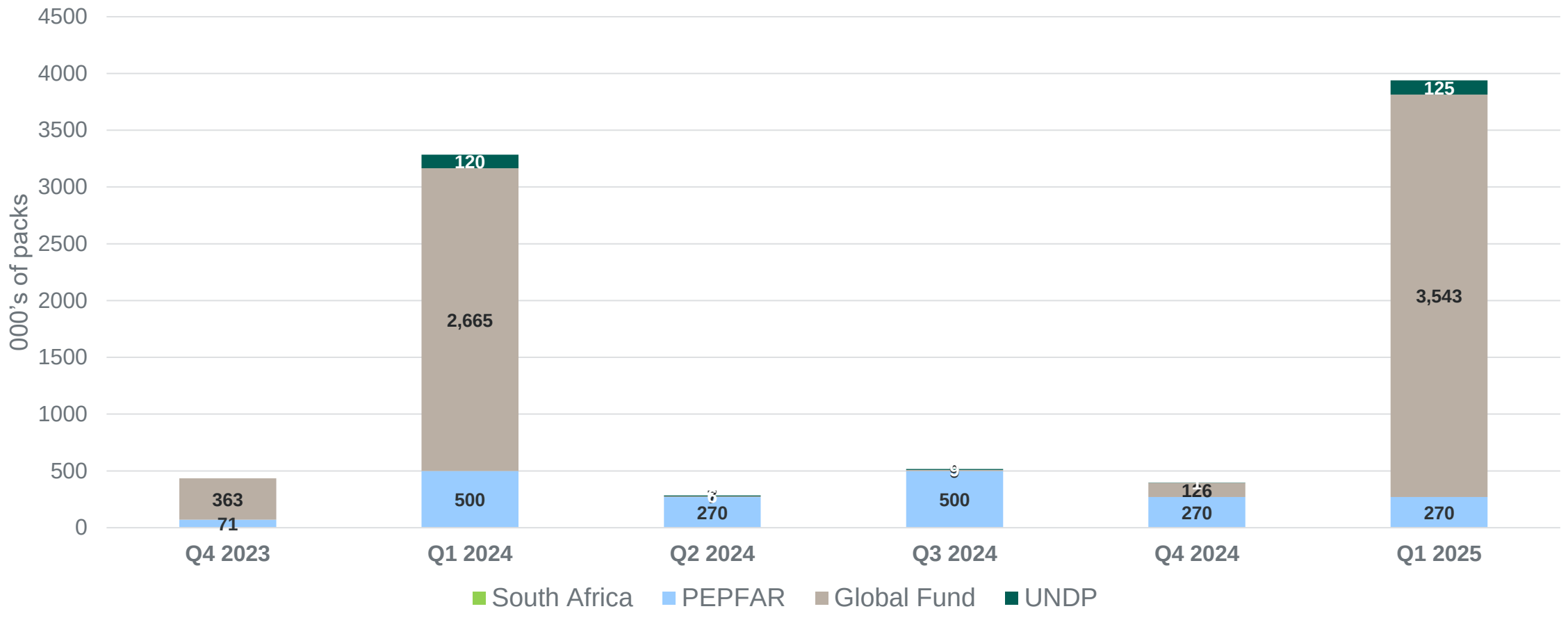
Source: Submissions from GHSC-PSM, Global Fund, South Africa, UNDP

TDF/FTC 300/200 MG, 30 TABLETS



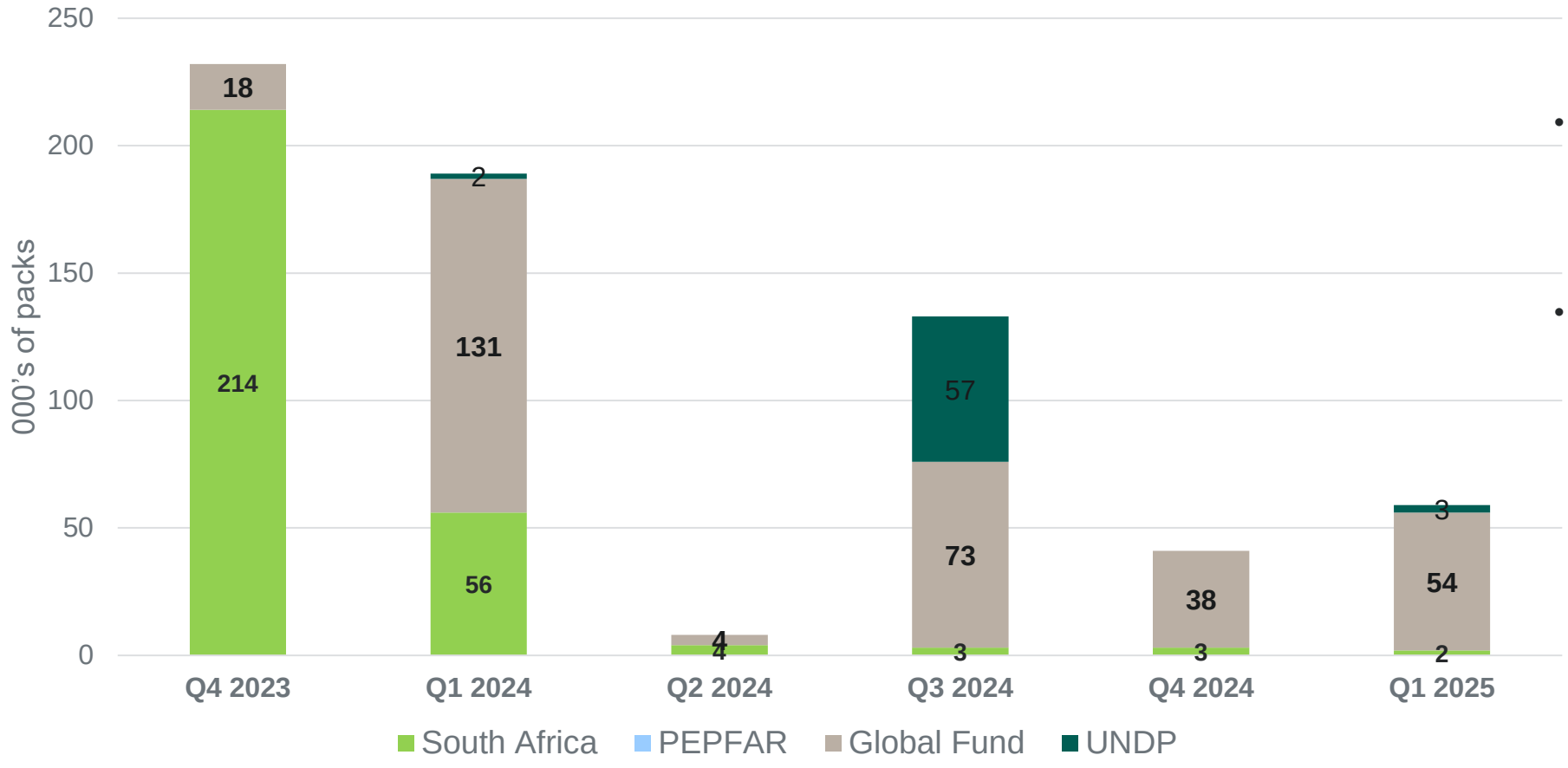
Source: Submissions from GHSC-PSM, Global Fund, South Africa, UNDP

TDF/3TC 300/300 MG, 30 TABLETS



Source: Submissions from GHSC-PSM, Global Fund, South Africa, UNDP

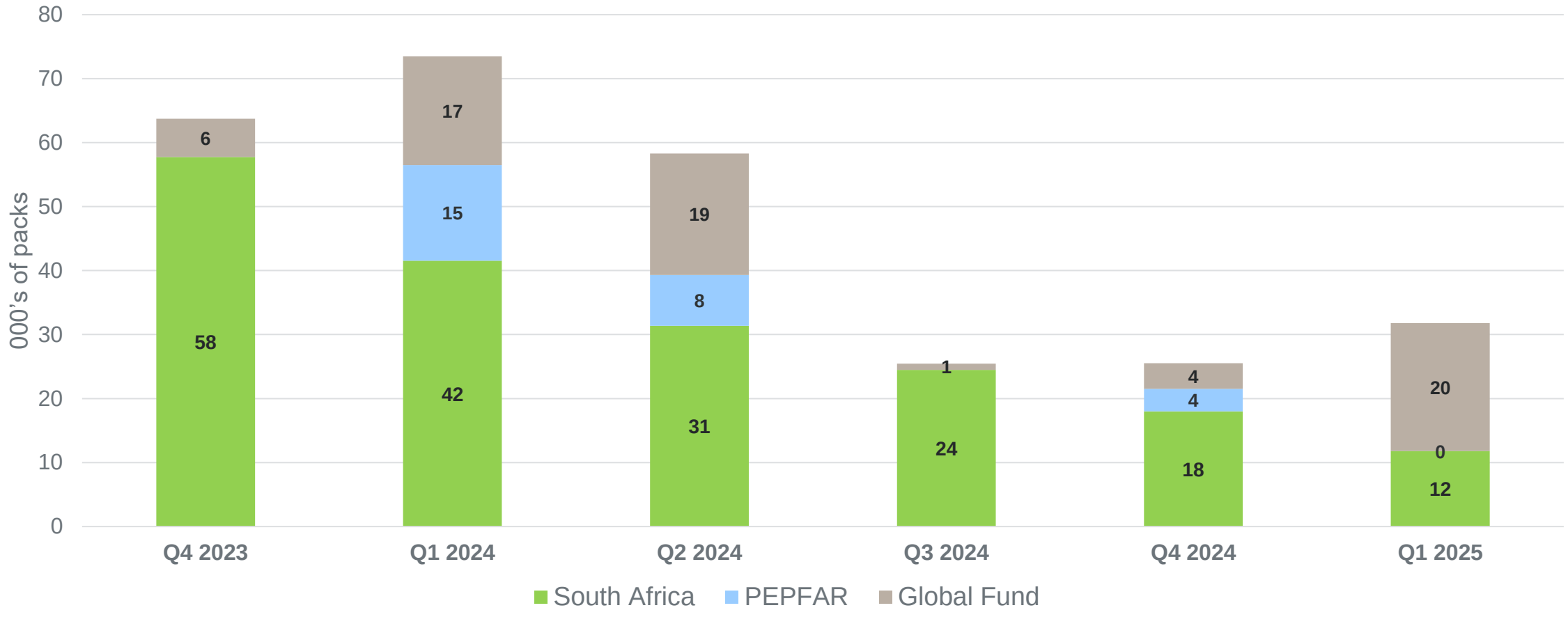
LPV/r 200/50 MG, 112-120 TABLETS



- High stock levels in South Africa should reduce orders in Q4 2023 and Q1 2024
- Declines indicated in South Africa is depend on pace of 2nd line patient transition based on ARV Guideline update

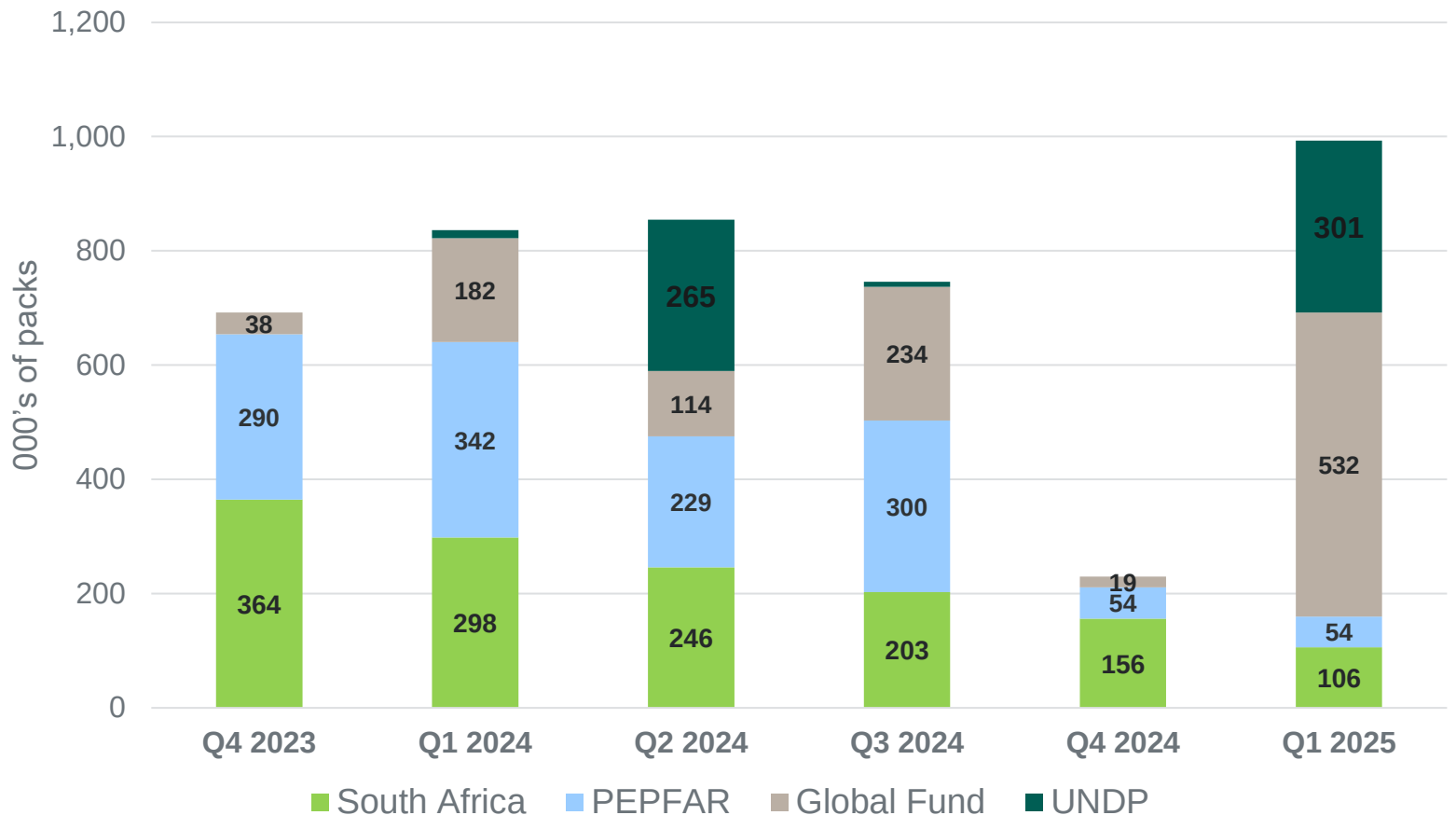
Source: Submissions from GHSC-PSM, Global Fund, South Africa, UNDP

LPV/r 100/25 MG, 56-60 TABLETS



Source: Submissions from PEPFAR, Global Fund, South Africa, UNDP
Notes:

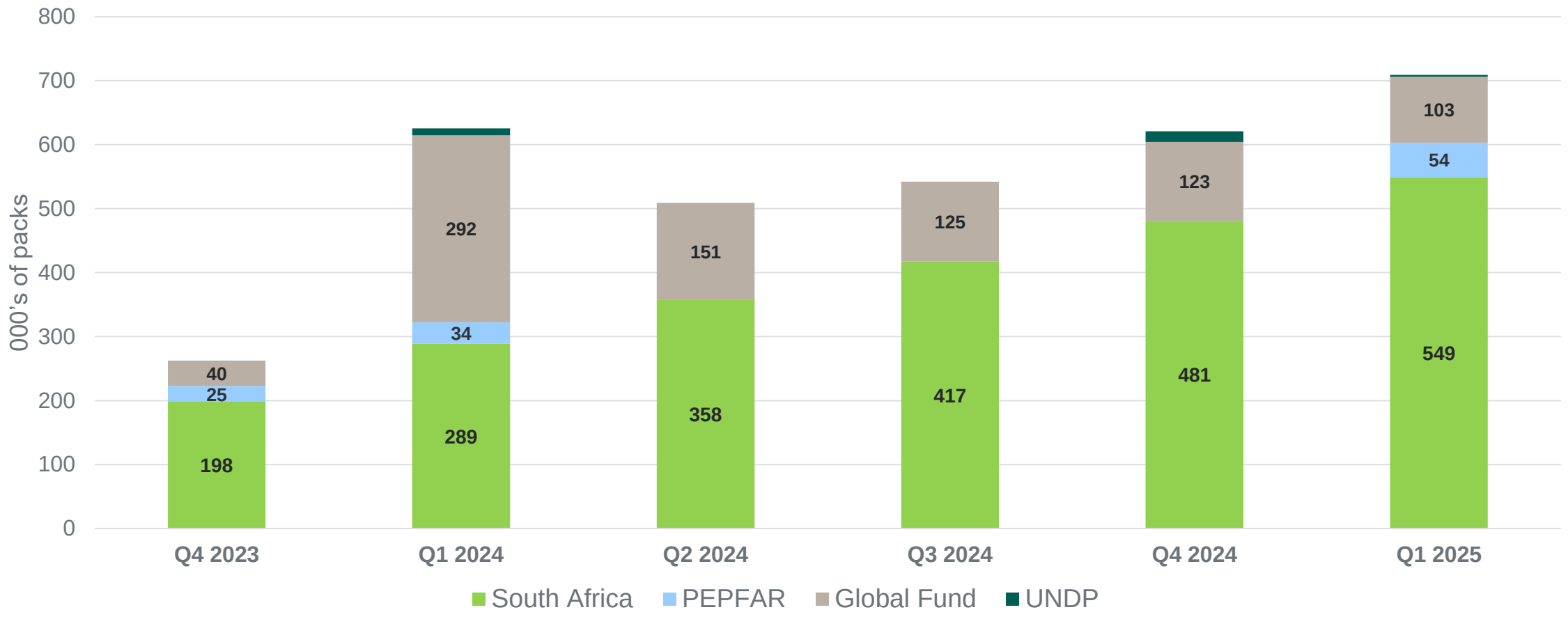
ABC/3TC 600/300 MG, 30 TABLETS



- Demand of this product reduces with the introduction of ABC/3TC/DTG

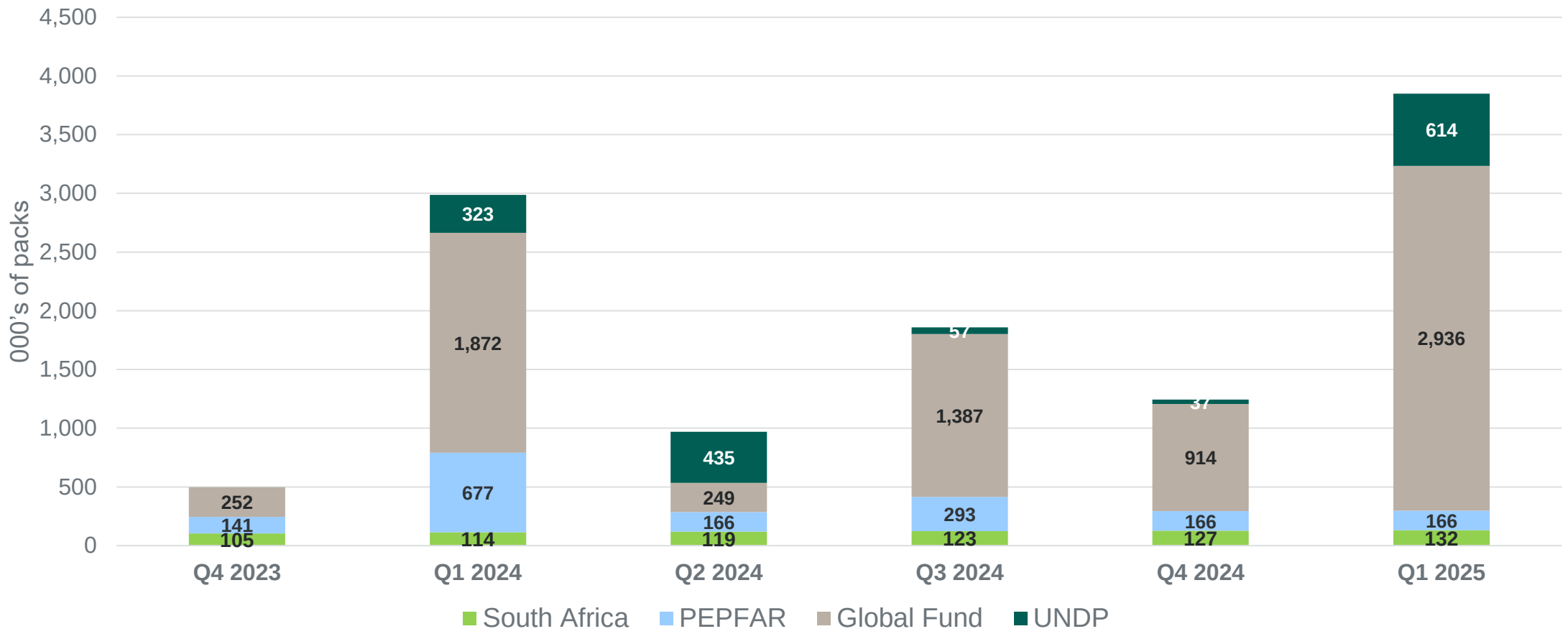
Source: Submissions from GHSC-PSM, Global Fund, South Africa, UNDP

ABC/3TC/DTG 600/300/50 MG, 30 TABLETS



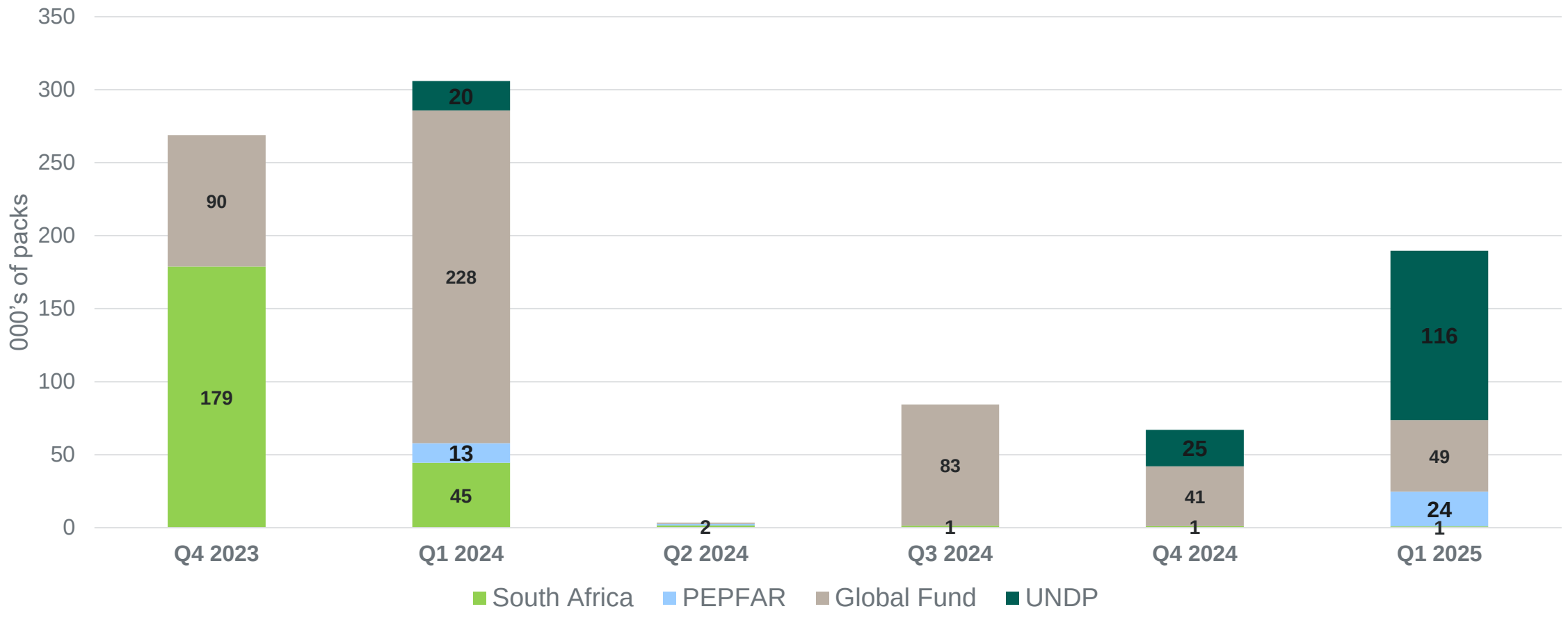
Source: Submissions from GHSC-PSM, Global Fund, South Africa, UNDP

ABC/3TC 120/60 MG, DISPERSIBLE 30 TABLETS



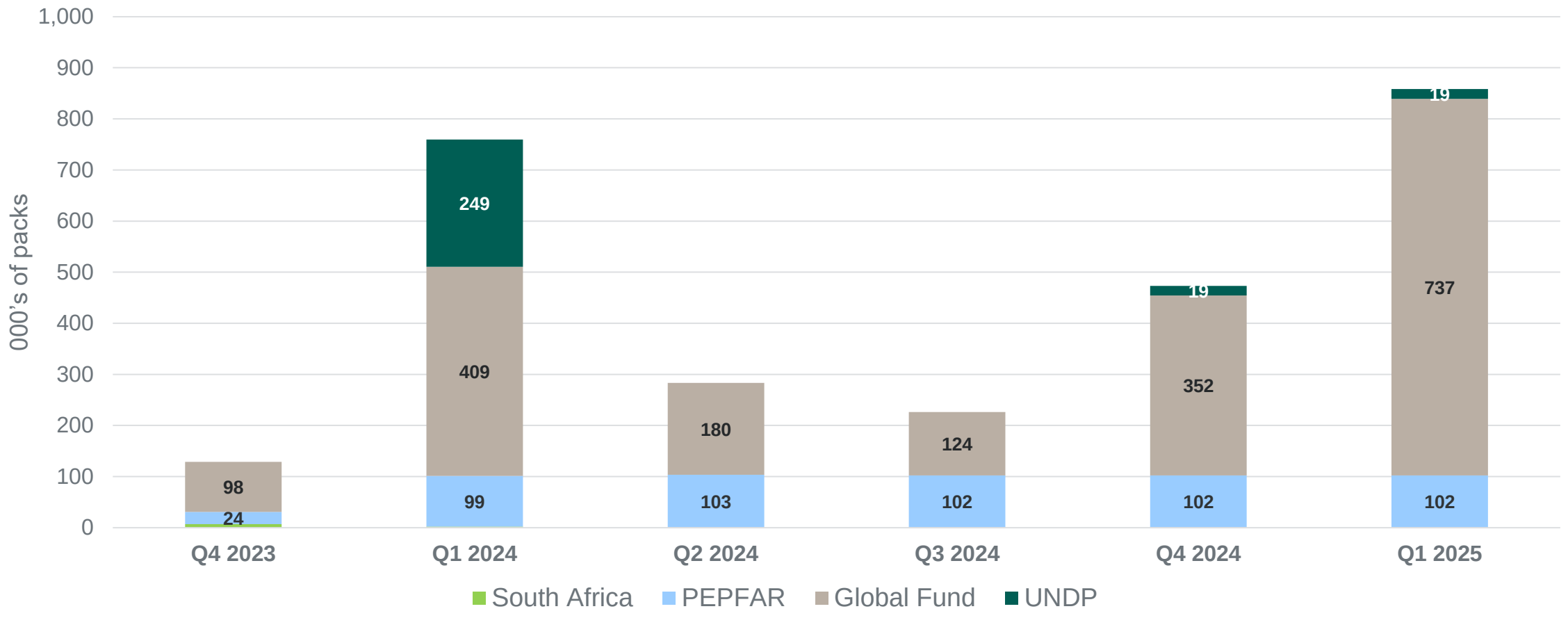
Source: Submissions from GHSC-PSM, Global Fund, South Africa, UNDP

AZT/3TC 300/150 MG, 56-60 TABLETS



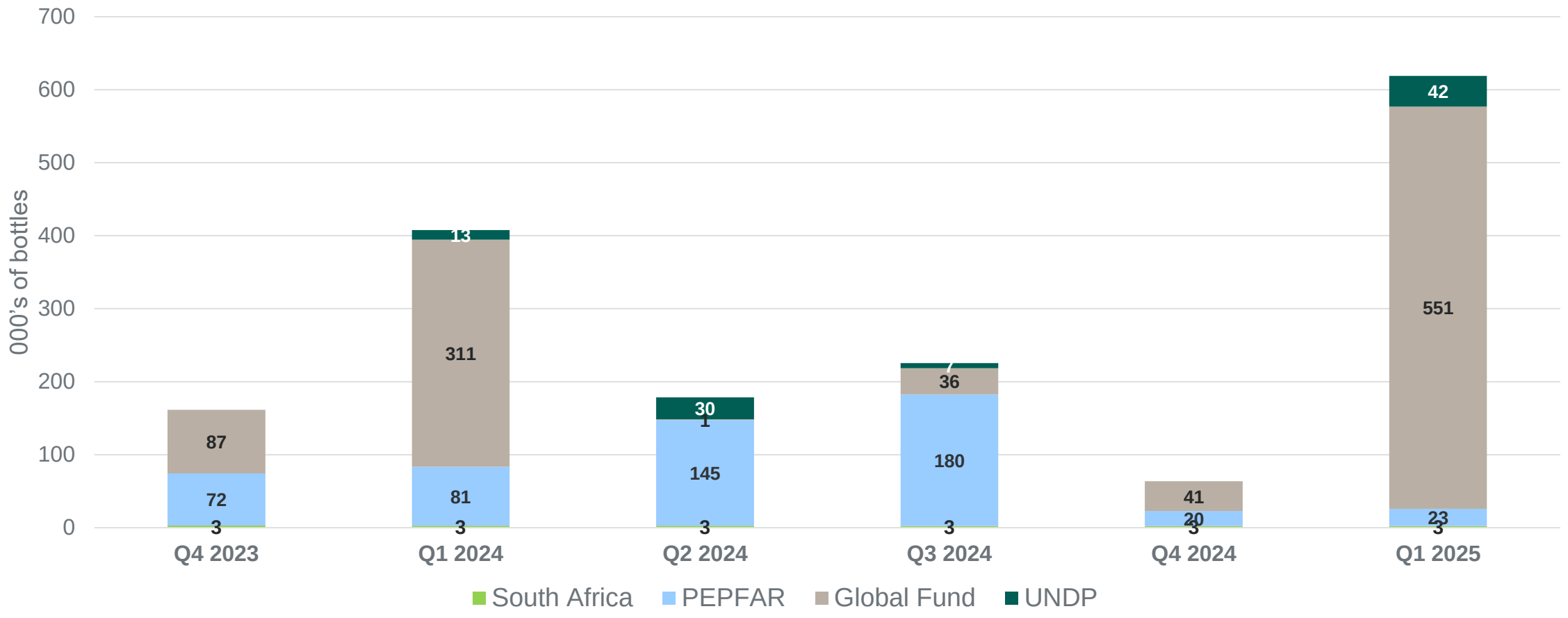
Source: Submissions from GHSC-PSM, Global Fund, South Africa, UNDP

ATV/r 300/100 MG, 30 TABLETS



Source: Submissions from GHSC-PSM, Global Fund, South Africa, UNDP

NEVIRAPINE 10 MG/ML ORAL SUSPENSION, 100 ML



Source: Submissions from GHSC-PSM, Global Fund, South Africa, UNDP

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health
Department:
Health
REPUBLIC OF SOUTH AFRICA

MINISTÉRIO DA SAÚDE

BREAK

Case study: Approach to strengthen demand forecast and planning

Martin Auton
Head of Planning, Procurement
and Transaction Management,
the Global Fund

Plan-To-Report

Case study: Approach to strengthen demand forecast and planning

31.10.2023

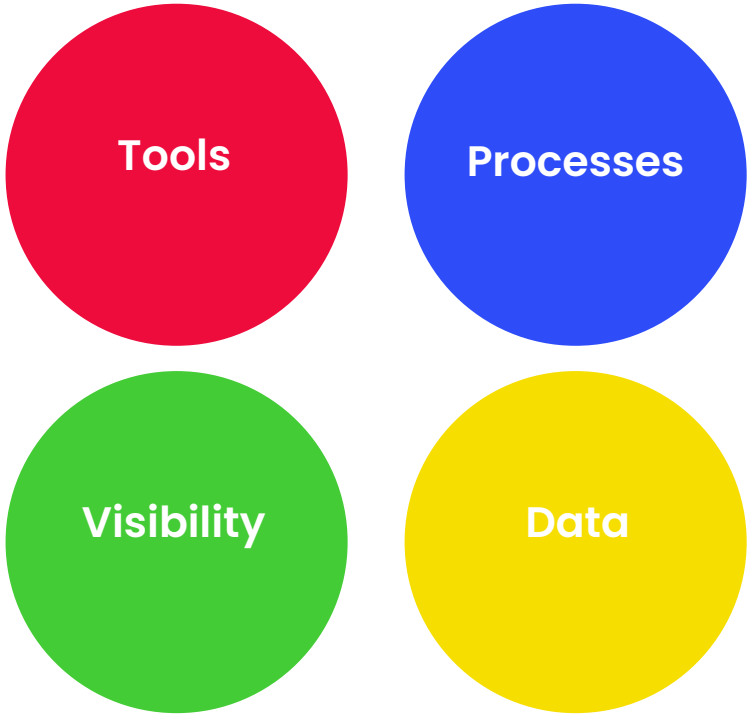
Agenda

- **Context & Background**
- **Plan-to-Report Vision**
  - Demand & Operations Planning (D&OP)
- **Plan-to-Report Success Factors**
  - Benefits for Principal Recipients (PRs)
  - Benefits for Suppliers
- **Progress so far & Next Steps**
- **Discussion**

Background & Context

The Plan-to-Report (PTR) project is designed to improve the (proactive) management of health products in grants at both grant and aggregate level.

Existing tools are outdated and can be improved to better manage health products demand, supply & budgets at different levels



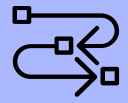
Current processes can be improved to facilitate easier tracking, reporting and decision making on health products demand, supply, budget and spend

There is a growing need for better visibility on the status of orders from budget through to delivery

There is a need for improved end-to-end data consistency to enable better integration across our systems and support data sharing

Plan-to-Report Vision

Our vision for the Plan-to-Report project has 6 core ideas

	**Clear and defined simple systemic business processes** to manage health product demand and health product budget both at grant and aggregate level
	**Appropriate organizational health product demand forecast and planning** to ensure an efficient management of health product procurement and supply for ongoing program implementation
	**Integrated fit-for-purpose easy-to-use tools** to facilitate the end-to-end tracking and reporting on health product grants and spend
	**Up-to-date visibility of orders** for PPM and (later) for non-PPM
	**End-to-end data consistency throughout the systems**. Grant lifecycle data is captured, processed, stored and shared adequately
	**Harmonized chain of responsibilities** (RACI) in line with the clearly defined business processes

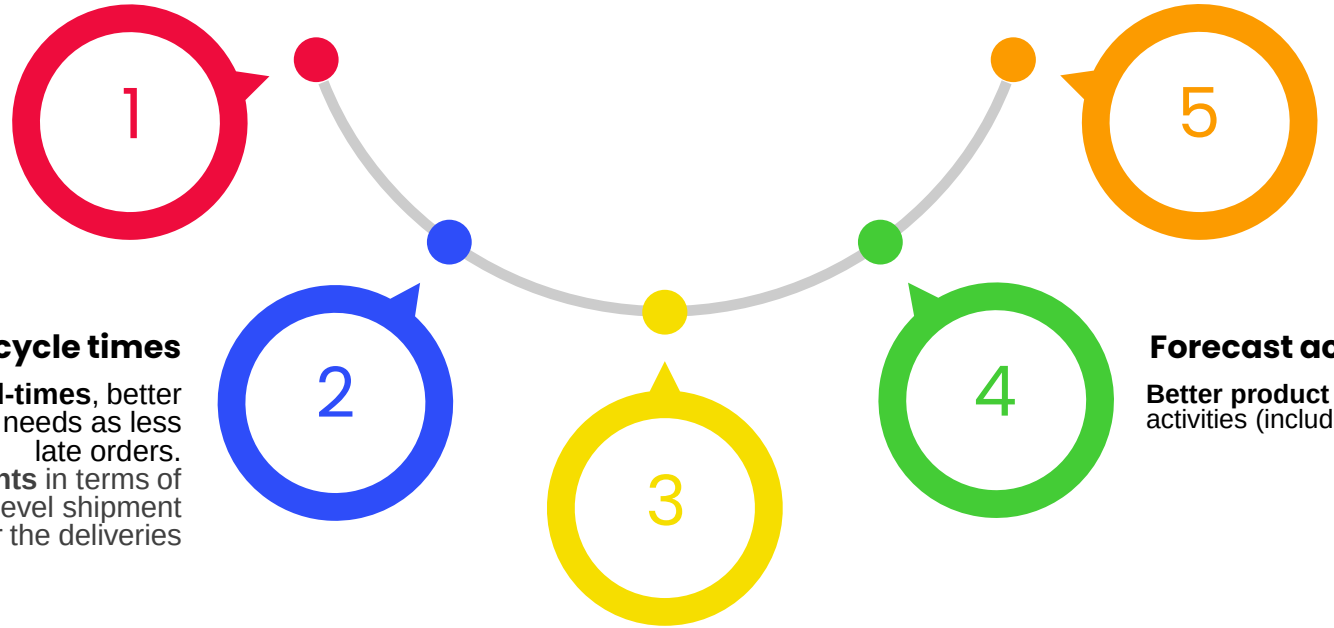
Demand & Operations Planning (D&OP)

Effective processes involve the balancing of multiple internal & external stakeholders' objectives and expectations through facilitated conversations that help to resolve existing challenges. That is D&OP!

- The operational planning & execution processes for the demand & supply of health products are aimed to enable optimizing of activities of all involved in the supply and management of health products to deliver greater impact
- Maximizing grant impact would be delivered through aligning activities - demand forecasting, supply of health products, and financial management - to the programmatic requirements in the countries.
- Parallel activities across many portfolios, countries, regions and at the global level require extra diligence to ensure delivery of the main objective.

Plan-to-Report Success Factors

What does the success look like ?



Proactive conversations

Through more and accurate information Principal Recipients and GF stakeholders on health product volumes and budgets.

Shorter cycle times

Reduced **delivery lead-times**, better able to deliver per PR needs as less late orders.
Optimized shipments in terms of reliability and cost, high-level shipment planning to stagger the deliveries

Shorter Financial ,cycle times

Analytics to optimize the use of funds enabling greater use of unutilized funds and earlier reprogramming

Forecast accuracy

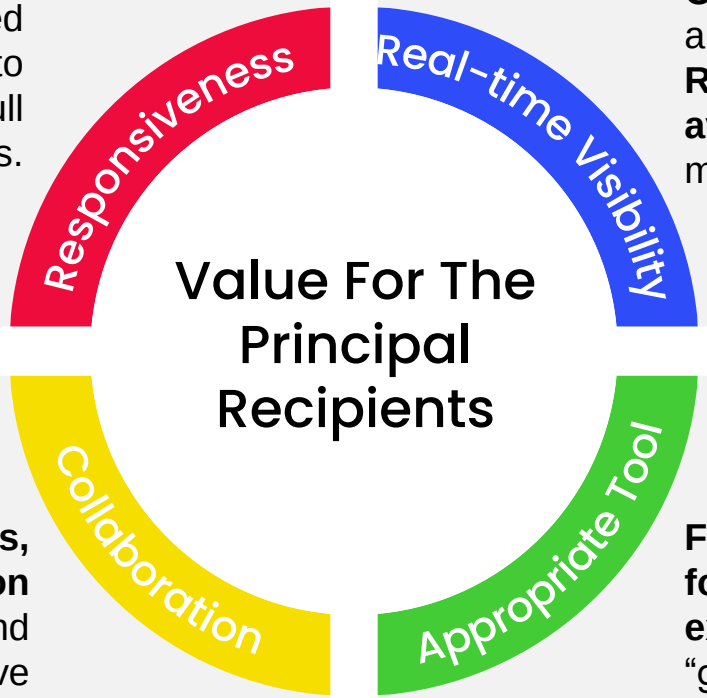
Better product forecast for sourcing activities (including within year timing)

Visibility

Through a **single and integrated system** for both PRs and the GF.

Benefits for Principal Recipients

Enabling a better & faster use of grant funds for health products, through ...



Shorter order cycle-times through better planning and improved procurement cycle time (by up to 50%) and improved On Time In Full (OTIF) of deliveries.

On-demand up-to-date reports and data analytics available to PRs. **Real-time updates and follow-ups available** to monitor their orders more closely

Improved communications, collaboration and information sharing between the Secretariat and PRs using a single collaborative platform.

Fit-for-purpose, user friendly tool for PRs, integrated with other existing systems. Potential to be a "global good" by striving to use open-source tools.

Benefits for Suppliers

Enabling better end-to-end support and visibility to suppliers , through ...

Improved supply planning

Improved forecast of volume and timing of the demand helps suppliers to manage capacity and reduce costs.

Collaboration

Improved forward visibility enables collaborative decision making between suppliers and the GF

Proactive Decision making

Increasing time-value added activities (less reactive work dealing with emergencies and less manual data manipulation)

Shorter order cycle times

Updated demand & supply plans ensure **shorter approval times for orders and quicker payments for delivered orders**

2023: “quick-wins” through the tactical roll out of D&OP processes !

Areas of intervention

- **In depth (manual) analyses of approved health product plans/budgets vs. supply/expenditures** (especially for 3-year grants ending in 2023)
  - Collaborative cross-functional reviews and validation of actuals vs. budget
  - Confirmation of pipeline order as well as future demand / orders.
  - Procurement planning for remaining orders to meet demand and optimize funds
- **Demand scenarios to support the scale up of the newly WHO recommended dual AI bed nets**
  - Support to the supply and demand side of accelerating the introduction of a “new” product

Impact

- **Improved absorption & re-investment of funds**
  - Maximized the use of fund for grants in the current cycle
  - Additional orders placed to manage transition between the funding cycles
  - Other interventions such as viral load funded in some countries
- **Supported sourcing and contracting activities**
  - To secure sustainable pricing and shorter lead times for the most used sizes and colored nets (with standard accessories and packaging) enabling significant rapid conversion

PTR project will enable automated data manipulation and more time on decision making related to opportunities (and challenges) and implementation of those.

Role out of processes & ways of working

Next Steps: Defining of D&OP processes

- **Calendar:** Timing for Demand and Operations Planning (D&OP) activities.
  - Demand planning & forecasting including New Product Introduction
  - Supply Planning
  - Disbursement forecasting
  - Aggregation and consolidation of demand to feed into Sourcing activities

- **Governance:** Forums or processes to support related decision making and approval of plans.
  - Participants
  - Cadence / frequency of engagements
  - Roles & responsibilities of relevant participants (RACI matrix)
  - Inputs and outputs of each process / sub-process

- **Performance Tracking**: How to assess the performance of Demand and Supply Planning.
  - KPIs and aligned definitions

THE GLOBAL FUND

Discussion

Quality Assurance Update

Deusdedit Mubangizi
Unit Head, Prequalification Unit
World Health Organization

Sandrine Cloëz
Specialist, Pharmaceutical Products
Quality Assurance, the Global Fund

World Health Organization

WHO Prequalification ensuring timely and equitable access to quality assured heath products and supporting innovation

ARV Summit, Maputo, Mozambique
30 October – 01 November 2023

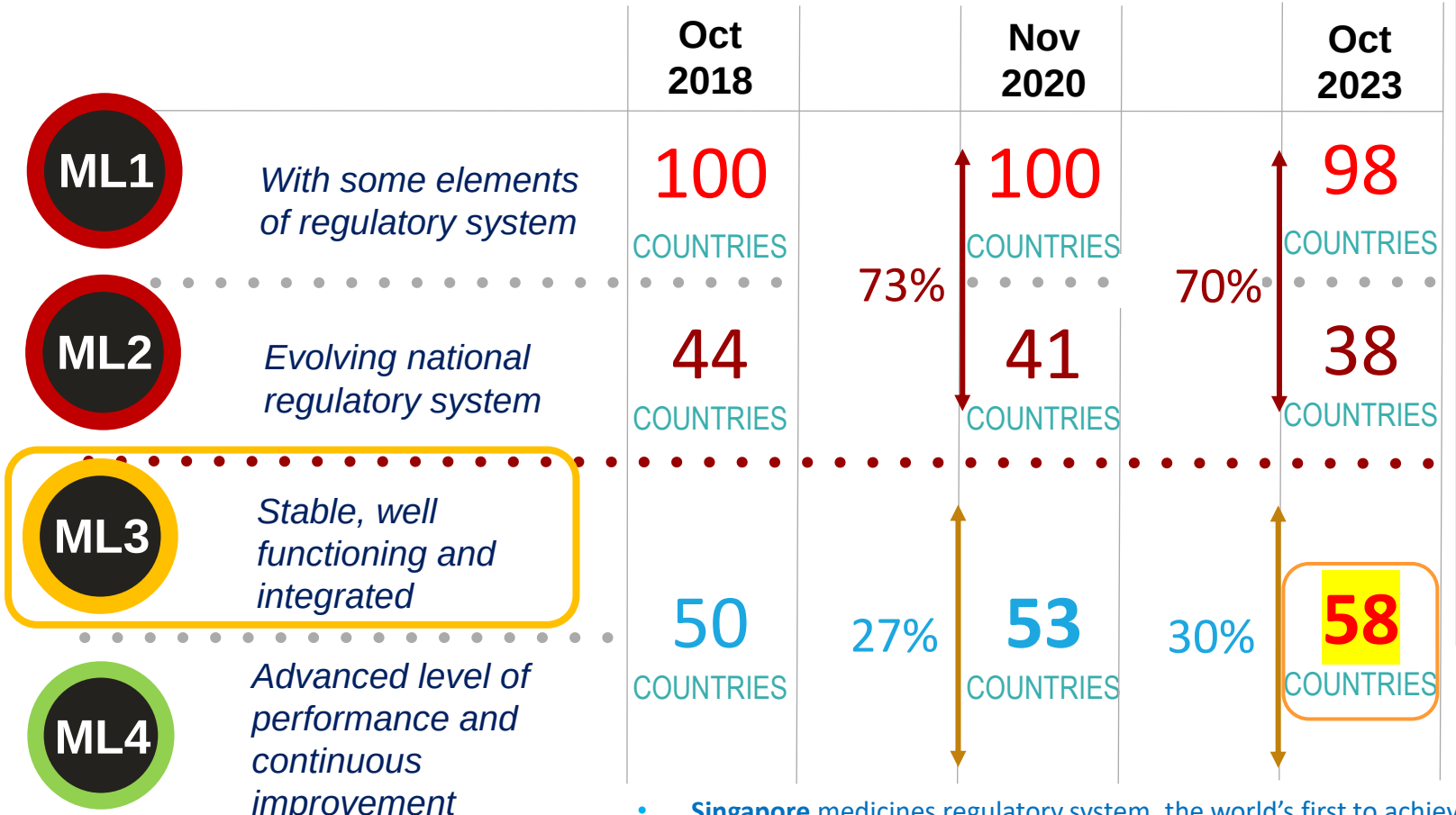
Deus Mubangizi
Unit Head
Prequalification Unit(PQ)
Regulation and Prequalification (RPQ)

Objectives

1. **Why prequalification and reliance?**
2. **What is prequalification**? – Mission, objectives, functions, scope, process, requirements, results and impact.
3. **Prequalification placing countries at the centre.**
4. **CRP: Prequalification facilitating reliance, equitable and timely access to quality assured health products – Universal Health Coverage.**
5. **Prequalification facilitating quality and sustainable local production.**
6. **New IT Database (ePQS): streamlining PQ processes, increasing transparency, monitoring and reporting on PQ KPIs.**
7. **Take home messages**.

Current levels of maturity of national regulatory systems

WHO GBT (for medicines and vaccines: as of June 2023)



Facts

- Over 70% of National regulatory authorities have inadequate regulatory functions
- Applicants face a landscape of disparate regulations, frequent delays and limited transparency.
- Globalization of production and supply chains

This has implications:

- Access to quality assured and safe medicines and vaccines in countries at ML 1 & 2 is not guaranteed:
  - high risk of Substandard and Falsified medical products
- Cost of inefficient regulatory systems drives up prices
- Regulators less prepared for public health emergencies

ML3 **GOAL of WHA Resolution 67.20**

ML: *(regulatory system) maturity level*

- **Singapore** medicines regulatory system, the world's first to achieve maturity level (ML4) *(Feb 2022)*
- **Egypt** vaccines regulatory systems reach ML3 *(Mar 2022)*
- **Nigeria** medicines regulatory systems reach ML3 (*Mar 2022)*
- **China** vaccines regulatory system reaches ML3 *(Jul 2022)*
- **South Africa** vaccines regulatory system reaches ML3 *(Oct 2022)*
- **Republic of Korea** achieves the highest WHO level for regulation of medicines and vaccines *(Nov 2022)*
- **Türkiye** regulatory system becomes fourteenth country to reach WHO Maturity Level 3 (Oct 2023)

World Health Organization

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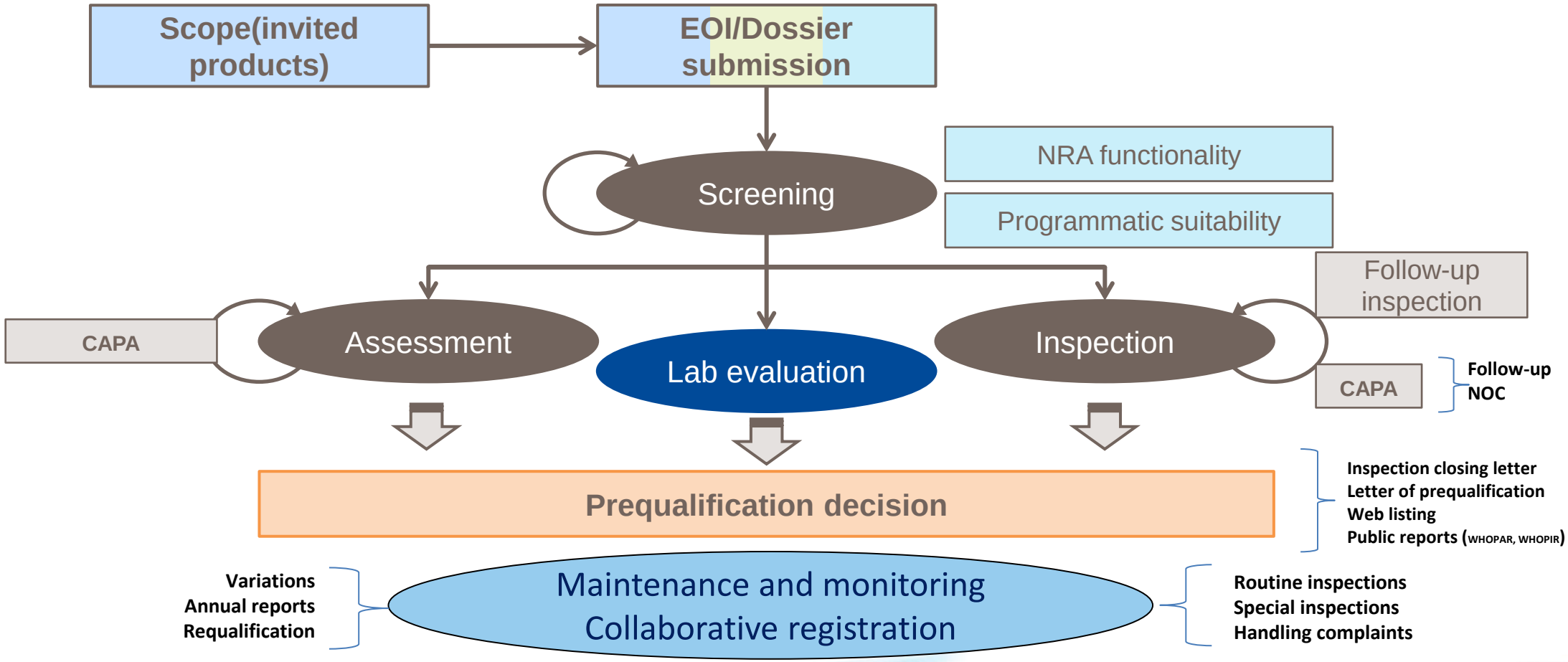
Why PQ: PQT Mission

WHO prequalification, in close cooperation with national regulatory agencies and partner organizations, aims to ensure access to key health products that meet global standards of quality, safety, and efficacy/performance, in order to optimize use of health resources and improve health outcomes. PQ is designed based on best international practice combined with assessing ***aspects of particular relevance for LMIC***.

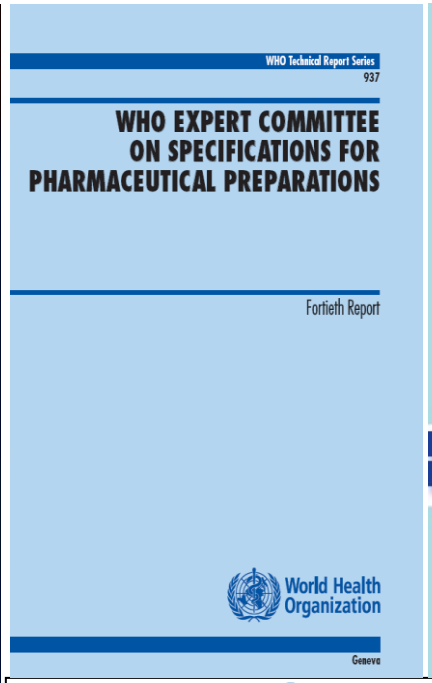
- WHO PQ responded to the need of procurement agencies and WHO Member States for quality-assured health products, by creating and applying quality-assurance mechanisms.
- WHO prequalification has become a trusted and reputed symbol for safety, quality and efficacy across stakeholders. WHO prequalification serves as a guarantee of good quality for health products, is a reference in terms of internal technical expertise and has the power to convene external expertise.
- PQ provides a model for **regulation in a globalized environment** (convening experts **from** countries, assessment of products for use **across** countries) – promoting harmonization of regulatory practice, norms and standards
- PQ has been instrumental in building national capacity for the manufacture, regulation and monitoring of health products – promoting harmonization, convergence, and reliance.

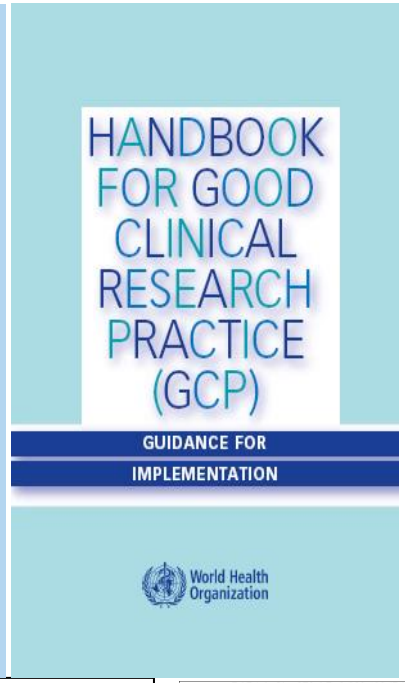
❑Prequalification process workflow

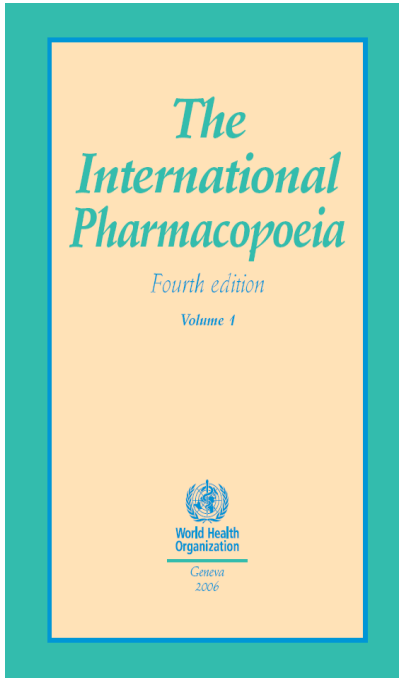
→ *For each type of product, prequalification includes a comprehensive dossier assessment and a manufacturing site inspection, as well as other product-specific elements of evaluation*

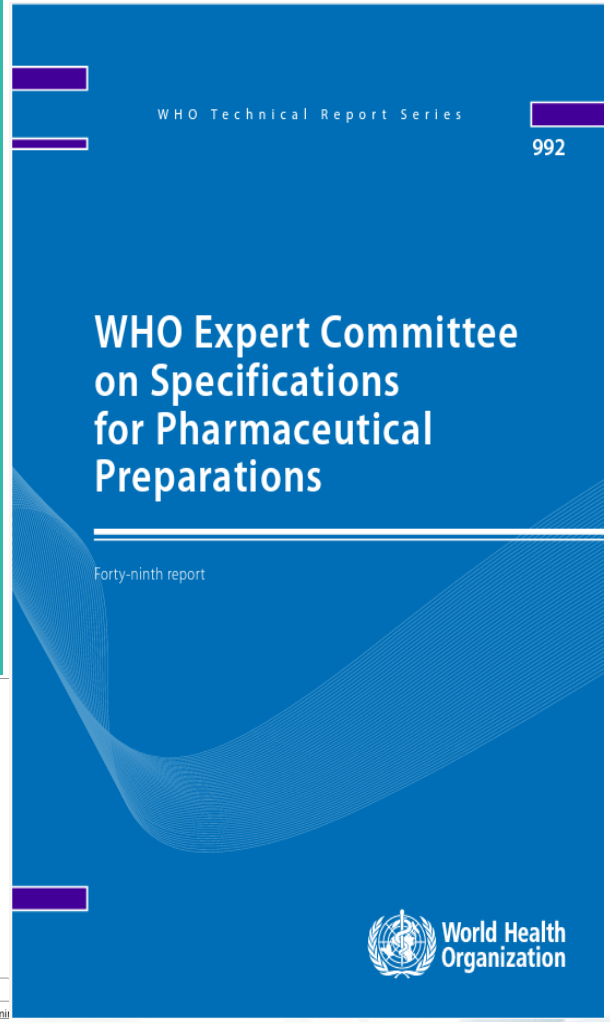


Prequalification Programme: International norms, standards and guidelines used to ensure wide applicability



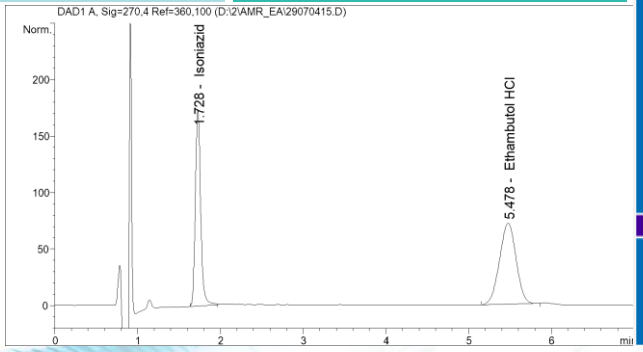






USP
BP
Ph. Eur.
Ph. Int.

Other guidelines
e.g. ICH, ISO



Fast track to prequalification

=

Good quality dossier at submission

+

prompt, complete, good-quality responses to PQ's questions, throughout the process.

→HIV/AIDS dossiers prequalified Oct 2022 to Oct 2023 - 13

•Dolutegravir/lamivudine/tenofovir 50mg/300mg/300mg tablets	2
•Abacavir/lamivudine/ 600mg/300mg tablets	1
•Efavirenz/lamivudine/tenofovir 600mg/300mg/300mg	1
•Efavirenz/lamivudine/tenofovir 400mg/300mg/300mg	2
•Darunavir 600mg tablets	1
•Atazanavir/ritonavir 300mg/100mg	1
•Lopinavir/ritonavir 100mg/25mg	1
•Lopinavir/ritonavir 200mg/50mg	1
•Ritonavir 100mg	1
•Sulfamethoxazole/trimethoprim Tablet 400 mg/80 mg	1
•Sulfamethoxazole/trimethoprim Tablet 800 mg/160 mg	1

Dossiers submitted in 2023 (10, so far)

❑Prequalified

- HA780; Darunavir (ethanolate) Tablet, Film-coated 600mg

❑Under assessment

- Dolutegravir (Sodium)/Lamivudine/Tenofovir disoproxil fumarate Tablet, Film-coated 50mg/300mg/300mg (2)
- Sulfamethoxazole/Trimethoprim Tablet 400mg/80mg
- Sulfamethoxazole/Trimethoprim Tablet 800mg/160mg
- Dolutegravir (Sodium) Tablet, Dispersible 5mg
- Dolutegravir (Sodium) Tablet, Dispersible 10mg
- Ritonavir 100mg
- Cabotegravir (sodium) Tablet, Film-coated 30mg
- Cabotegravir (sodium) Suspension for injection 600mg/3mL

→ HIV/AIDS EOI *revised* in April 2022

Added

- ❑Cabotegravir, suspension for intramuscular injection, 600mg/3ml (200mg/ml)
- ❑Cabotegravir, tablet 30 mg (*only as optional lead-in to injectable therapy*)

Comparators

- ❑Apretude (600mg/3ml suspension for i.m. injection, ViiV Healthcare Co.2)
- ❑Vocabria (30 mg tablet, ViiV Healthcare Co.2)

→ Guideline *update* (4 July 2023); Notes on the Design of Bioequivalence Study: Cabotegravir

- **Cabotegravir suspension for injection is a prolonged-release suspension product.**
- **Injection has long washout periods of up to 60 weeks - parallel BE design should be used.**
- **Based on available data;**
  - The 52-week sampling time has been removed
  - The duration of sampling has been revised to be at least 42 weeks
  - These changes will accelerate the timeline for a BE study by approximately 2.5 months
  - Sampling example; pre-dose and at 4, 8, 16, 24, 48, 96, 120, 144, 168, 192 hours, 2, 3, 4, 6, 8, 12, 20, 28, 36, and 42 weeks

→ Other updates

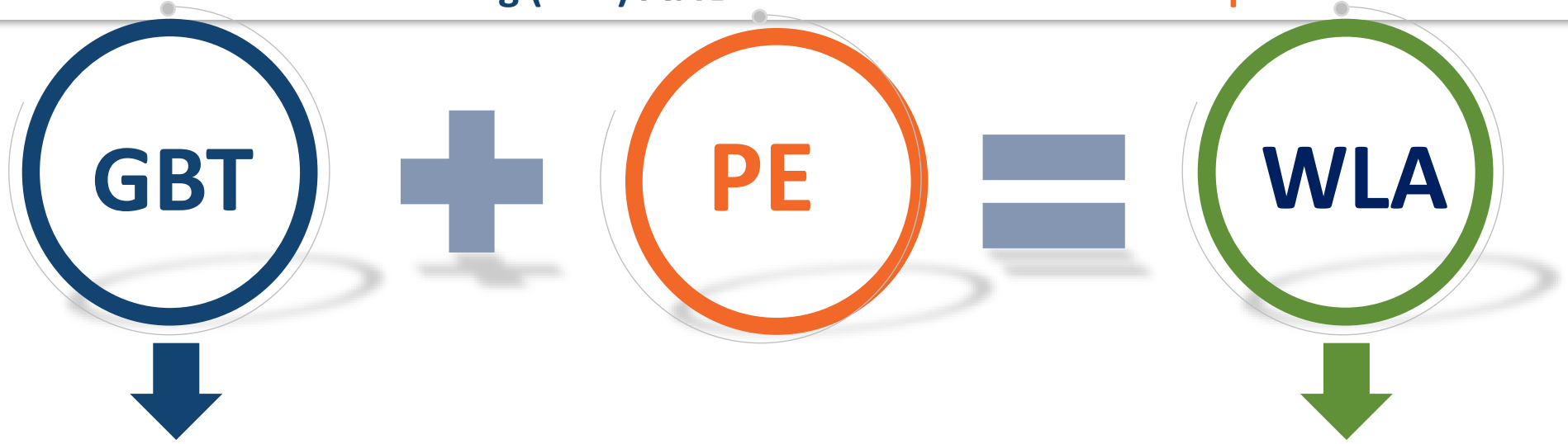
- **Face-to-face CPH medicines assessment sessions restarted in September 2022**
- More variations due to increasing number of prequalified products and requalification applications (over 300 variation applications received in 2023) – still PQT/MED is meeting its timelines
- 41 products requalified in 2023 (HIV/AIDS products - 21)
- Continued support to procurers (e.g., GF, GDF, UNITAID, UNICEF, NTD) through advice issued by the Medicines Expert Review Panel
- **Two virtual annual assessment trainings on quality of small molecules and biotherapeutic medicines to regulators (June 2023)**
- **Two annual workshops for manufacturers on small molecules and biotherapeutic products (Sept 2023).**
- Continued collaboration with the WHO Science Division and WHO disease programmes in the provision of scientific advice to product developers
- Ongoing discussions with FDA on **extending the CRP lite pilot**

Definition of WLA

adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) in Oct 2020 and published in Technical Report Series (TRS) 1033

A WHO Listed Authority (WLA) is a regulatory authority or a regional regulatory system which has been documented to comply with all the relevant indicators and requirements specified by WHO for the requested scope of listing based on an

established benchmarking (GBT) AND a Performance Evaluation process



Maturity Level (ML)

Risk-based performance evaluation (PE)

delinked from ML

World Health Organization

WLA initiative is NOT for capacity building

GBT-ML

Represents primary means by which the WHO objectively evaluates regulatory systems and measures their

Maturity Level

GBT benchmarking process incorporates **some elements** of performance measurement

Designed to provide a structured approach to analyzing the **inputs, regulatory processes** and intended **outputs** that together determine

how well a regulatory system is configured

Verify **establishment, appropriateness** and **implementation**
of Regulations, Processes, Procedures, Plans, etc.

WLA

Nature and extent of evaluation to provide a high degree of confidence in an **authority's performance (e.g., quality of reports, scientifically sound regulatory decisions, etc.)**

Documented consistency in adherence to international regulatory requirements and best practices, procedures and in producing **outputs, outcomes reaching a more efficient regulatory system**

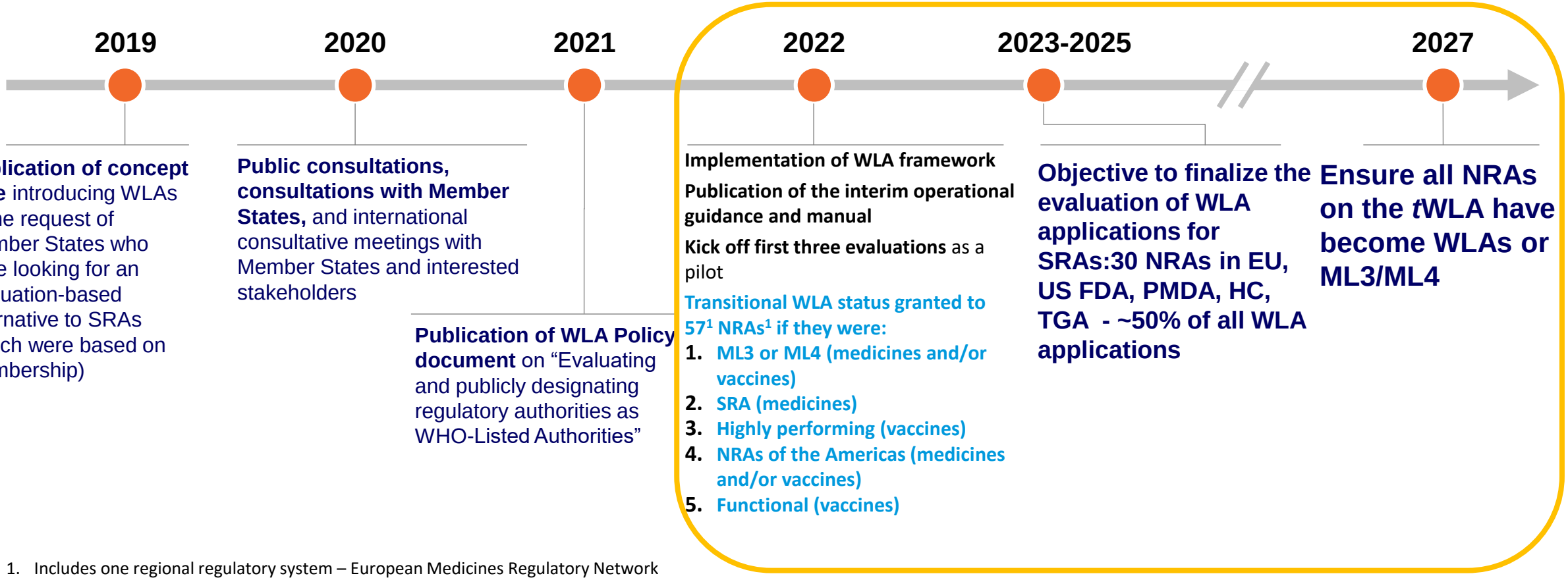
Expansion of performance measurement

to provide a more detailed picture of

how well a regulatory system operates

Measure **performance** and **impact**
of Regulations, Processes, Procedures, Plans, etc.

In summary … from the *concept to full implementation*



1. Includes one regional regulatory system – European Medicines Regulatory Network

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Outcome of the WLA pilots and next steps

Technical Advisory Group on WLA (TAG-WLA)

1st meeting
11-12 Sept 2023

ML4 NRA

tWLA

SRA

WLA
Decision and Listing eminent

TAG reviewed reports and rendered opinion on 3 regulatory authorities

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In summary

- GBT is a capacity building tool and measures maturity levels of regulatory systems
  - ✓ Great response with 95 member states using the GBT **(36 benchmarked & 59 self-benchmarked)**

- Not a single regulator can fulfil all regulatory work alone and independently
  - ✓ Implementation of the WLA initiative a game-changer in regulation of medical products

- Current scope for WLAs: medicines and vaccines, with potential expansion to other product streams
  - ✓ Open to all regulators at ML 3/ML 4

- WLA replaces SRAs and a unique tool for promoting reliance & global procurement

- Great support and buy-in from regulators and particularly the SRAs
  - ✓ Performance evaluation ongoing for majority of the SRAs likely to be concluded in 2024

- Transitional WLAs will by 2027 become either WLAs or ML3/ML 4 and will be removed from the WHO website if they do not transition into any of the two pathways

→ *The collaborative procedure enables NRAs to accelerate the registration of prequalified products so that they can enter local markets more quickly*

Process

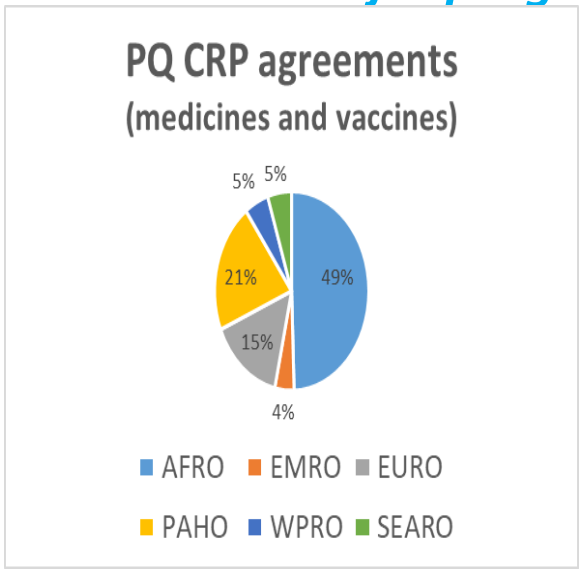
- WHO PQ shares the reports that served as the basis for the prequalification decision, so that NRAs do not conduct assessment and inspections
- National registration based on PQT evaluation

Principles of CRP

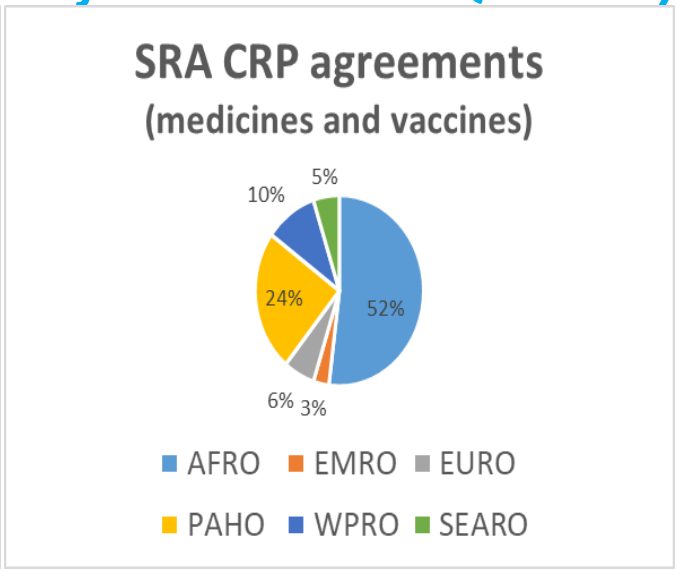
- **Voluntary** for both applicant and NRA
- Product and registration dossier in countries are **'the same'** as **prequalified by WHO.**
- Shared confidential information to support NRA decision making in **exchange for accelerated registration process**
- **'Harmonized product status'** is monitored and **maintained**

WHO Collaborative Registration Procedure – Countries

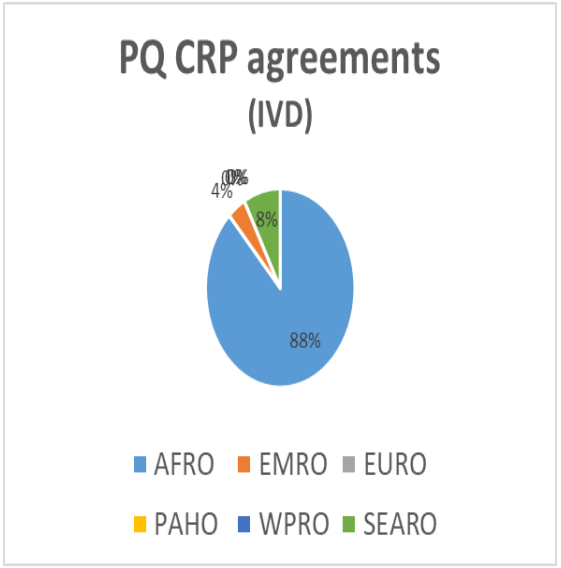
Major progress for both WHO PQ & SRAs/WLAs CRP



73
countries



63
countries



26
countries

Analysis as per RPQ impact assessment March 2023

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→ Collaborative registration procedure

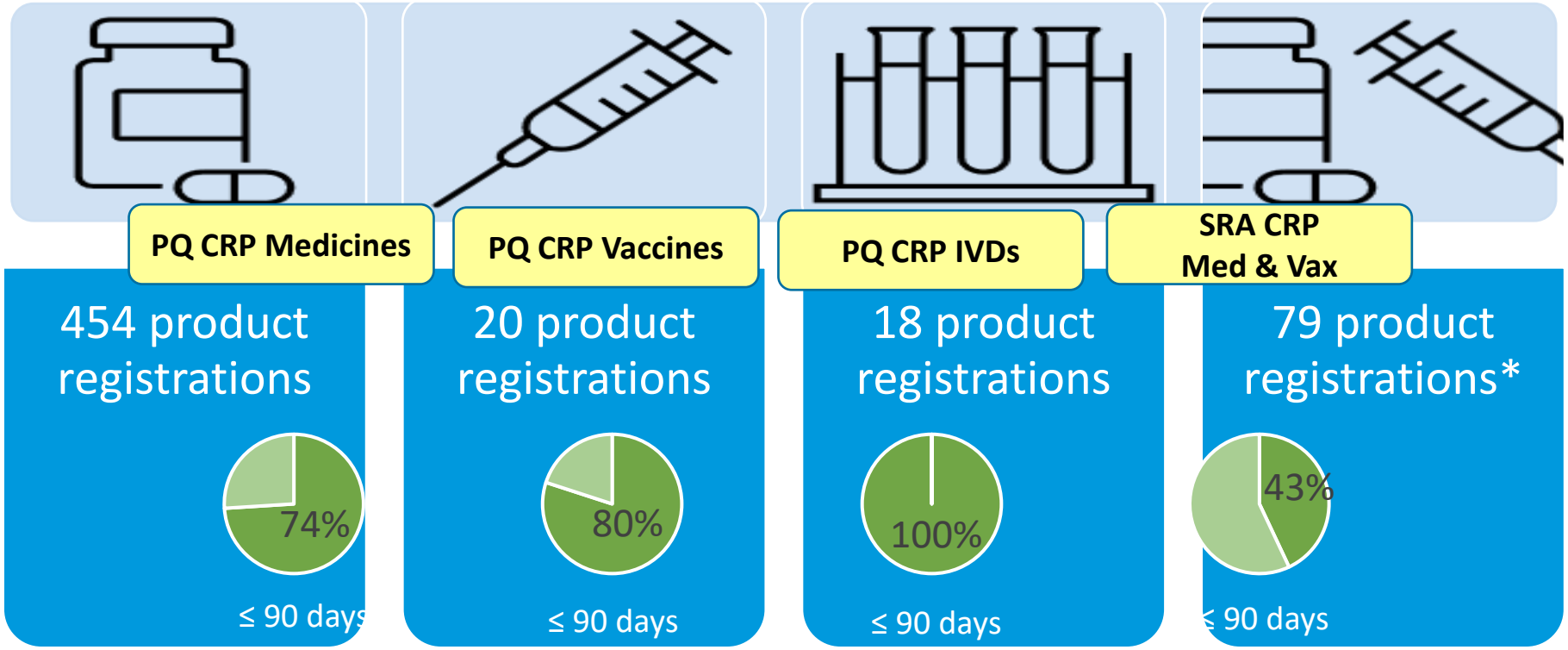
- Currently 62 countries and 1 REC (CARICOM) implementing CRP for medicines
- **6 countries** have signed up since the last update in October 2022 –
  - Türkiye, Liberia and Papua New Guinea, Central African Republic, Chad, and Guinea
- **Assessment reports for 53 products** provided to FPI team since Oct 2022 to share with countries
  - HIV/AIDS – 20 products
- Country registrations in 2023
  - HIV – 23 registrations

- More information; https://extranet.who.int/prequal/medicines/collaborative-procedure-accelerated-registration

Collaborative registration procedure – 2023 numbers

	Therapeutic Area	Product registrations (numbers)	Countries
1	HIV/AIDS	23	Mozambique (8), Rwanda (5), Eritrea (3), Botswana (2), Malawi (2), Zambia (2), Tanzania (1)
2	Tuberculosis	16	Eritrea (4), Zambia (3), Mozambique (2), Tanzania (2), Rwanda (2), Ghana (1), Uganda (1), Botswana (1)
3	Malaria	10	Mozambique (3) , Zambia (3), Botswana (1), Ghana (1), Tanzania (1), Rwanda (1)
4	Reproductive Health	6	Rwanda (2), Zambia (2), Mozambique (1), Botswana (1)
5	Covid - 19	3	Malawi (2), Botswana (1)
6	Diarrhea	2	Tanzania (1), Rwanda (1)
Total		60	

WHO Collaborative Registration Procedure – Registrations (2018 -2022)



*78% within 250 days

Analysis as per RPQ impact assessment March 2023

Regulation and Prequalification (RPQ) Department

Objectives/prerequisites of local production

- **Local production of heath products should aim and be trusted to meet the following objectives/prerequisites:**

1) Ensure quality/safety/efficacy.

2) Facilitate access.

3) Ensure sustainability.

Objective 1: Ensure quality/safety/efficacy:

❑ Robust development:

- R&D capacity, CSA with PQ and technical departments
- Technology transfer: C-TAP, mRNA Hub, bilateral.

❑ Robust production processes:

- Appropriate investment in sustainable GMP compliance.
- WHO collaboration to provide technical assistance (LPA: PQM+,GIZ, etc.)

❑ Robust evaluation:

- Regulatory system strengthening: GBT, IDP, WLA
- PQ facilitates robust evaluation of these products.
  - Involvement of African regulators in WHO evaluations.
  - Participating and facilitating Regional joint assessments (RECs/AVAREF/AMA).

Objective 2: Facilitate access

❑ Adequate production capacity:

- access to sustainable financing
- secure supply of raw materials
- human resources of appropriate quality and numbers

❑ Timely national authorization:

- efficient regulatory process – GBT
- applying reliance – CRP based on PQ, SRA/WLA,
  - PQ shares reports to facilitate national authorizations to facilitate timely and equitable access.

❑ Procurement and effective supply:

- Joint tenders and pooled procurement.
- Common QA policy for market shaping and aggregation of demand for quality assured products.

Objective 3: Ensure sustainability.

❑ Targeting a wider market – domestic and foreign:

- PQ in collaboration with RECs/AVAREF/AMA facilitates this by using international requirements, robust global assessments and building trust across countries and procurers.
  - PQ supports countries & procurers in lifecycle management.

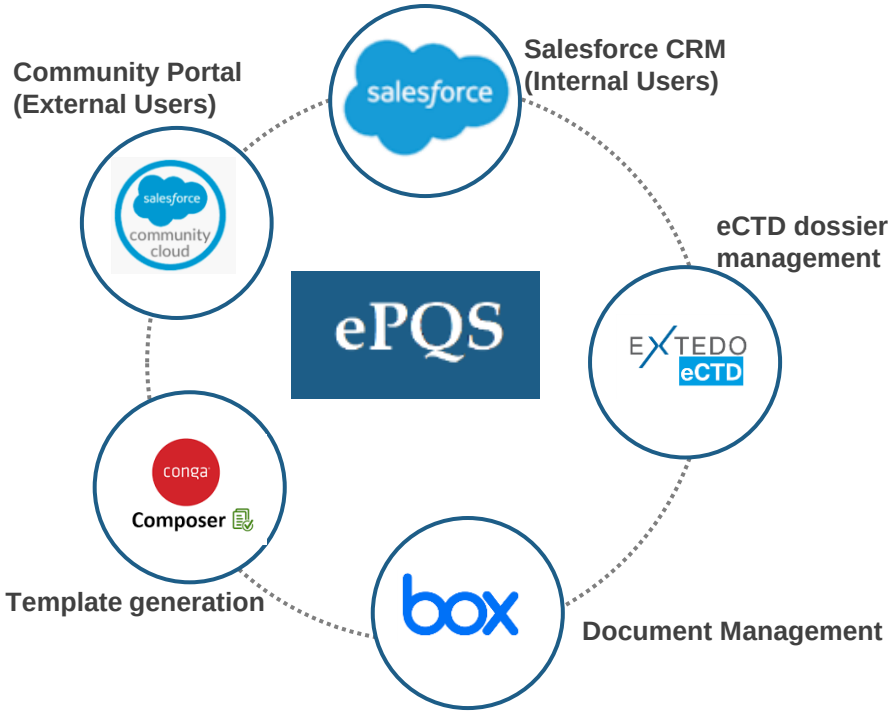
❑ Ensure a healthy product pipeline:

- Wide product pipeline and adaptive technology important for resilience and sustainability:
  - PQ updates EOIs in response to change in policy/guidelines, resistant variants, AMR and impact on product lifecycle.
  - Pipeline scanning for new innovations, CSA, presubmission advice

What is ePQS ?

ePQS (electronic Prequalification System) is a new IT solution that brings all of the core areas of work of WHO's Prequalification Unit into one centralized platform, including as well the WHO's Collaborative procedures and complaints testing. This encompasses 13 unique products types, 48 unique application types, plus many other supporting record types.

Key components of ePQS



Key benefits of ePQS

1 Transparency & Harmonization

From a single interface internal users will be able to manage and track progress of application resulting in improved harmonization across work-streams

2 External stakeholder focused

Provides different external users including Applicants Manufacturers, NRA and External Expert access to the External Portal

3 Enhanced features

Allow applicants to submit electronic Common Technical Document (eCTD) dossiers making the compiling and managing the lifecycle of product-related documentation efficient and time saving

4 Oversight and Reporting

Enable process related milestones to be captured in greater details resulting in better reporting of key performance indicators (KPI)

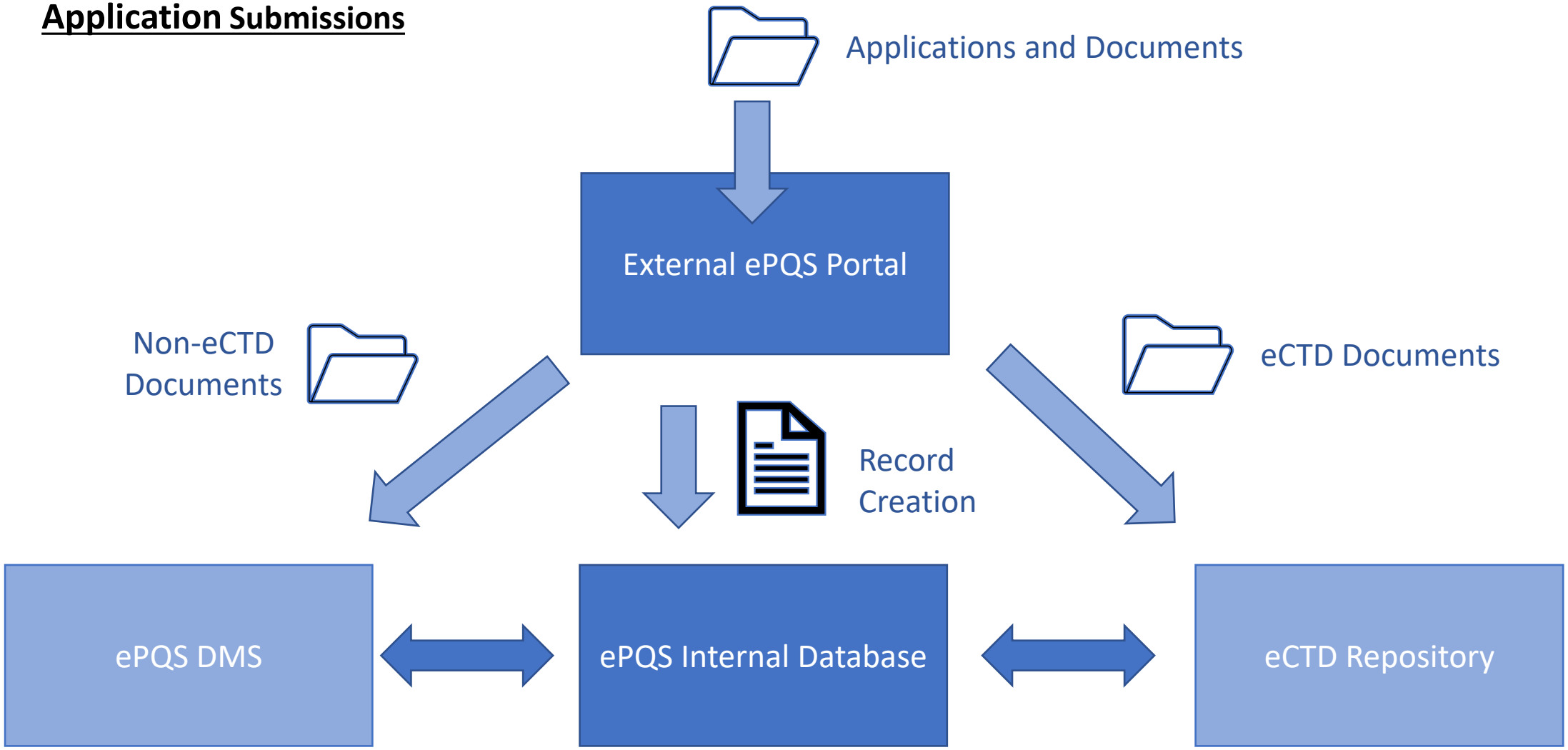
5 Integration

Allow automatic updating of various list of Prequalified and EUL products as well as application pipeline pages in real time on the PQT website

World Health Organization

ePQS system overview

Application Submissions



ePQS update

- Web publishing from the new database
- What is new?
  - Sites used for primary packaging now identified
  - Details of reference authority for abridged pathway included
  - Details of products with different packs now separate

FPP Packaging Only

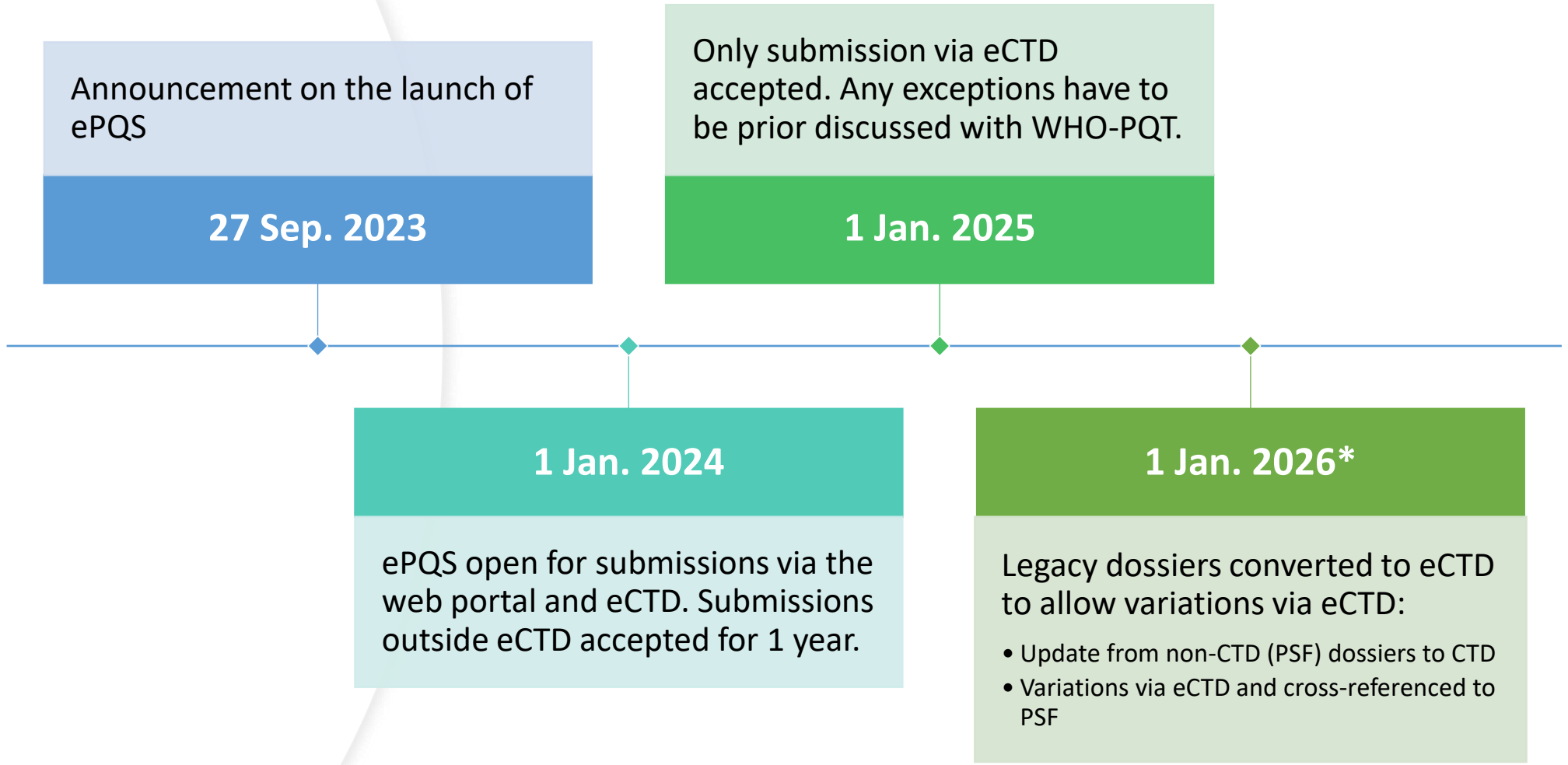
Packaging Coordinators, Inc.
3001 Red Lion Road, Philadelphia, PA, 19114, United States

Novartis Pharma AG
No 31 Yongan Road, Nanguan Chengguan Township, Changping District, Beijing, Beijing, 102 200, China

Packaging Type:	Blister, Alu/PVC/PVDC
Configuration:	10x10, 28x3, 28x24;
Shelf life (months):	24
Storage conditions:	Do not store above 25°C, store in dry condition, protect from light
Packaging Type:	Strip, Alu/Alu
Configuration:	10x10, 28x3, 28x24, 14x12
Shelf life (months):	36
Storage conditions:	Do not store above 30°C, store in dry condition, protect from light

Date of prequalification:	21 Mar 2023
Basis of listing:	Prequalification - Abridged
Therapeutic area:	Reproductive health
Type:	Finished Pharmaceutical Product
Dosage form:	Powder for suspension for injection + Solvent for parenteral use
Reference authority:	Agencia Española de Medicamentos y Productos Sanitorios
Applicant organization:	**LABORATORIO REIG JOFRE, S.A.**

ePQS



***We need manufacturers' feedback on the issue of conversion of legacy non-CTD dossiers to eCTD and the timelines.**

Some of our priorities for 2024 and beyond II

- ✓ Continue to **expand the pool of external experts** (through collaborations with NRAs and SRAs/WLAs)
- ✓ **Collaborate with the AMA** as they establish assessment procedures and practices
- ✓ Collaborate with FDA to **expand the CRP lite pilot**
- ✓ Design how PQT/MED will **use the decision/outputs of new WLAs/tWLAs (ML3/ML4 NRAs)** in its assessments.
- ✓ Fully implement the **new IT solutions (ePQS and eCTD)**
- ✓ **Expand the pipeline on the web to include additional details** on products under assessment (as for COVID-19 therapeutics)

New website: https://extranet.who.int/prequal/

For further questions, please contact:

- Deus Mubangizi, Unit Head, WHO Prequalification, Email: mubangizid@who.int
- Matthias Stahl, Team Lead, Prequalification Team, Medicines Email: stahlm@who.int

END

BACKUP SLIDES

PQT Functions

- Prequalification
  - Dossier assessment
  - Inspection of manufacturing and testing sites/facilities
  - Sample testing/Independent performance evaluation
- Maintain and monitor prequalified products
- Health products evaluation and/or risk assessment to support health emergencies, shortages and other needs outside scope of PQ
- Provide scientific advice to manufacturers and other stakeholders
- Capacity building for regulators and harmonization.
- Support product evaluation activities at international, regional, and national levels, including reliance
- Provide technical advice to other WHO programmes

PQT Objectives

- ✓ Prequalification of priority products and their life cycle maintenance, based on WHO and international norms and standards
- ✓ Promoting the quality agenda vis-a-vis National Medicines Regulatory Authorities (NMRAs) and procurers. Contribute expert input to WHO's norms and standards for safe, effective and appropriate use
- ✓ Providing a model for regulation in a globalized environment (convening experts from countries, assessment of products for use across countries) – promoting *harmonization of regulatory practice, norms and standards*
- ✓ ERP/D: Aiding procurement decisions in the absence of prequalified or SRA approved products
- ✓ Capacity building of country regulators.
- ✓ Capacity building of manufacturers, improving their dossiers to countries.

PQT/MED: Scope

Priority medicines in 15 therapeutic areas:

- **HIV/AIDS**
- Tuberculosis
- Malaria
- Reproductive health
- Influenza
- Neglected Tropical Diseases
- Diarrhoeal disease
- Hepatitis B and C
- Infections in newborn and young infants and childhood pneumonia
- Insulins and insulin analogues (BTPs)
- Certain cancers (BTPs)
- COVID-19 (BTPs and small molecules)
- Ebola Virus Disease (BTPs)
- **Treatment of multi-drug resistant bacterial infections (2023)**
- Products for cessation of tobacco use **(2023)**

Type of products:

- ✓ Finished Pharmaceutical Products
- ✓ Active Pharmaceutical Ingredients
- ✓ Biotherapeutics, incl biosimilars

Pathways:

- ✓ Full assessment of generics/biotherapeutics, including those that may be facilitated by access to SRA/WLA assessment reports
- ✓ Abridged pathway for innovator or generic/biotherapeutics products approved by an SRA, or in future ML4 WLA

Expert Review Panel (ERP) for FPPs and BTPs

→ Product dossiers submitted 2016 – October 2023

	2016	2017	2018	2019	2020	2021	2022	2023
HIV	24	16	36	23	17	5	9	10
TB	19	17	20	12	5	10	6	8
Malaria	17	8	10	12	14	5	11	3
Rep Health	9	11	6	6	4	5	5	3
Influenza	0	0	3	0	0	0	0	0
Diarrhoea	2	0	2	0	1	1	1	0
NTD	0	0	2	2	2	4	2	2
Hepatitis	7	8	11	3	0	4	2	0
Ebola	-	-	-	-	-	-	-	2
COVID 19	-	-	-	-	5	5	14	6
Total	78	60	90	58	48	39	50	34

Placing countries at the centre

"PQTm's mission is to work in close cooperation with national regulatory agencies and partner organizations to make quality priority medicines available for those who urgently need them. This is achieved through assessment and inspection activities, building national capacity for manufacture, regulation and monitoring of medicines, and working with regulators to register those medicines quickly." https://extranet.who.int/prequal/content/overview-history-mission

- Each bimonthly assessment session in CPH attracts ≥50 experts from across the globe, ≥35 from LMICs and ≥15 from well resourced NRMAs – best impact on capacity building and promoting convergence

What difference does WHO prequalification make?

Assessment of WHO-prequalification impact has demonstrated that:

- **it has enabled a large donor-funded market size of approximately US$ 3.5 billion of quality, safe and effective IVDs, medicines and vaccines:** it is likely that, in addition, prequalified IVDs, medicines and vaccines are procured by national governments, as well as private-sector organizations within country
- **helps ensure that products are developed for an LMIC context:** meaning that they are appropriate for use in the populations for which they intended and are not negatively affected by the conditions of the environment in which they may be transported or stored
- **plays an important role in guiding product innovation and early-stage development:** examples have included bringing paediatric TB products to market in sub-Saharan Africa and promulgating the deployment and use of HIV self-testing diagnostics
- **it has helped raised manufacturing standards in LMIC:** the number of medicines and vaccines MIC manufacturers participating successfully in WHO prequalification continues to grow: meaning that capacity and confidence with respect to LMIC production of quality-assured products in those countries is likewise growing; LMIC now represent more than 40% of all manufacturers with prequalified medicines and 50% of manufacturers with prequalified vaccines.

In addition, WHO prequalification has contributed to strengthening of country health and regulatory systems. This has included work in support of WHO's development of norms and standards, its contribution to strengthening of national regulatory authorities and regulatory harmonization, and its support to building national and global capacity for safety monitoring and vigilance for health products.

https://extranet.who.int/pqweb/about

Original Article | Published: 16 January 2014

A quiet revolution in global public health: The World Health Organization's Prequalification of Medicines Programme

Ellen F M 't Hoen ✉, Hans V Hogerzeil, Jonathan D Quick & Hiiti B Sillo

Journal of Public Health Policy 35, 137–161 (2014) | Cite this article

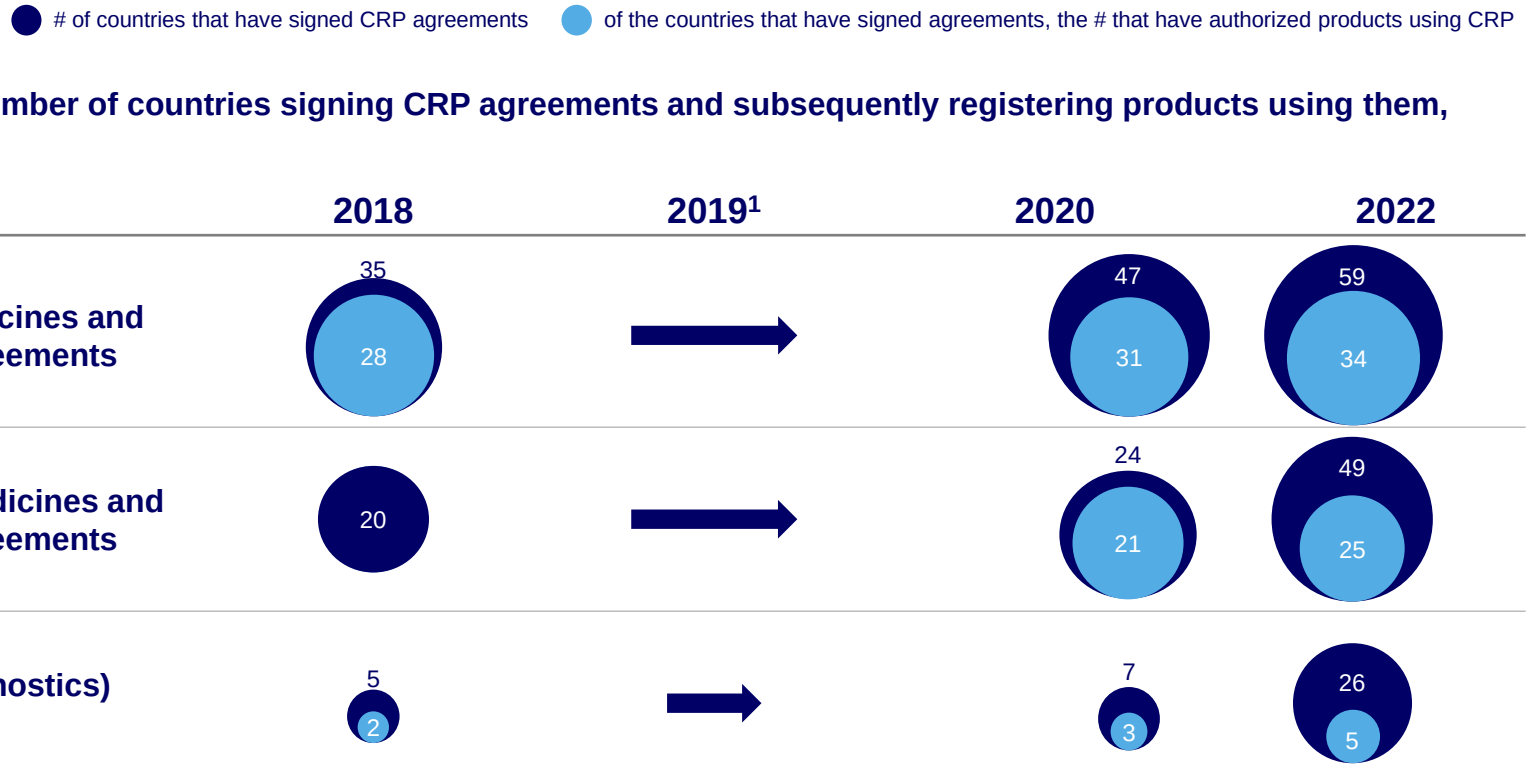
WHO Prequalification and National Regulators

The programme promotes interaction and close collaboration with and between national drug regulatory agencies, in both developing and wealthy countries. The legitimacy of the WHO PQP's decisions derives in part from this collaboration, and from its solid and transparent procedures and standards. The standards come out of an international consensus process conducted with Member States. The process concludes with review and adoption by the WHO Expert Committee on Specifications for Pharmaceutical Preparations. Transparency builds confidence. The WHO PQP goes beyond the current information-sharing practices of national drug regulators.

Saving Lives and Saving Money

From a public health perspective, WHO PQP's greatest achievement is improved quality of key medicines used by millions of people in developing countries. In a study of 12 958 ARV purchase transactions between 2002 and 2008, Brenda Waning concluded that five ARVs recommended by WHO in 2003 constituted 98 per cent of the ARVs purchased in 2004–2006. The price of the major FDCs decreased from $484 per person in 2002 to $88 in 2008. Purchases of new ARVs recommended by WHO in 2006 increased 16–20 times in the 2 following years. By 2008, 85–88 per cent of the ARVs procured by PEPFAR, the Global Fund, and UNITAID were prequalified.[29]

Exhibit 34: Number of countries that have signed PQ CRP agreements for vaccines and medicines and diagnostics, and SRA CRP agreements for vaccines and medicines between 2018 and 2022



1. PQ CRP for diagnostics started in 2019

Exhibit 36: Cumulative number of accelerated product registrations under PQ CRP for medicines

Cumulative number of product registrations under PQ CRP in an accelerated manner for medicines, 2018-2022, registrations within 250 days and registrations within 90 days

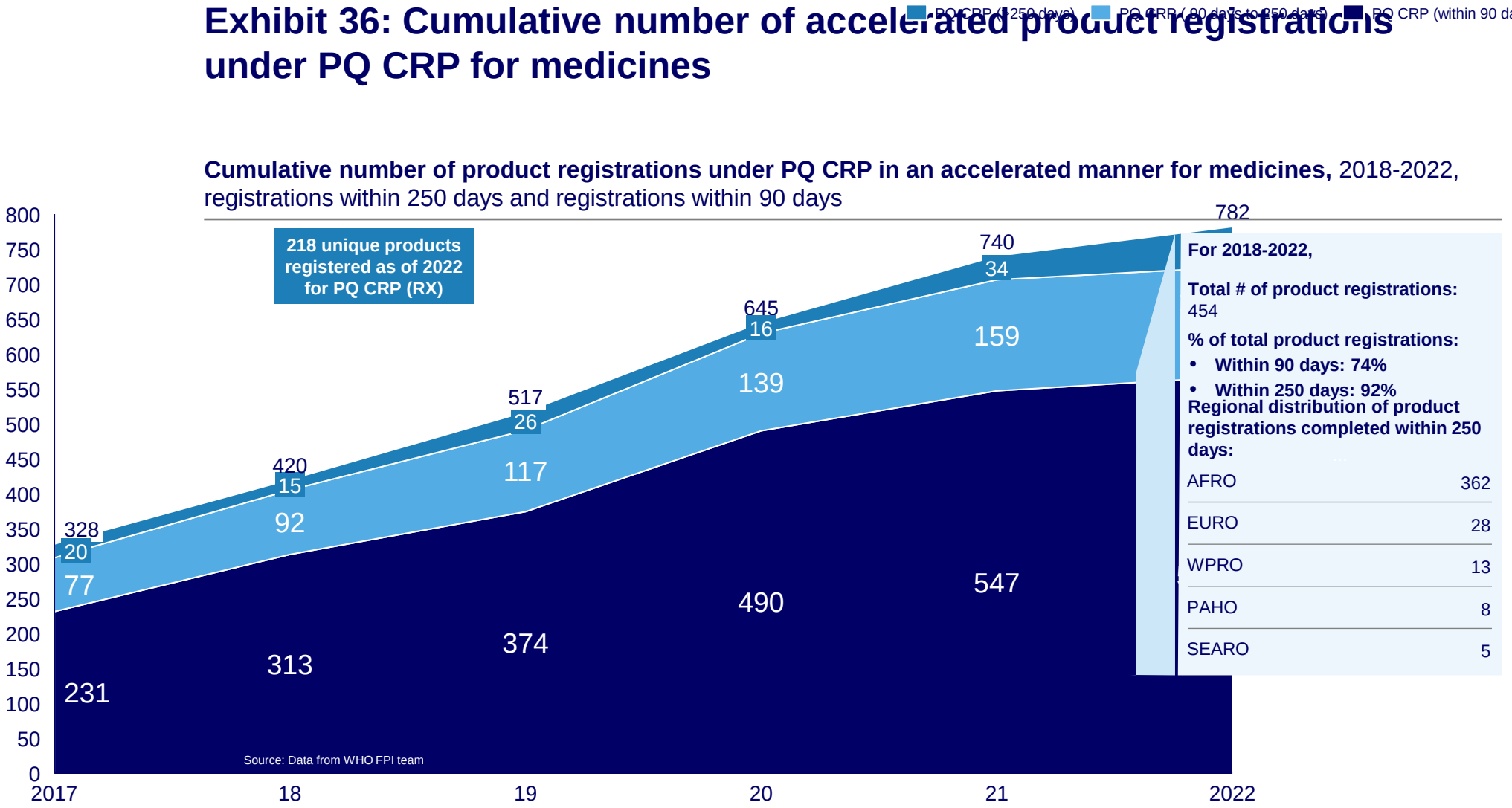


Exhibit 31: Overview of major donors requiring PQ for the procurement of medicines

Donor/ procurer perspective on PQ

New compared to 2018

Organization	HIV/AIDS	TB[2]	MALARIA	RH	Contingency approval process
PEPFAR	FDA (NDA or ANDA or tFDA [1])	-	-	-	-
PMI	-	-	PQ or SRA approval	-	Test prior or concurrent to shipment
USAID	FDA (NDA or ANDA or tFDA	-	PQ and SRA approval and preapproved by a USAID wholesaler	FDA NDA or ANDA or PQ or SRA approval	UNFPA ERP[2] (for RH only)
UNFPA	-	-	-	WHO/UNFPA PQ or SRA approval	UNFPA ERP or pre-shipment inspection of pharmaceuticals
Unitaid	PQ or SRA approval	PQ or SRA approval	PQ or SRA approval	-	ERP
unicef	PQ or SRA approval	PQ or SRA approval	PQ or SRA approval	PQ or SRA approval	ERP
The Global Fund	PQ or SRA approval	PQ or SRA approval	PQ or SRA approval	-	ERP or meet various ISO standards and GHTF authorization[3]
Stop TB Partnership GLOBAL DRUG FACILITY	-	PQ or SRA approval	-	-	ERP
MSF	PQ or SRA approval or tFDA[1]	PQ or SRA approval or tFDA[1]	PQ or SRA approval or tFDA[1]	PQ or SRA approval or tFDA[1]	ERP[3] or MSF qualification process[2]
UNDP	PQ or SRA approval	PQ or SRA approval	PQ or SRA approval	PQ or SRA approval	ERP
Pan American Health Organization	PQ or SRA approval (PQ preferred)	PQ or SRA approval (PQ preferred)	PQ or SRA approval (PQ preferred)	PQ or SRA approval (PQ preferred)	Internal PAHO mechanisms for quality assurance with NRAs
ICHC 6	PQ or SRA approval	PQ or SRA approval	PQ or SRA approval	PQ or SRA approval	-
IPPF	-	-	-	WHO/UNFPA PQ or SRA approval	ERP

1. Tentative FDA; 2. Includes a preassessment based on product and manufacturer questionnaires, a Good Manufacturing Practices (GMP) of the manufacturing site, a product evaluation based on product and/or manufacturer questionnaire(s) according to standards set by WHO, and based on a standard Product Questionnaire common to the Interagency Pharmacist Group (UNICEF, ICRC, The Global Fund, WHO procurement center, UNFPA, GDF and MSF) and active monitoring and follow up; 3. Expert Review Panel; 4. Specifically, the "WHO certification scheme on pharmaceuticals moving in International Commerce"; 5. Good Manufacturing Practice; 6. Details provided based on interviews with WHO colleagues / could not be validated with publicly available information

Future Priorities - PQT

- Maintaining and continuous improvement of current PQ activities (QMS and streamlining processes).
- Consolidation of activities to support response to emergences – EUL and facilitation of access health products at international, regional and national level.
- Expansion of resources for PQ under realities of cap on FTEs at HQ:
  - Use of full-time consultants
  - Expand the pool of external experts – measures to develops experts including from non-traditional sources (Annual training workshops).
- Complete and fully implement new IT solution (ePQS).
- Expansion of the scope of PQ:
  - Establish the PQ Team for priority medical devices (MD) and personnel protection equipment (PPE)
  - Expand therapeutic and/or product types covered by PQ assessments.
- Review approaches and criteria for defining eligibility:
  - Procedure for defining PPCs/TPPs and parallel progress to WHO guideline recommendation and eligibility for PQ/EUL.
  - Co-ordinated scientific advice (CSA) with Clinical/Disease programmes – initiated by the Science Division
- Adjusting to new realities and defining the role of PQ:
  - Strengthened NRAs – increasing number of ML3 NRAs.
  - Roll out of WLAs and replacement of SRAs.
  - Establishment of new regional regulatory systems – e.g., AMA, other regulatory networks
- Strengthening international collaboration:
  - ICMRA, ICH, IMDRF, RAG, Vaccine Cluster.
  - Expand list of SRAs/WLAs with confidentiality agreements with WHO/MHP/RPQ/PQT.
  - Expand collaboration with regional assessment arrangements: EMA, AMA, ASEAN, GCC, AVRAREF, etc.

Some of our priorities for 2024 and beyond I

- ✓ Continue to provide a list of internationally accepted quality assured priority products to procurers and partners – enabling harmonized procurement decisions
- ✓ Engage with WHO clinical departments, procurers and partners to expand into new therapeutic areas as per set priorities
- ✓ Collaborate with WHO clinical departments to implement development of treatment recommendations in parallel with prequalification for promising products to promote faster access (as applied for COVID-19 therapeutics), maybe gaining 6-12 months or more.
- ✓ Continue to collaborate with WHO Science division and clinical departments in the WHO Coordinated Scientific Advice (CSA) Procedure for new priority products or new uses of existing products
- ✓ Expand the abridged procedure to allow prequalification of SRA/WLA approved products (EMA Art 58, Swissmedic's MAGHP and other access programmes) and facilitate their national registrations via CRP
- ✓ Implement a new approach to increase availability of quality-assured human insulin: human insulin master file procedure

RPQ- Prequalification

Summary of achievements

- **13% more products were prequalified in the last 5-year period** (2018-2022) compared to the previous 5-year period
  - If adjusted by removing COVID-19 products – the numbers are the same
- **EUL: 3x more products EUL-listed in the last 5-year period** (2018-2022) compared to the previous 5-year period, almost 100% of them are COVID-19 products

  # Number of IVDs listed in EUL

  Covid-19: **38**, Ebola: **6**, Zika: **4**

- For medicines, COVID-19 products were eligible for PQ - team was able to **establish a fast-track process to proceed them achieving median times far lesser than target**
- **Increase in the therapeutic areas within PQ scope** - five added for medicines[1], three for vaccines[2] and three for diagnostics[3]

Challenges

- **Limited human resources** – staff and external experts.
- Ever **increasing workload with expansion of PQ scope** without corresponding increase in resources.
- Competition for capacity of laboratories for PQ Performance Evaluation.
- **Backlog as the result of the impact of the pandemic** on PQ internal and external resources and on timely response of the applicants.
- **Immature regulation, harmonisation** and diverse stakeholders plus **legacy of old programmes** in certain product areas (VCPs and IVDs).

New activities and opportunities

- **New procedures (CSA, Parallel procedures for Guideline & PQ) and strengthened QMS** – better pipeline scanning, streamlining procedures, etc.
- **Implementation of the new IT system (ePQS)** will facilitate streamlining of workflow, transparency and reporting.
- **Recent independent RPQ impact assessment** – tool for advocacy and continuous improvement
- **Increasing number of WLAs** – will help PQT extend its reliance on the work of others NRAs and a bigger pool for experts.
- **Continued support and recognition** of the work of PQT by stakeholders, including member states, development partners, procurers and clinical departments, as a trusted symbol for safety, quality and efficacy.

CSA = Coordinated scientific advise, QMS = Quality Management System, WLA = WHO Listed Authorities

1. Infections in new-born and young infants and childhood pneumonia; Insulins and insulin analogues (BTPs); Certain cancers (BTPs); COVID-19 (BTPs and small molecules); Ebola Virus Disease (BTPs);
2. Ebola, Pneumonia, Malaria;
3. G6PD, Cholera, Syphilis, TB

ePQS system overview

ePQS Internal Database	+	External ePQS Portal	+	ePQS DMS	+	Extedo EURSNext
• Single repository of information. • Harmonised product and application processes. • Automated webpage updating. • Application tracking. • KPI reporting. • Potential for external information sharing. • Document generation.		• Automated application creation. • Application and task tracking. • Secure document submission facility. • Secure document sharing with applicants. • Automated PQ list and pipeline updating.		• Document visibility via ePQS records. • Encrypted Document storage. • User-specific access to documents. • Secure submission of documents. • Secure sharing of documents with NRAs. • Secure sharing of documents with external consultants.		• Facilitated documentation review by assessors. • Reduced document management burden for PQT and Industry. • Secure sharing of individual dossiers with NRAs. • Secure sharing of individual dossier with external consultants

Aligning the WHO Prequalification process and the WHO guidelines process

Objective of the alignment

- **To facilitate timely access to new innovations to maximize public health impact**

Guiding principles:

1. Timely quality assurance of WHO procedures
2. Independence of the processes to be upheld
3. Coherent and coordinated organizational positions on medical products
4. Guidelines development and prequalification to proceed in parallel and not in a sequential manner.

Summary of the process and next steps:

1. Parallel processes and not sequential.
2. Formal trigger memo for the start of the parallel processes between Technical Department (TD)and Prequalification (PQ).
3. Regular communication along the way.
4. Decision on publication of the WHO Guidelines and PQ Listing NMT12 months from receipt of a specified complete dossier/data package from the manufacturer. “Stop clock” in case more information is requested.
5. Coordinated external communication of outcome between guidelines and PQ
6. Consultation with a bigger audience of internal and external stakeholders in the next few weeks.
7. Experience with SAGE Immunization and therapeutics during COVID-19 pandemic.

Review and update of Quality Assurance Policies

ARV Summit Meeting

31_October_2023

Disclaimer: This presentation describes changes to current Global Fund QA Policies that are recommended by the Global Fund Secretariat and the Global Fund Strategy Committee. The proposed changes are under consideration by the Global Fund Board for decision in mid November 2023

Proposed updates to the QA Policies to The Global Fund Board in November

What are the gaps in the current QA Policies, and why updating them now?

RATIONALE

1. The transitioning from SRA to WLA is happening now, and WLA is meant to replace the concept of SRA.
2. As part of Public Health Emergency Preparedness and Response, QA Policies need to include provisions such as EUL to permit rapid access to quality assured health products during health emergencies.
3. Global Fund-financed procurement of medical devices has increased significantly over time, with more investment in system strengthening, including the priority shifts with C19RM investments.
4. The two current QA Policies were last updated at different points in time, resulting in discrepancies across the policies.

APPROACH

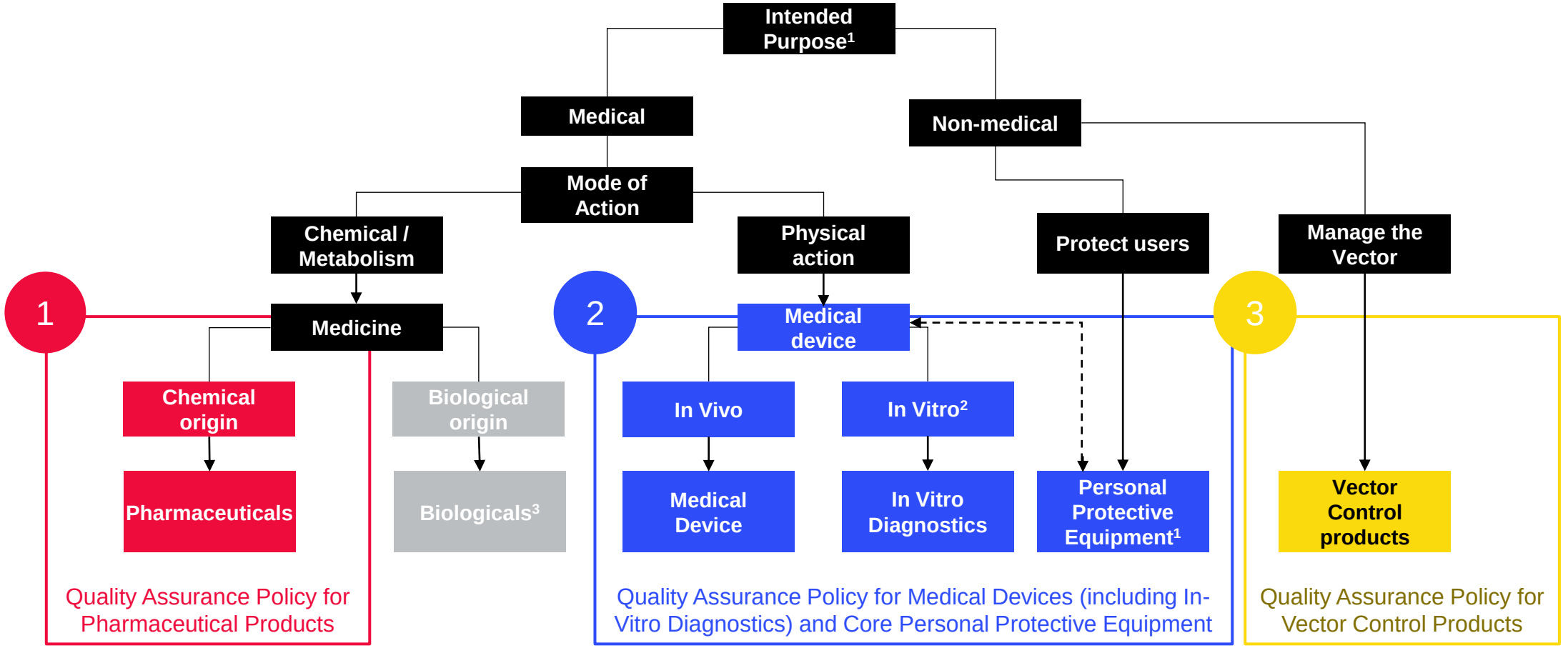
1. Encompassing key product categories procured with significant Global Fund funding
2. Consistency across QA Policies to facilitate operationalization
3. Principle-based policy to inform enhancements to operational guidance for implementation
4. Intended to drive compliance and encourage capacity building
5. Ongoing dialogue with partners on accelerated, streamlined and complementary regulatory pathways to inform future policy review and update

C19RM: COVID-19 Response Mechanism EUL: Emergency Use Listing PPPR: Pandemic Prevention, Preparedness and Response SRA: Stringent Regulatory Authority WLA: WHO-listed authority

What will the final QA Policy Framework look like?

3 harmonized policies covering the range of Global Fund-financed health products

Schematic Representation of Health Product Classes*



* Simplified overview. For more detail, please refer to the standardized definition of each health product class.

1. Some products may meet the conditions for more than one product category. In such cases, quality assurance requirements for both categories apply. Examples include: medical cement, surgical masks and injectable insulin device with online testing for glucose. See dotted line above.
2. On samples taken from the human body.
3. Current Global Fund spend on Biologicals is negligible and thus does not warrant development of a QA policy at this time

What are the key changes proposed to the Board?

What are the key proposed changes for FPP ?

	CURRENT QA POLICY
Reference	***QA Pharma Policy***
Product applicability	For all pharmaceutical products
Clinical requirements	Medicines listed in current National/Institutional Standard Treatment Guidelines (STGs)/ Essential Medicines List (EML) and/or WHO STGs/EML
Registration & Authorization Quality Requirements	1. Authorized by NRA And only for ARVs, anti-TB and antimalarial pharmaceutical products 2. Prequalified by the WHO Prequalification Programme Or Authorized for use by SRA Or Recommended for use by Expert Review Panel

	NEW QA POLICY
Reference	***QA Pharma Policy***
Product applicability	For all pharmaceutical products
Clinical requirements	Medicines listed in current National STGs/EML or WHO STG/rapid communication/EML
Registration & Authorization Quality Requirements	1. Authorized by NRA And only for ARVs, anti-TB and antimalarial pharmaceutical products 2. Prequalified by the WHO Prequalification Programme Or Authorized for use by SRA Or **Authorized for use by WLA** Or Recommended for use by Expert Review Panel **For Emergencies (PHEIC);** **Approved under the WHO EUL** **Or** **Under SRA/WLA Emergency procedures**

What is the proposed timeline and next steps?

1. Board will review the Strategy Committee’s recommendation on 13th November
2. Following the Board decision, the Secretariat will update operational guidance for implementation of the QA Policy updates and notify Suppliers and Principal Recipients of the updated requirements.
3. The Secretariat will communicate the transition period and process for the changes to come into effect.

THE GLOBAL FUND

THANK YOU

Closing remarks: Call to action

1 November Wednesday – Day 3		
Time	**Session**	
8:30 – 12:30	**One on One sessions**	Breakout rooms

U.S. FOOD & DRUG ADMINISTRATION

Summary of Resources: PEPFAR User Fee Waiver Request PIND Meeting Request

FDA/Office New Drugs

Division of Antivirals

November 2023

PEPFAR Application Fee Waivers (PDUFA)

- NDA Applicant holders may submit a written request at least 45 days in advance of submission of an original application so that the request can be evaluated before the fee is due. Submit requests via email to CDERCollections@fda.hhs.gov.
- For more information regarding user fees or how to submit a waiver request, please contact the Office of Management, PDUFA User Fee Staff at CDERCollections@fda.hhs.gov or (301) 796-7900.
- Refer to the following guidances for industry:
  - PDUFA (final Oct 2019)
  - PDUFA PEPFAR (draft Aug 2023)

Division of Antivirals Pre-IND Program

- To obtain pre-submission guidance for PEPFAR original NDAs, use the Division of Antivirals' Pre-IND Consultation Program
  - This program is useful to discuss specific product quality questions (e.g., RLD, dissolution method (including profile and acceptance criterion), morphic form stabilization).
  - We can have a teleconference or provide written responses only.
- Requesting a Pre-assigned Application Number
- Refer to the following guidances for industry:
  - Formal Meetings Request (draft Sept 2023)
  - FC PEPFAR (draft Aug 2023)
- Point of Contacts for NDAs
  - David Araojo; Email: david.araojo@fda.hhs.gov
  - Monica Zeballos; Email: monica.zeballos@fda.hhs.gov


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Jennifer Mercier at 301-796-0957 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2023
Procedural
Revision 1

Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

and/or

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2023
Procedural
Revision 1

TABLE OF CONTENTS

Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations to industry on formal meetings between the Food and Drug Administration (FDA) and sponsors or applicants relating to the development and review of drug or biological drug products (hereafter referred to as *products*) regulated by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). This guidance does not apply to abbreviated new drug applications, applications for biosimilar biological products, or submissions for medical devices. For the purposes of this guidance, *formal meeting* includes any meeting that is requested by a sponsor or applicant (hereafter referred to as *requester(s)*) following the procedures provided in this guidance and includes meetings conducted in any format (i.e., in person face-to-face, virtual face-to-face (video conference), teleconference, and written response only (WRO) see in section IV, Meeting Formats).

This guidance discusses the principles of good meeting management practices and describes standardized procedures for requesting, preparing, scheduling, conducting, and documenting such formal meetings. The general principles in this guidance may be extended to other nonapplication-related meetings with external constituents, insofar as this is possible.[2]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] The guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants* (December 2017) and the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (June 2018) have been withdrawn.

II. BACKGROUND

Each year, FDA review staff participate in many meetings with requesters who seek advice relating to the development and review of investigational new drugs and biologics, and drug or biological product marketing applications. Because these meetings often represent critical points in the drug and biological product development, it is important that there are efficient, consistent procedures for the timely and effective conduct of such meetings. The good meeting management practices in this guidance are intended to provide consistent procedures that will promote well-managed meetings and to ensure that such meetings are scheduled within a reasonable time, conducted efficiently, and documented appropriately.

FDA review staff and requesters are expected to adhere to the meeting management goals that were established under reauthorizations of the Prescription Drug User Fee Act (PDUFA).[3] They are described individually throughout this guidance and summarized in the Appendix.

III. MEETING TYPES[4]

There are six types of formal meetings under PDUFA that occur between requesters and FDA staff: Type A, Type B, Type B (end of phase (EOP)), Type C, Type D, and Initial Targeted Engagement for Regulatory Advice on CDER and CBER ProducTs (INTERACT).

A. Type A Meeting

Type A meetings are those that are necessary for an otherwise stalled product development program to proceed or to address an important safety issue. Reasons for a Type A meeting include the following:

- Dispute resolution meetings as described in 21 CFR 10.75, 312.48, and 314.103 and in the guidance for industry and review staff *Formal Dispute Resolution: Sponsor Appeals Above the Division Level* (November 2017).[5]

- Meetings to discuss clinical holds: (1) in which the requester seeks input on how to address the hold issues; or (2) in which a response to hold issues has been submitted, and

[3] See PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027, available at https://www.fda.gov/media/151712/download.

[4] The meeting types and goal dates were negotiated under the Prescription Drug User Fee Act (PDUFA) and apply to formal meetings between FDA staff and requesters of PDUFA products; they do not apply to meetings with CDER Office of Generic Drugs, CDER Office of Compliance, or CDER Office of Prescription Drug Promotion. See the Prescription Drug User Fee Act (PDUFA) web page at https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

[5] We update guidances periodically. For the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs.

reviewed by the FDA, but the FDA and the requester agree that the development is stalled and a new path forward should be discussed.

- Meetings that are requested after receipt of an FDA Nonagreement Special Protocol Assessment letter in response to protocols submitted under the special protocol assessment procedures as described in the guidance for industry *Special Protocol Assessment* (April 2018).

- Post-action meetings requested within 3 months after receipt of an FDA regulatory action other than an approval (e.g., issuance of a complete response letter).

- Meetings requested within 30 days of FDA issuance of a refuse-to-file letter. To file an application over protest, applicants must first request and have this meeting (21 CFR 314.101(a)(3)).

B. Type B Meeting

Type B meetings are as follows:

- Pre-investigational new drug application (pre-IND) meetings.

- Pre-emergency use authorization meetings.

- Pre-new drug application (pre-NDA)/pre-biologics license application (pre-BLA) meetings (21 CFR 312.47).

- Post-action meetings requested 3 or more months after receipt of an FDA regulatory action other than an approval (e.g., issuance of a complete response letter, refuse to file).

- Meetings regarding risk evaluation and mitigation strategies or postmarketing requirements that occur outside the context of the review of a marketing application.

- Meetings held to discuss the overall development program for products granted breakthrough therapy or regenerative medicine advanced therapy (RMAT) designation status. All subsequent meetings for breakthrough therapy or RMAT-designated products will be considered either Type B or possibly Type A meetings if the meeting request meets the criteria for a Type A meeting.

C. Type B (EOP) Meeting

Type B (EOP) meetings are as follows:

- Certain end-of-phase 1 meetings (i.e., for products that will be considered for marketing approval under 21 CFR part 312, subpart E, or 21 CFR part 314, subpart H, or similar products)

- End-of-phase 2 (i.e., pre-phase 3) meetings (21 CFR 312.47)

D. Type C Meeting

A Type C meeting is any meeting other than a Type A, Type B, Type B (EOP), Type D, or INTERACT meeting regarding the development and review of a product, including meetings to facilitate early consultations on the use of a biomarker as a new surrogate endpoint that has never been previously used as the primary basis for product approval in the proposed context of use.

E. Type D Meeting

A Type D meeting is focused on a narrow set of issues that are used to discuss issues at key decision points to provide timely feedback critical to move the program forward (e.g., often one, but typically not more than two issues and associated questions). Requests could include the following:

- A follow-up question that raises a new issue after a formal meeting (i.e., more than just a clarifying question about an FDA response from a prior meeting)

- A narrow issue on which the sponsor is seeking Agency input with only a few (e.g., three to five questions total) associated questions

- A general question about an innovative development approach that does not require extensive, detailed advice

Type D meetings should be limited to no more than two focused topics. If the sponsor has more than two focused topics or a highly complex single issue that includes multiple questions, a Type C meeting should be requested rather than requesting a Type D meeting. A Type C meeting should also be requested when there are more questions than appropriate for a Type D meeting. Sponsors should not request several Type D meetings in temporal proximity instead of a single Type C meeting. In addition, the issue should not require input from more than three disciplines or divisions. If the scope of the meeting is broad or includes complex questions/issues that require input from more than three disciplines or divisions, or requires cross-center responses, or additional regulatory review, then FDA will inform the sponsor that the Agency will be converting the meeting to the appropriate meeting type (Type B or C) and the sponsor can either withdraw their request or accept the FDA's meeting-type conversion without resubmitting a new meeting request.

Examples and Scenarios

- A sponsor has a specific question about an aspect of a complex or innovative trial design (e.g., innovative pediatric design approach)

- A sponsor has a specific question about presenting data following a pre-BLA/NDA meeting

- A sponsor has a specific follow-up question about a new idea stemming from a Type C meeting

F. INTERACT Meeting

INTERACT meetings are intended for novel products and development programs that present unique challenges in early development (i.e., before filing of an IND or before having a pre-IND meeting). The issues typically relate to IND requirements, for example, questions about design of IND-enabling toxicity studies (e.g., species, endpoints), complex manufacturing technologies or processes, development of innovative devices used with a drug or biologic, or the use of New Approach Methodologies. INTERACT meetings are intended to facilitate IND-enabling efforts when the sponsor is facing a novel, challenging issue that might otherwise delay progress of the product toward entry into the clinic in the absence of this early FDA input. The sponsor needs to have selected a specific investigational product or a product-derivation strategy to evaluate in a clinical study before requesting an INTERACT meeting.

Questions and topics within the scope of an INTERACT meeting include the following:

- Questions for novel products and development programs that present unique challenges in early development for all CDER and CBER products (i.e., questions for which there is no existing guidance or other information in writing the company could reference from FDA).

- Issues that a sponsor needs to address before a pre-IND meeting, including issues such as the following:

  - Choice of appropriate preclinical models or necessary toxicology studies for novel drug platforms or drug candidates

  - Chemistry, manufacturing, and controls issues or testing strategies aimed to demonstrate product safety adequate to support first-in-human study

  - Overall advice related to the design of proof-of-concept or other pilot safety/biodistribution studies necessary to support administration of an investigational product in a first-in-human clinical trial

  - General recommendations about a future first-in-human trial in a target clinical population for which the population is novel and there is no prior precedent or guidance

  - Recommendations on approach for further development of an early-stage product with limited chemistry, manufacturing, and controls; pharmacology/toxicology; and/or clinical data that were collected outside of a U.S. IND

  - Other topics that would be agreed upon by FDA

IV. MEETING FORMATS

There are four meeting formats: In person face-to-face, virtual face-to-face, teleconference, and WRO, as follows:

1. In person face-to-face — Core attendees[6] from the FDA and the sponsor/applicant participate in person at the FDA; such meetings will be hybrid with a virtual component to allow non-core participants to join virtually. Because the intent is that the primary discussion occurs face-to-face in person, all sponsors and FDA individuals who are key to such discussions (i.e., "core" attendees) should participate, if at all feasible, in person. Individuals expected to have a more peripheral role (e.g., may be called on to comment on a single question) may participate virtually. If core sponsor personnel are suddenly unable to attend the in person meeting due to illness or unexpected travel issues, they can join the meeting virtually. If core sponsor personnel are not planning to attend in person, the meeting should be requested as a virtual face-to-face meeting.

2. Virtual face-to-face (video conference) — Attendees participate remotely via virtual meeting platform (e.g., Zoom) (with core attendees' cameras on).

3. Teleconference — Attendees participate via an audio only connection (e.g., telephone, virtual meeting platform without cameras on).

4. Written Response Only (WRO) — Written responses are sent to requesters in lieu of meetings conducted in one of the other formats described above.

V. MEETING REQUESTS

To make the most efficient use of FDA resources, requesters should use the extensive sources of product development information that are publicly available before seeking a meeting (e.g., guidances). To disseminate a broad range of information in a manner that can be easily and rapidly accessed by interested parties, the FDA develops and maintains web pages, portals, and databases, and participates in interactive media as a means of providing information on scientific and regulatory issues.

To promote efficient meeting management, requesters should try to anticipate future needs and, to the extent practical, address relevant and related product development issues in the fewest possible meetings while avoiding meetings with too many questions (or subparts of questions) that would be impractical to discuss in the context of any single meeting. Furthermore, having

[6] FDA will have its core participants with a primary speaking roles participate in person while others may join virtually (see https://www.fda.gov/industry/prescription-drug-user-fee-amendments/update-person-face-face-formal-meetings-fda).

too many questions is not recommended when the topics are complex or if the combined issues would involve voluminous material for FDA review. As discussed below, there should generally be no more than 10 total questions to the FDA.

When a meeting is needed, a written request must be submitted to the FDA via the electronic gateway or, in CDER, via the CDER Nextgen Portal, as appropriate.[7] For additional ways to submit to CBER, please see https://www.fda.gov/about-fda/about-center-biologics-evaluation-and-research-cber/regulatory-submissions-electronic-and-paper. Requests should be addressed to the appropriate Center and review division or office and, if previously assigned, submitted to the application (e.g., investigational new drug application (IND), new drug application (NDA), biologics license application (BLA), pre-application tracking system (PTS) Number (CBER)). If necessary, noncommercial IND holders may also submit the meeting request via the appropriate center's document room.

The meeting request should include adequate information for the FDA to assess the potential utility of the meeting and to identify FDA staff necessary to discuss proposed agenda items.

The meeting request should include the following information:

1. The application number (if previously assigned).
2. The product name.
3. The chemical name, established name, and/or structure.
4. The proposed regulatory pathway (e.g., 505(b)(1), 505(b)(2)).
5. The proposed indication(s) or context of product development.
6. The meeting type being requested (i.e., Type A, Type B, Type B (EOP), Type C, Type D, or INTERACT).
7. Pediatric study plans, if applicable.
8. Human factors engineering plan, if applicable.
9. Combination product information (e.g., constituent parts, including details of the device constituent part, intended packaging, planned human factors studies), if applicable.
10. Suggested dates and times (e.g., morning or afternoon) for the meeting that are consistent with the appropriate scheduling time frame for the meeting type being requested (see Table 2 in section VI.B., Meeting Granted). Dates and times when the requester is not available should also be included.

[7] See the guidance for industry *Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act* (December 2014).

11. A list of proposed questions, grouped by FDA discipline. For each question there should be a brief explanation of the context and purpose of the question.

The meeting request must include the following information:[8]

1. The proposed meeting format (i.e., in person face-to-face, virtual face-to-face, teleconference, and WRO (see section IV, Meeting Formats)).

2. The date the meeting package will be sent by the requester (see section VII.A., Timing of Meeting Package Submission). Meeting packages should be included with the meeting request for all Type A meetings, Type C meetings where the objective is to facilitate early consultation on the use of a biomarker as a new surrogate endpoint that has never been previously used as the primary basis for product approval in the proposed context of use, all Type D meetings, and all INTERACT meetings.

3. A brief statement of the purpose of the meeting that should include a background of the issues underlying the agenda and a summary of completed or planned studies and clinical trials or data that the requester intends to discuss at the meeting. The statement should then include a description of the general issues being raised of the questions to be asked and where the meeting fits in overall development plans. Although the statement should not provide the details of trial designs or completed studies and clinical trials, it should provide enough information to facilitate understanding of the issues, such as a small table that summarizes major results that are necessary to provide the FDA an understanding of the questions to be addressed at the meeting.

4. A proposed agenda, including estimated time needed for discussion of each agenda item.

5. A list of planned attendees from the requester's organization, including their names and titles. The list should also include the names, titles, and affiliations of consultants and interpreters, if applicable.

6. A list of requested FDA attendees and/or discipline representative(s). Requests for attendance by FDA staff who are not otherwise essential to the application's review may affect the ability to hold the meeting within the specified time frame of the meeting type being requested. Therefore, when attendance by nonessential FDA staff is requested, the meeting request should provide a justification for such attendees and state whether a later meeting date is acceptable to the requester to accommodate the nonessential FDA attendees.

A well-written meeting request that includes the above components can help the FDA understand and assess the utility and timing of the meeting related to product development or review. The list of requester attendees and the list of requested FDA attendees can be useful in providing or preparing for the input needed at the meeting. However, during the time between the request and the meeting, the planned attendees can change. Therefore, an updated list of attendees with their

[8] See PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027, available at https://www.fda.gov/media/151712/download.

titles and affiliations should be included in the meeting package and a final list provided to the appropriate FDA contact before the meeting (see section VII.C., Meeting Package Content).

The objectives and agenda provide overall context for the meeting topics, but it is the list of questions that is most critical to understanding the kind of information or input needed by the requester, whether or not the questions can be feasibly addressed within the time frame associated with the meeting type requested, and to focus the discussion should the meeting be granted. Each question should be precise and include a brief explanation of the context and purpose of the question. The questions submitted within a single meeting request should be limited to those that can be reasonably answered within the allotted meeting time, taking into consideration the complexity of the questions submitted. Similar considerations about the complexity of questions submitted within a WRO should be applied. In general, there should be no more than 10 questions listed consecutively regardless of discipline. The FDA requests that meeting requesters not submit subquestions, as they will be counted toward the overall number of questions. For example, if Question 1 has three parts, the numbering should be 1, 2, and 3 rather than numbering them 1a, 1b, and 1c (i.e., with each as "subquestions"). If there are three clinical questions and three nonclinical questions, for a total of six questions, each question should have its own number (i.e., 1, 2, 3, 4, 5, 6, not Clinical 1, 2, 3 and then Nonclinical 1, 2, 3). The numbering of each question in the meeting request (see section VI, Assessing and Responding to Meeting Requests) should be identical to the numbering of each question in the meeting package.

VI. ASSESSING AND RESPONDING TO MEETING REQUESTS

For any type of meeting, the sponsor may request a WRO to its questions rather than another meeting format. The FDA will review the request and make a determination on whether a WRO is appropriate or whether an in person face-to-face, virtual face-to-face, teleconference, or WRO (see section IV., Meeting Formats) meeting is necessary. If a written response is requested and deemed appropriate, the FDA will notify the requester of the date it intends to send the written response in the Agency's response to the meeting request.

For pre-IND, Type C, Type D, and INTERACT meetings, although the sponsor may request an in-person, virtual, or teleconference meeting, the Agency may determine that a written response to the sponsor's questions would be the most appropriate means for providing feedback and advice to the sponsor. When it is determined that the meeting request can be appropriately addressed through a written response, the FDA will notify the requester of the date it intends to send the written response in the Agency's response to the meeting request. If the sponsor believes a meeting is needed, the sponsor may provide a rationale in a follow-up correspondence to the division, explaining their rationale for the meeting. The FDA will consider the follow-up correspondence and may or may not convert the WRO back to an appropriate format.

Requests for Type B and Type B (EOP) meetings will be honored if the sponsor is at the appropriate stage of development to make such a meeting productive. For example, a request for an EOP2 meeting should clearly describe the status of the phase 2 trial(s) and whether summary efficacy and safety data from these trial(s) will be available in the briefing document, as the lack

of these data will render an EOP2 meeting request premature. With the exception of products granted breakthrough therapy or RMAT designation status, the FDA generally will not grant more than one of each of the Type B meetings for each potential application (e.g., IND, NDA, BLA) or combination of closely related products developed by the same requester (e.g., same active ingredient but different dosage forms being developed concurrently), but the FDA can do so when it would be beneficial to hold separate meetings to discuss unrelated issues. For example, it may be appropriate to conduct more than one end-of-phase 2 meeting with different review divisions or disciplines for concurrent development of a product for unrelated claims or a separate meeting to discuss manufacturing development when the clinical development is on a different timeline. For novel programs, with many complex issues, discussion with the relevant division may lead to an agreement that additional meetings are needed.

A. Meeting Denied

If a meeting request is denied, the FDA will notify the requester in writing according to the timelines described in Table 1. The FDA's letter will include an explanation of the reason for the denial. Denials will be based on a substantive reason, not merely on the absence of a minor element of the meeting request or meeting package items. For example, a meeting can be denied because it is premature for the stage of product development or because the meeting package does not provide an adequate basis for the meeting discussion (see section IX., Rescheduling and Canceling Meetings, for the effect of inadequate meeting packages on other meeting types when the package is received after the meeting is granted). The FDA may also deny requests for meetings that do not have substantive required elements described in section V., Meeting Requests. A subsequent request to schedule the meeting will be considered as a new request (i.e., a request that merits a new set of time frames as described in section below, Meeting Granted).

B. Meeting Granted

If a meeting request is granted, the FDA will notify the requester in writing according to the timelines described in Table 1. For in person face-to-face, virtual face-to-face, and teleconference meetings, the FDA's letter will include the date, time, conferencing arrangements, and/or location of the meeting, as well as expected FDA participants. For WRO requests, the FDA's letter will include the date the FDA intends to send the written responses (see Table 3 for FDA WRO response timelines). As shown in Tables 2 and 3, FDA WRO response timelines are the same as those for scheduling an in-person face-to-face, virtual face-to-face, or teleconference meeting of the same meeting type.

For in person face-to-face, virtual face-to-face, and teleconference meetings, the FDA will schedule the meeting on the available date at which all expected FDA staff are available to attend; however, the meeting should be scheduled consistent with the type of meeting requested (see Table 2 for FDA meeting scheduling time frames). If the requestor's requested date for any meeting type is greater than the specified time frame, the meeting date should be scheduled by the FDA within 14 calendar days of that requested date.

Table 1. FDA Meeting Request/WRO Request Response Timelines

Meeting Type (any format)	Response Time (calendar days from receipt of meeting request/WRO request)
A	14 days
B	21 days
B (EOP)	14 days
C	21 days
D	14 days
INTERACT	21 days

Table 2. FDA Meeting Scheduling Time Frames

Meeting Type	Meeting Scheduling (calendar days from receipt of meeting request)
A	30 days
B	60 days
B (EOP)	70 days
C	75 days
D	50 days
INTERACT	75 days

Table 3. FDA WRO Response Timelines

Meeting Type	WRO Response Time (calendar days from receipt of WRO request)
A	30 days
B	60 days
B (EOP)	70 days
C	75 days
D	50 days
INTERACT	75 days

VII. MEETING PACKAGE

Premeeting preparation is critical for achieving a productive discussion or exchange of information. Preparing the meeting package should help the requester focus on describing its principal areas of interest. The meeting package should provide information relevant to the discussion topics and enable the FDA to prepare adequately for the meeting. In addition, the timely submission of the meeting package is important for ensuring that there is sufficient time for meeting preparation, accommodating adjustments to the meeting agenda, and accommodating appropriate preliminary responses to meeting questions. Requestors are encouraged to include their meeting package for all meeting types, if possible, but must meet the required due dates for certain meetings (see Table 4 below).

A. Timing of Meeting Package Submission

Requesters must submit the meeting package for each meeting type (including WRO) according to the meeting package timelines described in Table 4.[9]

Table 4. Requester Meeting Package Timelines

Meeting Type	FDA Receipt of Meeting Package (calendar days)
A, C*, D, INTERACT	At the time of the meeting request
B	No later than 30 days before the scheduled date of the meeting or WRO response time
B (EOP)	No later than 50 days before the scheduled date of the meeting or WRO response time**
C	No later than 47 days before the scheduled date of the meeting or WRO response time***

*For Type C meetings that are requested as early consultations on the use of a new surrogate endpoint to be used as the primary basis for product approval in a proposed context of use, the meeting package is due at the time of the meeting request.
** If the scheduled date of a Type B (EOP) meeting is earlier than 70 days from FDA receipt of the meeting request, the requester's meeting package will be due no sooner than 6 calendar days after FDA response time for issuing the letter granting the meeting (see Table 1 in section VI.B., Meeting Granted).
*** If the scheduled date of a Type C meeting is earlier than 75 days from FDA receipt of the meeting request, the meeting package will be due no sooner than 7 calendar days after FDA response time for issuing the letter granting the meeting (see Table 1 in section VI.B., Meeting Granted).

B. Where and How Many Copies of Meeting Packages to Send

Requesters should submit the archival meeting package to the relevant application(s) (e.g., pre-IND, IND, NDA, BLA or PTS (CBER)) via the electronic gateway or, in CDER, via the CDER Nextgen Portal (https://cdernextgenportal.fda.gov/), as applicable.[10] For additional ways to submit to CBER, please see https://www.fda.gov/about-fda/about-center-biologics-evaluation-and-research-cber/regulatory-submissions-electronic-and-paper. If necessary, noncommercial IND holders may also submit the package via the appropriate center's document room.

C. Meeting Package Content

The meeting package should provide *summary* information relevant to the product and any supplementary information needed to develop responses to issues raised by the requester or review division. It is critical that the entire meeting package content support the intended meeting objectives. The meeting package content will vary depending on the product, indication, phase of product development, and issues to be discussed. FDA and ICH guidances

[9] See PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027, available at https://www.fda.gov/media/151712/download.

[10] See the guidances for industry *Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act* and *Providing Regulatory Submissions in Electronic Format — General Considerations* (January 1999).

identify and address many issues related to product development and should be considered when planning, developing, and providing information needed to support a meeting with the FDA. If a product development plan deviates from current guidances, or from existing precedent, the deviation should be identified and explained. Known difficult design and questions about providing substantial evidence of effectiveness should be raised for discussion (e.g., use of a surrogate endpoint, reliance on a single study, use of a noninferiority design, adaptive designs). Also, merely describing a result as *significant* does not provide the review division with enough information to give the most constructive advice or identify important problems the requester may have missed.

To facilitate FDA review, the meeting package content should be organized according to the proposed agenda. The meeting package should be a sequentially paginated document with a table of contents with appropriate electronic linkage, appropriate indices, appendices, and cross references. It should enhance reviewers' navigation across different sections within the package, both in preparation for and during the meeting. Meeting packages generally should include the following information, preferably in the order listed below:

Meeting packages should include the same first nine items provided for the meeting request (see above section V.), and in addition, should include:

1. A list of all individuals, with their titles and affiliations, who will attend the requested meeting from the requester's organization, including consultants and interpreters.

2. A background section that includes the following:

    a. A brief history of the development program and relevant communications with the FDA before the meeting

    b. Substantive changes in product development plans (e.g., new indication, population, basis for a combination), when applicable

    c. The current status of product development (e.g., drug development plan)

3. A brief statement summarizing the purpose of the meeting and identifying the type of meeting, if applicable.

4. A proposed agenda, including estimated time needed for discussion of each agenda item.

5. A list of the final questions for discussion grouped by FDA discipline and with a brief summary for each question to explain the need or context for the question.

6. Data to support discussion organized by FDA discipline and question. Protocols, full study reports, or detailed data generally are not appropriate for meeting packages; the summarized material should describe the results of relevant studies and clinical trials with some degree of quantification and any conclusion about clinical trials that resulted. The

trial endpoints should be stated, as should whether endpoints were altered or analyses changed during the course of the trial.

For example, for an end-of-phase 2 meeting, this section of the meeting package should include the following: A description and the results of controlled trials conducted to determine dose-response information, summary efficacy and safety data from the phase 2 trial(s); adequately detailed descriptors of planned phase 3 trials identifying major trial features such as population, critical exclusions, trial design (e.g., randomization, blinding, and choice of control group, with an explanation of the basis for any noninferiority margin if a noninferiority trial is used), dose selection, and primary and secondary endpoints; and major analyses (including planned interim analyses and adaptive features, and major safety concerns).

VIII. PRELIMINARY RESPONSES

Communications before the meeting between requesters and the FDA, including preliminary responses, can serve as a foundation for discussion or as the final meeting responses. Preliminary responses should not be construed as *final* unless there is agreement between the requester and the FDA that additional discussion is not necessary for any question (i.e., when the meeting is canceled because the responses and comments are clear to the requester), or a particular question is considered resolved allowing extra time for discussion of the more complex questions during the meeting. Preliminary responses communicated by the FDA are not intended to generate the submission of new information or new questions. If a requester nonetheless provides new data or a revised or new proposal, the FDA may not be able to provide comments on the new information, or it may necessitate the submission of a new meeting request by the requester.

The FDA holds an internal meeting to discuss the content of meeting packages and to gain internal alignment on the preliminary responses. The FDA will send the requester its preliminary responses to the questions in the meeting package no later than 5 calendar days before the meeting date for Type B (EOP), Type C, Type D, and INTERACT meetings. The requester will notify the FDA no later than 3 calendar days following receipt of the FDA's preliminary responses for these meeting types of whether the meeting is still needed, and if it is, the requester will send the FDA a revised meeting agenda indicating which questions the requestor considers as resolved and which questions the requestor will want to further discuss within the allotted time as reasonable.[11] For Type A and Type B (other than Type B (EOP)), the FDA intends to send the requester its preliminary responses no later than 2 calendar days before the meeting.

IX. RESCHEDULING AND CANCELING MEETINGS

[11] See PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027, available at https://www.fda.gov/media/151712/download.

Occasionally, circumstances arise that necessitate rescheduling or canceling a meeting. If a meeting needs to be rescheduled, it should be rescheduled as soon as possible after the original date. A new meeting request should not be submitted. However, if a meeting is canceled, the FDA will consider a subsequent request to schedule a meeting to be a new request (i.e., a request that merits a new set of time frames as described in section VI., Assessing and Responding to Meeting Requests). Requesters and the FDA should take reasonable steps to avoid rescheduling and canceling meetings (unless the meeting is no longer necessary). For example, if an attendee becomes unavailable, a substitute can be identified, or comments on the topic that the attendee would have addressed can be forwarded to the requester following the meeting. It will be at the discretion of the review division whether the meeting should be rescheduled or canceled depending on the specific circumstances.

The following situations are examples of when a meeting can be rescheduled. Some of the examples listed also represent reasons that a meeting may be canceled by the FDA. This list includes representative examples and is not intended to be an exhaustive list.

- The requester experiences any delay in submitting the meeting package. The requester should contact the FDA project manager to explain why it cannot meet the time frames for submission and when the meeting package will be submitted.

- The review team determines that the meeting package is inadequate, or additional information is needed to address the requester's questions or other important issues for discussion, but it is possible to identify the additional information needed and arrange for its timely submission.

- There is insufficient time to review the material because the meeting package is voluminous (see section VII.C., Meeting Package Content), despite submission within the specified time frames and the appropriateness of the content.

- After the meeting package is submitted, the requester sends the FDA additional questions or data that are intended for discussion at the meeting and require additional review time.

- It is determined that attendance by additional FDA personnel not originally anticipated or requested is critical and their unavailability precludes holding the meeting on the original date.

- Essential attendees are no longer available for the scheduled date and time because of an unexpected or unavoidable conflict or an emergency situation.

The following situations are examples of when a meeting can be canceled:

- The meeting package is not received by the FDA within the specified time frames (see section VII.A., Timing of Meeting Package Submission) or is grossly inadequate. Meetings are scheduled on the condition that appropriate information to support the discussion will be submitted with sufficient time for review and preparatory discussion. Adequate planning should avoid this problem.

- The requester determines that preliminary responses to its questions are sufficient for its needs and additional discussion is not necessary (see section VIII., Preliminary Responses). In this case, the requester should contact the FDA project manager to request cancellation of the meeting. The FDA will consider whether it agrees that the meeting should be canceled. Some meetings, particularly milestone meetings, can be valuable because of the broad discussion they generate and the opportunity for the division to ask about relevant matters (e.g., dose-finding, breadth of subject exposure, particular safety concerns), even if the preliminary responses seem sufficient to answer the requester's questions. If the FDA agrees that the meeting can be canceled, the reason for cancellation will be documented and the preliminary responses will represent the final responses and the official record.

X. MEETING CONDUCT

Meetings will be chaired by an FDA staff member and begin with introductions and an overview of the agenda. FDA policy prohibits audio or visual recording of discussions at meetings.

Presentations by requesters are usually unnecessary because the information necessary for review and discussion should be part of the meeting package. If a requester plans to make a presentation, the presentation materials should be provided ahead of the meeting. All presentations should be kept brief to maximize the time available for discussion. The length of the meeting will not be increased to accommodate a presentation. If a presentation contains more than a small amount of content distinct from clarifications or explanations of previous data and that were not included in the original meeting package submitted for review, FDA staff may not be able to provide commentary.

Either a representative of the FDA or the requester should summarize the important discussion points, agreements, clarifications, and action items. Summation can be done at the end of the meeting or after the discussion of each question. Generally, the requester will be asked to present the summary to ensure that there is mutual understanding of meeting outcomes and action items. FDA staff can add or further clarify any important points not covered in the summary, and these items can be added to the meeting minutes. At pre-NDA and pre-BLA meetings for applications reviewed under the PDUFA Program for Enhanced Review Transparency and Communication for New Molecular Entity (NME) NDAs and Original BLAs (also known as *the Program*),[12] the requester and the FDA should also summarize agreements regarding the content of a complete application and any agreements reached on delayed submission of certain minor application components.

XI. MEETING MINUTES

Because the FDA's minutes are the official records of meetings, the FDA's documentation of meeting outcomes, agreements, disagreements, and action items is critical to ensuring that this

[12] See https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm327030.htm.

information is preserved for meeting attendees and future reference. The FDA will issue the official, finalized minutes to the requester within 30 calendar days after the meeting.

The following are general considerations regarding meeting minutes:

- FDA minutes will outline the important agreements, disagreements, issues for further discussion, and action items from the meeting in bulleted format. The minutes should be sufficiently detailed that they provide clarity about the agreements, such as on study design elements, or statistical testing, or enrollment criteria and similar important areas of the development program. The minutes are not intended to represent a transcript of the meeting.

- FDA project managers will use established templates to ensure that all important meeting information is captured.

- The FDA may communicate additional information in the final minutes that was not explicitly communicated during the meeting (e.g., pediatric requirements, data standards, abuse liability potential) or that provides further explanation of discussion topics. The FDA's final minutes will distinguish this additional information from the discussion that occurred during the meeting.

- For INTERACT meetings, preliminary responses will be annotated and resent within 30 days if advice provided changes as a result of the meeting.

- In cases of a WRO, the WRO will serve as meeting minutes.

The following steps should be taken when there is a difference of understanding regarding the minutes:

- Requesters should contact the FDA project manager if there is a significant difference in their and the FDA's understanding of the content of the final meeting minutes issued to the requesters

- If after contacting the FDA project manager there are still significant differences in the understanding of the content, the requester should submit a description of the specific disagreements either:

  – To the application; or

  – If there is no application, in a letter to the division director, with a copy to the FDA project manager

- The review division and the office director, if the office director was present at the meeting, will take the concerns under consideration

- If the minutes are deemed to accurately and sufficiently reflect the meeting discussion, the FDA project manager will convey this decision to the requester and the minutes will stand as the official documentation of the meeting.

- If the FDA deems it necessary, changes will be documented in an addendum to the official minutes. The addendum will also document any remaining requester objections, if any.

For input on additional issues that were not addressed at the meeting, the requester should submit a new meeting request, a WRO request, or a submission containing specific questions for FDA feedback.

For all meeting types, to ensure the sponsor's understanding of FDA feedback from meeting discussions or a WRO, sponsors may submit a "follow-up opportunity/clarifying questions" correspondence to the agency in a formal submission to their application. Only questions of a clarifying nature should be submitted (i.e., to confirm something in minutes or in a WRO issued by the FDA) rather than new issues or new proposals. If the FDA determines that the requests are not in scope (i.e., are not simply clarifications of advice provided at the meeting), the division may advise the sponsor to request a new meeting to address the issue. However, if the out-of-scope issue is narrow and focused, the review division, at their discretion, may provide a response (as a general correspondence) as soon as reasonably possible. The clarifying questions should be sent in writing as a "Request for Clarification" to the FDA within 20 calendar days following receipt of the meeting minutes or WRO, to include if the preliminary comments serve as the final minutes for a cancelled meeting. For questions that meet the criteria, the FDA will issue a response in writing within 20 calendar days of receipt of the clarifying questions. The FDA's response will reference the original minutes or WRO.

REFERENCES

Related Guidances[13]

Guidance for industry and review staff *Best Practices for Communication Between IND Sponsors and FDA During Drug Development* (December 2017)

Guidance for review staff and industry *Good Review Management Principles and Practices for PDUFA Products* (April 2005)

Related CDER MAPP[14]

MAPP 6025.6 *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics*

Related CBER SOPPs[15]

SOPP 8101.1 *Regulatory Meetings With Sponsors and Applicants for Drugs and Biological Products*

SOPP 8404.1 *Procedures for Filing an Application When the Applicant Protests a Refusal to File Action (File Over Protest)*

[13] Guidances can be found on the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[14] MAPPs can be found on the CDER Manual of Policies and Procedures web page at https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm.

[15] SOPPs can be found on the Biologics Procedures (SOPPs) web page at https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/default.htm.

APPENDIX:
SUMMARY OF MEETING MANAGEMENT PROCEDURAL GOALS

Table A is a summary of Prescription Drug User Fee Act meeting management procedural goals.

Table A. Meeting Management Procedural Goals

Meeting Type	FDA Response to Request	FDA Receipt of Meeting Package	FDA Preliminary Responses to Requester (if applicable†)	Requester Response to FDA Preliminary Responses (if applicable†)	FDA Scheduled Meeting Date (days from receipt of request)	FDA Meeting Minutes to Requester (if applicable†)
A	14 days	With meeting request	No later than 2 days before meeting	--	Within 30 days	30 days after meeting
B	21 days	No later than 30 days before meeting	No later than 2 days before meeting	--	Within 60 days	30 days after meeting
B (EOP)*	14 days	No later than 50 days before meeting**	No later than 5 days before meeting	No later than 3 days after receipt of preliminary responses	Within 70 days	30 days after meeting
C	21 days	No later than 47 days before meeting***	No later than 5 days before meeting	No later than 3 days after receipt of preliminary responses	Within 75 days	30 days after meeting
D	14 days	With meeting request	No later than 5 days before meeting	No later than 3 days after receipt of preliminary responses	Within 50 days	30 days after meeting
INTERACT	21 days	With meeting request	No later than 5 days before the meeting	No later than 3 days after receipt of preliminary responses	Within 75 days	Preliminary responses annotated 30 days after meeting

† Not applicable to written response only.
* EOP = end of phase.

** If the scheduled date of a Type B (EOP) meeting is earlier than 70 days from FDA receipt of the meeting request, the requester's meeting package will be due no sooner than 6 calendar days after FDA response time for issuing the letter granting the meeting (see Table 1 in section VI.B., Meeting Granted).

*** If the scheduled date of a Type C meeting is earlier than 75 days from FDA receipt of the meeting request, the meeting package will be due no sooner than 7 calendar days after FDA response time for issuing the letter granting the meeting (see Table 1 in section VI.B., Meeting Granted). For Type C meetings that are requested as early consultations on the use of a new surrogate endpoint to be used as the primary basis for product approval in a proposed context of use, the meeting package is due at the time of the meeting request.

Prescription Drug User Fee Act Waivers, Reductions, and Refunds for Drug and Biological Products

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2019
User Fees

Prescription Drug User Fee Act Waivers, Reductions, and Refunds for Drug and Biological Products

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
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Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
and/or
Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
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Phone: 800-835-4709 or 240-402-8010
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2019
User Fees

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Contains Nonbinding Recommendations

Prescription Drug User Fee Act Waivers, Reductions, and Refunds for Drug and Biological Products Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations to applicants regarding requests for waivers, refunds, and reductions of user fees assessed under sections 735 and 736 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) for drugs, including biological products.[2] This guidance is a revision of the guidance for industry entitled *User Fee Waivers, Reductions, and Refunds for Drug and Biological Products*, issued in September 2011.

This revised guidance describes (1) the types of waivers, refunds, and reductions available under the user fee provisions of the FD&C Act, (2) the procedures for requesting waivers, refunds, or reductions, and (3) the process for requesting a reconsideration or appeal of an FDA decision. The guidance also provides clarification on related issues such as user fee exemptions for orphan drugs.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Division of User Fee Management and Budget Formulation, Office of Management, Center for Drug Evaluation and Research, in consultation with the Center for Biologics Evaluation and Research.

[2] For the purposes of this document, unless otherwise specified, references to "drugs" or "drug products" include drugs submitted under section 505(b) of the FD&C Act and biological products licensed under section 351(a) of the PHS Act, other than biological products that also meet the definition of a device in section 201(h) of the FD&C Act (21 U.S.C. 321(h)).

II. BACKGROUND

The Prescription Drug User Fee Act of 1992 (PDUFA I) amended the FD&C Act, and authorized FDA to collect user fees for 5 years from companies that produce certain human drug and biological products. PDUFA must be reauthorized every 5 years, and has been reauthorized 5 times since PDUFA I, most recently in 2017 under Title I of the FDA Reauthorization Act of 2017 (PDUFA VI).

PDUFA VI authorizes FDA to assess application fees for certain human drug and biological product applications when those applications are submitted. In addition, PDUFA VI authorizes FDA to assess annual prescription drug program fees (program fees) for certain approved drug and biological products.[3]

Because of the way the user fee program is structured in the FD&C Act, the total amount FDA collects in user fees is independent of the number of waivers or reductions in fees that are granted. Target revenues are established in accordance with a statutory formula, and the amount of each type of fee (application and program) is determined based on historical data of how many applications and products were assessed fees in the previous fiscal years. Therefore, the number of waivers, refunds, and reductions granted in a fiscal year is factored into the statutory formula and may result in an increase or decrease in application and program fees for the following year to meet the annual statutory revenue targets.

III. DEFINITIONS

For purposes of this guidance:

- The term ***affiliate*** means a business entity that has a relationship with a second business entity if, directly or indirectly, (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities.[4]

- The term ***applicant*** means the owner, holder, or sponsor of a new drug application (NDA), submitted under section 505 of the FD&C Act, or biologics license application (BLA), submitted under section 351(a) of the Public Health Service (PHS) Act.

- The term ***application*** includes both NDAs, submitted under section 505 of the FD&C Act, and BLAs, submitted under section 351(a) of the PHS Act.

- The term ***drug*** includes drug and biological products.

[3] Information on application and program fees, including fee rates, PDUFA goals, and other user fee related issues can be found on FDA's PDUFA website: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.
[4] Section 735(11) of the FD&C Act.

- The term ***human drug application*** means an application for (1) approval of a new drug submitted under section 505(b) of the FD&C Act or (2) licensure of a biological product under section 351(a) of the PHS Act.[5] For purposes of this guidance, the term ***human drug application*** does not include the following:

    - A supplement to such an application;
    - An application with respect to whole blood or a blood component for transfusion;
    - An application with respect to a bovine blood product for topical application licensed before September 1, 1992;
    - An application for an allergenic extract product;
    - An in vitro diagnostic biologic product licensed under section 351 of the PHS Act;
    - An application with respect to a large volume parenteral drug product approved before September 1, 1992;
    - An application for a licensure of a biological product for further manufacturing use only; and
    - An application submitted by a State or Federal Government entity for a drug that is not distributed commercially.[6]

- The term ***person*** means the person subject to fees and includes any affiliates of that person.[7] The term ***person*** includes an individual, partnership, corporation, and association.[8] This document will also use the term ***person*** when referring to an applicant.

- The term ***prescription drug product*** means a specific strength or potency of a drug in final dosage form --

    - for which a human drug application has been approved,
    - which may be dispensed only by prescription under section 503(b) of the FD&C Act, and
    - which is on the list of products described in section 505(j)(7)(A) of the FD&C Act (not including the discontinued section of such list) or is on a list created and maintained by FDA of products approved under human drug applications under section 351(a) of the PHS Act (not including the discontinued section of such list).[9]

    For purposes of this guidance, such term does not include:

    - Whole blood or a blood component for transfusion;
    - A bovine blood product for topical application licensed before September 1, 1992;

[5] Section 735(1) of the FD&C Act.
[6] Id.
[7] Section 735(9) of the FD&C Act.
[8] Section 201(e) of the FD&C Act.
[9] Section 735(3) of the FD&C Act.

- An allergenic extract product;
- An in vitro diagnostic biologic product licensed under section 351 of the PHS Act;
- A biological product that is licensed for further manufacturing use only; and
- A drug that is not distributed commercially and is the subject of an application or supplement submitted by a State or Federal Government entity.[10]

- The term ***supplement*** means a request to FDA to approve a change in a human drug application that has been approved.[11]

- The term ***financial resources*** means the current financial assets, including cash and any other income available other than cash in the form of liquid securities and credit lines, of an applicant and its affiliates. See section IV.C. for more information.

IV. TYPES OF WAIVERS AND REDUCTIONS

According to section 736(d) of the FD&C Act, FDA will grant to an applicant a waiver of or reduction in one or more user fees assessed under section 736(a) of the FD&C Act where it finds that:

- A waiver or reduction is necessary to protect the public health;

- The assessment of the fee would present a significant barrier to innovation because of limited resources available to the person or other circumstances; or

- The applicant is a small business submitting its first human drug application to FDA for review.

Sections IV.A through IV.D describe FDA's considerations for each type of waiver.[12]

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[10] Section 735(3) of the FD&C Act.

[11] Section 735(2) of the FD&C Act.

[12] There are three additional special circumstances that may affect an applicant's eligibility for waivers or reductions under the public health and barrier to innovation waiver provision:

(1) for applicants participating in the President's Emergency Plan for AIDS Relief (PEPFAR), see guidance for industry, *User Fee Waivers for FDC and Co-Packaged HIV Drugs for PEPFAR*;

(2) for applicants submitting combination products under 21 Code of Federal Regulations 3.2(e), see guidance for industry, *Application User Fees for Combination Products*; and

(3) for applicants submitting applications for certain types of positron emission tomography (PET) drugs (specifically, FDG F 18 injection, ammonia N 13 injection, and sodium fluoride F 18 injection), see 21 FR 12999, 13004 (Mar. 10, 2000), and guidance for industry, *FDA Oversight of PET Drug Products: Questions and Answers*. Please note that the waivers for these PET drugs only apply to application fees; applicants who would like program fees waived may request a public health or barrier-to-innovation waiver, as is further described in this guidance. Any applicant submitting an application that may present these special circumstances should consult the relevant guidance and statutory provisions. FDA updates guidances periodically. To make sure you have the most recent version of a guidance, visit the FDA Drugs guidance website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

A. Public Health

Under section 736(d)(1)(A) of the FD&C Act, an applicant may qualify for a waiver of or reduction in application or program fees if the waiver or reduction is necessary to protect the public health. Under this provision, FDA considers the following questions in determining whether to grant a public health waiver or reduction in user fees:

- Does the product protect the public health?

- Is the waiver or reduction ***necessary*** to continue an activity that protects the public health?

Applicants should address both of these questions when applying for a public health waiver or reduction in fees.

1. Does the product protect the public health?

For user fee purposes, a product that has been approved for marketing in the United States is not automatically deemed to be a product that protects the public health. In evaluating whether a product protects the public health, the Agency generally intends to ask, for example, questions similar to the following:

- Is the drug product a significant improvement (or does it have the potential to be a significant improvement if the drug product is not yet approved) compared to other marketed products, including other dosage forms or routes of administration and non-drug products or therapies?

- Are there other treatment alternatives in the U.S. market? The existence of comparable treatment alternatives would weigh against a determination that a product is necessary to protect the public health.

- Has the drug product been designated as a priority drug, accepted into one of FDA's expedited programs for serious conditions,[13] granted fast track status,[14] or determined to be a new molecular entity? Affirmative answers to these questions may indicate that a product protects the public health.

- Does the drug product demonstrate an increased effectiveness in the treatment, prevention, or diagnosis of disease?

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[13] Further information regarding priority drugs can be found in the guidance for industry, *Expedited Programs for Serious Conditions – Drugs and Biologics*, available at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf, and in CDER's Manual of Policies and Procedures (MAPP) 6020.3R, *Review Designation Policy: Priority (P) and Standard (S).* MAPP 6020.3R is available at https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm082000.pdf.

[14] Further information regarding fast track status is available at https://www.fda.gov/forpatients/approvals/fast/ucm20041766.htm.

- Does it eliminate or substantially reduce a treatment-limiting drug reaction?
- Does the drug product enhance patient adherence to treatment?
- Has the drug product shown potential evidence of safety and effectiveness for a new or underserved subpopulation (e.g., treatment for a drug resistant microbe or response to a homeland security concern)?
- Is the drug product intended for the diagnosis or treatment of a serious or life-threatening condition?
- Does the drug product address unmet medical needs or demonstrate the potential to do so?
- Is the product designated as a drug for a rare disease or condition under section 526 of the FD&C Act (i.e., does it have an orphan designation)?
- If the drug product is approved, is the product recognized as an effective treatment option that significantly impacts the public health?
- If the product is approved, is it available to the public? There is no benefit to the public health if a product is not made available to the public.[15]

2. Is the waiver or reduction necessary to continue an activity that protects the public health?

To determine whether a waiver or reduction in user fees is necessary to continue an activity that protects the public health, the Agency considers not only the benefit of the activity to the public health, but also whether the waiver or reduction is necessary. The legislative history of PDUFA I indicates that FDA may waive or reduce fees unless such a waiver or reduction is not necessary to protect the public health, or it is apparent that the fee will not be a disincentive to innovation.[16] It also indicates that FDA should consider the "limited resources" of the applicant when evaluating a request for a fee waiver or reduction under section 736(d).[17] Therefore, the Agency believes that a financial test is appropriate for the public health waiver provision. The Agency considers the relationship between current liabilities and the financial resources of the applicant, including affiliates, requesting the waiver or reduction. The financial considerations are discussed in section IV.C.

[15] FDA would consider products stockpiled for homeland security concerns as available to the public for user fee waiver purposes.
[16] See House Report 102-895 (1992) at 17; 138 Cong. Rec. S. 17239 (Oct. 7, 1992).
[17] Id.

B. Barrier to Innovation

Under section 736(d)(1)(B) of the FD&C Act, an applicant may qualify for a waiver or reduction in application or program fees when the assessment of the fees would present a significant barrier to innovation because of limited resources available to the applicant or other circumstances. Under this provision, FDA considers the following questions in deciding whether to grant a barrier-to-innovation waiver:

- Is the product or other products or technologies under development by the applicant innovative?

- Would the fee(s) be a ***significant barrier*** to the applicant's ability to develop, manufacture, or market innovative products or to pursue innovative technology?

To qualify for a waiver or reduction in user fees under this provision, an applicant should address both questions.

1. *Is the product innovative or is the company pursuing other innovative drug products or technologies?*

A product that has been approved for marketing in the United States is not automatically deemed to be innovative for user fee purposes. In evaluating requests for barrier-to-innovation user fee waivers or reductions, the Agency generally intends to consider the following questions:

- Does the drug product or technology demonstrate advanced "breakthrough" research; new progressive methods and forward thinking in the treatment or diagnosis of disease; or has it demonstrated the potential to be at the forefront of new medical technology?

- Are there other treatment alternatives available in the U.S. market? The existence of comparable alternatives would weigh against a determination that a product is innovative.

- Does the drug product or technology introduce a unique or superior method for diagnosing, curing, mitigating, treating, or preventing a disease, or for affecting a structure or function of the body?

- Does the applicant have an *active* investigational new drug application (IND) under which the applicant is evaluating a potentially unique or superior method for diagnosing, curing, mitigating, treating, or preventing a disease, or for affecting a structure or function of the body? To determine whether an applicant's IND would be considered *active*, the Agency may consider the following:

    - Is the applicant currently conducting a clinical trial for the investigational drug?[18]

[18] FDA may use any available information, including but not limited to ClinicalTrials.gov, to determine whether the applicant is currently conducting a clinical trial.

- Has the applicant recently participated in meetings and discussions with FDA about the IND progress?
- Is the applicant actively developing the investigational drug? Does the applicant detail such development in its IND annual report?

- Has the drug product been designated as a priority drug, accepted into one of FDA's expedited programs for serious conditions,[19] granted fast track status,[20] or determined to be a new molecular entity?

- Has the applicant recently received a Federal grant for innovation? An example of a Federal grant program that may qualify as innovative is the National Institutes of Health's Small Business Innovative Research Program.

2. Does the fee create a significant barrier to the applicant's ability to develop, manufacture, or market innovative products or to pursue innovative technology?

To determine whether a fee would be a significant barrier to an applicant's ability to develop, manufacture, or market innovative products or to pursue innovative technology, the Agency considers the relationship between the current liabilities and financial resources of the applicant and its affiliates. The financial considerations are discussed below.

C. Financial Considerations for Public Health and Barrier-to-Innovation Waivers and Reductions

1. Financial Resources of the Applicant and Affiliates

When evaluating requests for waivers or reductions in user fees under the public health or barrier-to-innovation provisions, the Agency considers the financial resources of the applicant and its affiliates.

Section 736(d)(2) of the FD&C Act states that, in determining whether to grant a waiver or reduction in a user fee, FDA shall consider only the circumstances and financial resources of the applicant and any affiliate of the applicant. Under the FD&C Act, the applicant is the person[21] who is responsible for payment of the fees and the person who must qualify for a waiver or reduction in user fees.[22] Accordingly, the statute does not allow persons other than those legally subject to user fees, such as a distributor that is not an affiliate, to qualify for or receive waivers or reductions of user fees.

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[19] Further information regarding priority drugs can be found in the guidance for industry, *Expedited Programs for Serious Conditions – Drugs and Biologics*, available at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf, and in CDER's MAPP 6020.3R, *Review Designation Policy: Priority (P) and Standard (S).* MAPP 6020.3R available at https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm082000.pdf.

[20] Further information regarding fast track status is available on the internet at https://www.fda.gov/forpatients/approvals/fast/ucm20041766.htm.

[21] Under section 735(9) of the FD&C Act, *person* includes an affiliate thereof.

[22] See sections 736(a)(1), 736(a) (2), and 736(d) of the FD&C Act.

2. Consideration of Limited Financial Resources

The limited financial resources of an applicant and its affiliates are an important indicator of whether user fees are a barrier to innovation or a waiver or reduction is necessary to protect the public health. Based on over 25 years of experience in implementing the user fee program, FDA has determined that most applicants that, including the resources of their affiliates, have financial resources of less than $20 million of working capital are those least able to pay the fees. Therefore, the Agency generally intends to use $20 million as its marker for evaluating whether an applicant and its affiliates have limited resources such that a waiver or reduction is *necessary* to protect the public health and whether the fees are a *significant barrier* to innovation. An applicant with $20 million or more in financial resources, including the financial resources of affiliates, generally will not be considered to have limited resources for user fee purposes.

FDA generally intends to consider the working capital of an applicant and its affiliates to determine whether the applicant has limited financial resources. Working capital is an objective measure of the resources available to the applicant and is defined by generally accepted accounting principles. To calculate working capital, FDA intends to review current assets and current liabilities of applicants and their affiliates to determine if an applicant has limited financial resources. In addition, net proceeds that increase the cash flow of an applicant and affiliates may also be an important factor in determining whether the applicant and its affiliates have limited financial resources. FDA recommends that applicants provide financial information according to the fiscal year, which begins October 1 and ends September 30. If an applicant's financial records are not organized by the U.S. government's fiscal year, an applicant may submit financial information from the 12 months preceding the date of the waiver request. Section VI.C. provides more information on the type of documentation applicants may submit to support its assertions of its limited resources. If such information is not provided, FDA may not be able to determine whether the applicant and its affiliates have limited resources and therefore may deny the public health or barrier-to-innovation waiver request.

FDA does not intend to deduct marketing costs when calculating an applicant's working capital. Because even a very large applicant with extensive financial resources may have operating losses, FDA does not intend to consider lack of profitability as evidence of limited resources. The Agency also does not intend to consider product sales figures to be evidence of limited resources, because even a large and profitable company can have low sales figures for an individual product, but not need a waiver to continue an activity that is necessary to protect the public health. In such cases, the fees would not present a significant barrier to innovation.

FDA considers the financial resources of applicants that are State or Federal government entities differently. The Agency generally intends to consider State or Federal government entities with less than $20 million in total annual revenue from the sale of the drug being evaluated by the Agency for a waiver or reduction to have limited resources for user fee purposes. A government entity is able to devote only a small amount of money to drug development activities relative to the entity's budget and the total State or Federal budget. In addition, government entities generally receive only a small amount of revenue from commercial distribution of a drug, as compared with total revenues. FDA believes that Congress intended to minimize the burden on State and Federal government entities by focusing attention on their drug development revenues,

not the overall revenues of the entity or the State or Federal government.[23] Section V.B. provides information on exemptions from application and program fees for State or Federal government entities that do not distribute commercially.

D. Small Business

Under section 736(d)(1)(C) of the FD&C Act, an applicant is eligible for a waiver of the ***application fee*** if the applicant is a small business submitting its first human drug application to the Agency for review and does not have another product approved under a human drug application and introduced or delivered for introduction into interstate commerce.[24]

To qualify for a small business waiver of the application fee, an applicant must:

- Employ fewer than 500 employees, including employees of affiliates;[25]
- Not have a drug product that has been approved under a human drug application and introduced or delivered for introduction into interstate commerce;[26] and
- Be submitting its first human drug application, including its affiliates. [27]

1. Small Business Waiver and Refund Requests

To qualify for a small business waiver of the application fee, an applicant should submit to FDA Form FDA 3971, attached as Appendix 1 and available at https://www.fda.gov/media/108984/download. If an applicant submitted an NDA or BLA with a payment and would like to request a small business waiver and refund, the applicant should submit Form FDA 3971 to request the refund within 180 calendar days of when the application fee is due. Section VI.D provides further information about Form FDA 3971 and the waiver request process.

FDA recognizes that some information provided by companies may be confidential. FDA will treat confidential commercial or financial information consistent with applicable federal laws and regulations (see section IX).

2. Expiration Date of the Small Business Waiver

If a small business waiver is granted, the applicant should submit its human drug application within 1 year after the date of the small business determination since circumstances supporting a small business waiver can change rapidly. For example, an applicant could merge with a larger

[23] For example, the FD&C Act exempts a State or Federal government entity from application and program fees for a drug product that is not distributed commercially. Sections 735(1) and (3) of the FD&C Act.
[24] There is no specific provision in the FD&C Act for a waiver or reduction of program fees for small businesses. However, small businesses may apply for a waiver or reduction of program fees through the public health or barrier-to-innovation waiver provisions. See discussions in sections IV.A-IV.C.
[25] Section 736(d)(3)(A) of the FD&C Act.
[26] Id.
[27] Section 736(d)(1)(C) of the FD&C Act.

company and therefore no longer be considered a small business. Similarly, an applicant could purchase an NDA from an unaffiliated company and, therefore, would have a drug product that has been approved under a human drug application and introduced into or delivered for introduction into interstate commerce.

If an applicant is granted a small business waiver and is unable to submit the application within 1 year of the determination, the applicant should request a new small business waiver by following the instructions provided in section VI.D. The Agency generally intends to examine the newly submitted information to confirm that the applicant is still eligible for a small business waiver.

3. Small Business Waivers of Application Fees for Future Human Drug Applications

After an applicant or its affiliate is granted a small business waiver and submits its first human drug application, the applicant and all affiliates are no longer eligible for a small business waiver. That means that the applicant or its affiliate is not eligible to receive a small business waiver for any subsequent human drug application, even if the first application is withdrawn or refused for filing.[28] An applicant that received a small business waiver for an application that was later refused for filing or withdrawn, however, may renew its request for a small business waiver if the applicant resubmits the same application.

If an applicant does not submit the application for which it was granted a small business waiver, the applicant may qualify again for a small business waiver. Applicants should contact the Division of User Fee Management and Budget Formulation at CDERCollections@fda.hhs.gov for further guidance.

V. EXEMPTIONS AND REFUNDS

A. Orphan Designated Products

1. Application Fees

Under section 736(a)(1)(F) of the FD&C Act, a human drug application for a product that has been designated as a drug for a rare disease or condition (referred to as an orphan drug) under section 526 of the FD&C Act is not subject to an application fee unless the human drug application includes an indication for other than a rare disease or condition.

If an application qualifies for an orphan exemption, the applicant does not need to send FDA a written request. The applicant should simply notify FDA that it is claiming the orphan exemption when it completes and submits the User Fee Cover Sheet, Form FDA 3397.[29] The User Fee Cover Sheet should be included with the application, and a brief statement claiming the orphan exception should be included in the cover letter. ***If the applicant paid the application fee***

[28] Section 736(d)(3)(B) of the FD&C Act.

[29] For more information about completion and submission of the User Fee Cover Sheets, see http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119184.htm.

in advance of receiving the orphan drug designation, the applicant must submit a written request for a refund no later than 180 calendar days after such fee was due.[30] For an applicant who paid the application fee in advance and has not yet received an orphan drug designation, FDA recommends that the applicant request a refund in the cover letter at the time the applicant submits the application, in anticipation of receiving orphan drug designation. If orphan designation is granted more than 180 calendar days after the application is submitted, the applicant will not be eligible for a refund at that time *unless* it submitted a refund request within 180 calendar days of submitting the application. Section VI provides further information about refund requests.

2. Program Fees

Under section 736(k) of the FD&C Act, a drug product designated under section 526 of the FD&C Act for a rare disease or condition and approved under section 505 of the FD&C Act or section 351 of the PHS Act is exempt from the program fee if it meets the public health requirements contained in the FD&C Act as such requirements are applied to requests for waivers of the program fee. In addition, the applicant must have less than $50 million in gross worldwide revenue during the year preceding the request for exemption.[31]

An applicant seeking to avail itself of this exemption should submit a certification that its gross worldwide revenues, including affiliates, did not exceed $50 million for the 12 months before the request.[32] The applicant should also submit financial documentation that supports the certification, such as financial statements that show intangible assets, other income, net gain on financial assets, foreign exchange gains, and interest income.

Upon review of an applicant's certification and accompanying information, FDA may contact the applicant to request further information, if needed, and for clarification of the information asserted in the applicant's certification. FDA may request information about the applicant and its affiliates, such as financial statements, annual reports, and documents identifying affiliate relationships. If such information is not provided, FDA may not be able to verify an applicant's certification and therefore may deny the orphan drug exemption request. Section VI provides information about how to submit a request for an exemption or refund of the program fee.

B. State or Federal Government Entity

An application submitted by a State or Federal government entity for a drug that is ***not distributed commercially*** is not considered a "human drug application" under section 735(1) of the FD&C Act. If the application is not considered a human drug application, then application fees are not assessed and the program fee does not apply.

For the purposes of the State and Federal exemption from user fees under the FD&C Act, FDA interprets ***distributed commercially*** to mean any distribution in exchange for financial reimbursement, goods, or services, whether or not the amount of the charge covers the full costs

[30] Section 736(i) of the FD&C Act.
[31] Section 736(k)(1)(B) of the FD&C Act.
[32] Section 736(k)(2) of the FD&C Act.

associated with the product. Under FDA's interpretations, any recovery by the applicant of all or part of the costs of manufacture or distribution of a product would make the distribution commercial.

C. No Substantial Work

Under section 736(a)(1)(G) of the FD&C Act, if an application is withdrawn after the application is filed, FDA may refund the fee or a portion of the fee if no substantial work was performed on the application after the application was filed. FDA has sole discretion in determining whether any portion of the fee may be refunded. A determination by FDA concerning a refund in such instance is not eligible for review.[33]

VI. SUBMITTING REQUESTS FOR WAIVERS, REDUCTIONS, AND REFUNDS

A. Address for Submitting Requests

Applicants may submit written requests (for both CDER and CBER products) via email to CDERCollections@fda.hhs.gov.

Please indicate the type of request and the applicant name in the subject line of the email. Examples of types of request that may be used in the subject line are: Orphan Drug Exemption, Public Health Waiver Request, Barrier-to-Innovation Waiver Request, and Small Business Waiver Request.

Alternatively, applicants may mail requests to FDA via the carrier of their choice. For the most updated mailing address, visit the following FDA website: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

B. Timing of Requests

1. Deadline to Request a Waiver, Reduction, or Refund

Under section 736(i) of the FD&C Act, to qualify for a waiver of or reduction in user fees as well as a refund for a fee paid, an applicant must submit to FDA a written request for a user fee waiver, reduction, or refund no later than 180 calendar days after the fee is due.

For example, if an applicant receives a program fee invoice from FDA, FDA expects the invoice to be paid by the due date. The applicant can then submit a written request for a waiver, reduction, or refund of the fee(s) within 180 calendar days from the date when the invoice is due. If the request is submitted within 180 calendar days of the due date (i.e., if the request is timely), FDA will evaluate the applicant's request. If FDA determines that the applicant made a timely request and qualifies for a waiver, reduction, or refund, the Agency will grant the applicant's request.

[33] Section 736(a)(1)(G) of the FD&C Act.

To avoid having to pay a fee, an applicant can submit a request for a waiver or reduction in advance of when the program fee invoice is due, or in advance of submitting an application (see sections VI.B.3 and 4).

If the applicant submits a waiver or exemption request and pays the relevant fee before receiving a determination from FDA on the waiver or exemption, the applicant should submit a refund request not later than 180 calendar days after such fee is due in order to qualify for a refund.

2. Consequences for Failure to Pay User Fees Due to Waiver or Reduction Delays

A human drug application or supplement submitted by a person subject to fees under section 736(a) of the FD&C Act is considered incomplete and will not be accepted for filing until all such fees owed by the person have been paid. For example, if a person submits an application without an application fee or if the person is in arrears[34] for nonpayment of any prescription drug program fees,[35] the application will be incomplete and FDA will not accept it for filing. Note that the term person as used here includes an affiliate of the person, which means that an affiliate's failure to pay all of the user fees that it owes will affect the applicant's ability to file an application.

3. Recommended Time Frame to Submit a Request for a Waiver or Reduction of the Application Fee

FDA encourages applicants to submit a request for a waiver of or reduction in an application fee approximately 3 to 4 months before submission of the application. Under normal circumstances and depending on available resources, FDA will try to make its determination on the waiver request before the application is submitted upon which the fee is due.

FDA discourages applicants from submitting application fee waiver or reduction requests more than 4 months before the submission of an application because the circumstances that support an applicant's request are subject to change. FDA considers it unreasonable to assume that those circumstances will continue to exist for longer than 4 months before the submission of an application.

4. Recommended Time Frame to Submit a Request for a Waiver or Reduction of the Program Fee

The time frame to submit a request for a waiver or reduction of the program fee is the same as for an advance request for an application fee waiver or reduction: an applicant seeking a waiver or reduction of the program fee should generally submit a request for a waiver or reduction 3 to 4 months before the fee is due. Annual program fees are due on October 1, or the first business day after the enactment of the appropriations act providing for the collection and obligation of

[34] Section 736(e) of the FD&C Act.

[35] Annual program fees are due on October 1, or the first business day after the enactment of the appropriations act providing for the collection and obligation of PDUFA fees for that fiscal year, whichever occurs later. Section 736(a)(2)(A) of the FD&C Act.

PDUFA fees for that fiscal year, whichever occurs later.[36, 37] Thus, an applicant that wishes to obtain a waiver or reduction in advance should submit its request between June 1 and July 1. Under normal circumstances and depending on available resources, FDA will try to complete its evaluation of the request before the due date of the program fee.

The FD&C Act does not provide for deferral of user fees, and FDA does not grant deferrals of user fees based on pending waiver or reduction requests. FDA therefore expects that all program fees will be paid without regard to a pending request for a fee waiver or reduction. This approach ensures that the steady funding stream Congress intended will be achieved, and it should deter the filing of frivolous waiver or reduction requests.

Ordinarily, FDA expects to grant a reduction or waiver of a program fee only for the current year. If an applicant wishes to have a program fee waived or reduced for assessments in future years, it should make a new request for a waiver or reduction each year.

C. Content and Format of Requests, Excluding Small Business Waiver Requests

1. General Information

Requests for CDER user fee waivers, reductions, and refunds will be reviewed and granted or denied by the Division of User Fee Management and Budget Formulation within CDER. Requests for CBER user fee waivers, reductions, and refunds will be reviewed and granted or denied by CBER's Center Director or designee.

FDA recommends that each waiver, reduction, or refund request be submitted in writing on official company letterhead and that it contain the following information:

- Name of applicant requesting the waiver, reduction, or refund, including company name, address, contact, telephone number, and email address
- Tax Identification Number (required for all U.S. applicants) and/or DUNS Number
- If an agent is submitting the request on behalf of an applicant, authorization from the applicant for the agent to act on the applicant's behalf
- Application number, i.e., NDA, BLA, or IND
- Trade and established names of product(s) covered by the request
- Identification of the specific fee(s) for which the waiver, refund, or reduction is requested
- Date on which the user fee payment was made or will be made for which a waiver, reduction or refund is requested

[36] Section 736(a)(2)(A) of the FD&C Act.
[37] Section 736(e) of the FD&C Act.

- Statutory provision under which a waiver, reduction, or refund is requested
- Information and analyses demonstrating eligibility for the waiver, reduction, or refund
- Rationale for why the waiver, reduction, or refund request should be granted
- List of the applicant's affiliates[38]
- For public health and barrier-to-innovation waivers, a current annual financial report for the applicant and the applicant's affiliates. If a current annual financial report is not available, a report that includes total cash and cash equivalents, accounts receivables, inventories, short and long-term investment marketable securities, deferred revenue, prepaid expenses, and any other net proceeds received during the fiscal year that will increase the applicant's and its affiliates' cash flow even if not recorded under current assets.
- For requests for an orphan drug exemption to the program fee, a certification that its gross worldwide revenues, including affiliates, did not exceed $50 million for the 12 months before the request and financial documentation that supports the certification, such as financial statements that show intangible assets, other income, net gain on financial assets, foreign exchange gains, interest income, and net proceeds.

2. Additional Specific Information for Application Fee Waiver or Reduction Requests

In addition to the general information specified above, requests for waivers or reductions in **application fees** should include the following:

- Date the application was or is intended to be submitted
- Whether clinical data are expected to be required for approval

3. Additional Specific Information Requested for Program Fee Waiver or Reduction Requests

In addition to the general information specified above, requests for waivers of or reductions in the **program fee** should include the following:

- Name of the application holder, if different from the name of the applicant requesting the waiver
- Specific strength, dosage form, and route of administration

[38] When determining whether parties are affiliated, the critical factor is whether one party controls or has the power to control another entity, or if a third party has the power to control both entities. In such cases, FDA recommends that the applicant submit any agreements between an applicant and the other entities that demonstrate the nature of the relationship the applicant has with the entity.

- Invoice date and number (or copy of the invoice)

D. Content and Format of Request for a Small Business Waiver

To qualify for a small business waiver of the application fee, an entity must submit to FDA a written request for such a waiver and a certification that the entity meets the requirements for the waiver. Applicants should submit requests for a small business waiver of the application fee and refund due to the small business waiver via Form FDA 3971, attached as Appendix 1 and available at https://www.fda.gov/media/108984/download. The completed form should be submitted via email to CDERCollections@fda.hhs.gov with the subject line, Small Business Waiver Request – [Applicant Name].

Upon receipt of Form FDA 3971, FDA may contact the applicant to request additional information and clarification of the information supporting the assertions in Form FDA 3971. Examples of information that may be requested include, but are not limited to the following:

- A copy of the applicant's Articles of Incorporation and Bylaws;
- The applicant's last annual statement to shareholders; and
- A breakdown of the number of persons employed full time, part time, temporarily, or otherwise by the applicant and affiliates during each of the pay periods for the 12 months preceding the company's certification.

Occasionally, FDA finds entities to be affiliated with the applicant that the applicant did not identify as one of its affiliates in its initial waiver or exemption submission. When determining whether parties are affiliated for purposes of user fee assessment under PDUFA, the critical factor is whether one party controls or has the power to control another entity, or if a third party has the power to control both entities.[39] In such cases, FDA recommends that the applicant submit copies of any agreements between an applicant and the other entities that demonstrate the nature of the relationship the applicant has with the entity. If the requested supporting documentation is not submitted, FDA may deny the small business waiver request on the grounds that there is insufficient evidence that the applicant meets the requirements in section 736(d)(1)(C) of the FD&C Act.

Once FDA has identified and confirmed which entities are properly considered affiliates of the applicant and determined whether the applicant qualifies as a small business, it will evaluate whether the applicant is eligible for the small business waiver. Specifically, FDA determines whether the applicant or any of its affiliates has previously submitted a human drug application, and whether the applicant has a drug product that has been approved under a human drug application and introduced or delivered for introduction into interstate commerce. After FDA assesses the applicant's eligibility for a small business waiver FDA will notify the applicant whether the waiver is granted.

[39] See section 735(11) of the FD&C Act.

E. Refund Requests

To qualify for an application or program fee refund, an applicant must submit to FDA a written request for a refund not later than 180 calendar days from the date the fee is due.[40] This is the case even if the applicant has submitted a citizen petition that may relate to a potential claim for a refund (e.g., a citizen petition requesting that FDA determine that a drug product is therapeutically equivalent to another drug product for the purposes of the "same product as another product" exception under section 736(a)(2)(B)(ii) of the FD&C Act). Further, if a pending refund request does not expressly cover a subsequent time frame for which an applicant wishes to claim a refund, FDA interprets the statute to require that the applicant to submit another written request for refund that expressly covers the subsequent time frame. For example, if an applicant has a request for a FY 2020 program fee refund that is pending at the time of a program fee assessment for FY 2021, and the applicant believes it is also eligible for a refund for FY 2021 and wishes to claim a FY 2021 refund, a timely request for a refund for FY 2021 must be submitted.[41]

Applicants may submit their written request for an application fee refund in the submission cover letter of their application. A copy of the cover letter or program fee refund request (for both CBER and CDER products) should be submitted via email to CDERCollections@fda.hhs.gov.

Alternatively, an applicant may mail the request to FDA via the carrier of its choice. For the most updated mailing address, visit the following FDA website: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

VII. FDA RESPONSES TO REQUESTS FOR WAIVERS, REDUCTIONS, AND REFUNDS

FDA will review waiver, refund, and reduction requests, consulting with relevant Agency officials and official Agency records or other resources as appropriate. If needed to support applicants' assertions that the applicant qualifies, FDA may request additional information and documentation from the applicant during its review of a waiver, reduction, or refund request. Failure to provide the requested information or documentation may result in a denial of a waiver, reduction, or refund. The Agency will respond to all such requests in a timely fashion based on available resources and collection time for additional information.

[40] Section 736(i) of the FD&C Act.
[41] See id.

VIII. APPEALS PROCESS

A. Reconsideration Request

If FDA fully or partially denies a request for a waiver, refund, or reduction of user fees, the applicant may request reconsideration of that decision. A request for reconsideration should be made within 30 calendar days of the issuance of FDA's decision to fully or partially deny a request for a waiver, refund, or reduction of user fees.

FDA recommends that requests for reconsideration state the applicant's reasons for believing that the decision is in error and include any additional information, including updated financial information that is relevant to the applicant's position. The Agency will issue a response upon reconsideration, setting forth the basis for the decision.

All requests for reconsideration (for both CBER and CDER regulated products) should be submitted via email to CDERCollections@fda.hhs.gov and should be addressed to the Division of User Fee Management and Budget Formulation, Attention: Division Director, Center for Drug Evaluation and Research.

Alternatively, an applicant may mail the request to FDA via the carrier of its choice. For the most updated mailing address, visit the following FDA website: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

B. Appeal Request

If a request is denied upon reconsideration, the applicant may choose to appeal the denial. A request for an appeal should be made within 30 calendar days of the issuance of FDA's decision to affirm its denial of a request for a waiver, refund, or reduction of user fees. The following information should be included in the appeal:

- The original waiver request
- The denial of the original waiver request
- The reconsideration request
- The denial of the reconsideration request
- A statement of the applicant's belief that the prior conclusions were in error.

No new information or new analyses should be presented in the appeal request. If new information and/or analyses are presented in the appeal request, the appeal will not be accepted and the matter will be referred back to the original deciding official to consider the new information or analyses.

All requests for appeals (for both CBER and CDER products) should be submitted to the Director of CDER's Office of Management via CDERCollections@fda.hhs.gov and a copy should be submitted to the CDER Formal Dispute Resolution Project Manager, whose contact information can be found on the CDER Formal Dispute Resolution Web page.[42]

Alternatively, an applicant can mail the request to FDA via the carrier of its choice. For the most updated mailing address, visit the following FDA website: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

After FDA reviews the information submitted in the appeal request, for CDER regulated products, the Director of CDER's Office of Management will issue a written decision on the applicant's request; for CBER regulated products, the Director of CBER will issue a written decision on the applicant's request.

CDER Products

If the applicant's appeal is denied at one management level, the applicant can appeal the same matter to the next higher management level in the Center chain of command. A new request should be submitted for each appeal to the next management level and should follow the process provided in this guidance. If the applicant has exhausted the Center's management levels and remains unsatisfied with the decision, the applicant may request review of the matter by the Commissioner of Food and Drugs (Commissioner) under 21 CFR 10.75(c). Requests for review by the Commissioner should be submitted to FDA's Ombudsman, with copies provided to the Center that denied the appeal. Review of such matters by the Commissioner is discretionary.[43]

CBER Products

If the applicant's appeal is denied by the Director of CBER, the applicant may request review of the matter by the Commissioner under 21 CFR 10.75(c). Requests for review by the Commissioner should be submitted to the FDA's Ombudsman, with copies provided to the Center that denied the appeal. Review of such matters by the Commissioner is discretionary.

IX. DISCLOSURE OF PUBLIC INFORMATION

FDA may disclose information publicly about its actions granting or denying waivers, refunds and reductions. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

[42] See https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ContactCDER/ucm444092.htm.

[43] See 40 FR 40682, 40693 (Sep. 3, 1975).

X. PAPERWORK REDUCTION ACT OF 1995

This guidance contains information collection provisions that are subject to review and approval by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). "Collection of information" is defined in 44 U.S.C. 3502(3) and 5 C.F.R. 1320.3(c) and includes Agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. The guidance refers to the following forms: (1) Form FDA 3397 and (2) Form FDA 3971.

The information collections of this guidance have been submitted for OMB renewal of approval under OMB control number 0910-0693.

Collection of information for completing and submitting Form FDA 3397 (Prescription Drug User Fee Cover Sheet) is previously approved under OMB control number 0910-0297. Collections of information associated with the submission of a new drug application or biologics license application are approved under OMB control numbers 0910-0001 and 0910-0338, respectively.

The time required to complete the information collections included in this guidance are estimated to average 16 hours for a request for a waiver, reduction, refund, or exemption of certain user fees; 24 hours per response for a reconsideration of a request; and 12 hours for an appeal of a waiver, reduction, or refund decision. These estimates include the time to review instructions, gather the data needed, and complete and review the information collection.

Form FDA 3971 is the collection of information submitted when requesting the small business waiver. Use of Form FDA 3971 does not change the burden previously approved under OMB control number 0910-0693 for submitting or evaluating small business waivers. It facilitates the presentation of the information required for evaluation of the small business waiver with the use of a standardized form and an electronic fillable format.

Send any comments regarding the burden estimate or suggestions for reducing this burden to the following:

Department of Health and Human Services
Food and Drug Administration
Office of Operations
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

APPENDIX 1: FORM FDA 3971

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Prescription Drug and Biosimilar User Fee Acts

Small Business Waiver and Refund Request

Form Approved: OMB No. 0910-0693
Expiration Date: October 31, 2020
See PRA Statement on last page.

Section I: Applicant Information

1. Applicant Name

Former Names *(if applicable)*

2. Telephone Number *(Including area and country codes)*

3. Fax Number *(Including area and country codes)*

4. Address *(No P.O. boxes allowed)*

Address 1 *(Street address)*

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

City | State/Province/Region

Country | ZIP or Postal Code

5. Federal Tax ID Number *(Required for all U.S. applicants)*

6. DUNS Number

7. Number of Employees

8. User Fee Program for which the action is requested *(Select one)*

☐ PDUFA ☐ BsUFA

9. Human Drug/Biosimilar Biological Product Applications (Applicant)

Product Name

Application Number | Submission Date | Application Status *(Select from drop-down list)*

Is this the first application the Applicant has submitted to the FDA for review? ☐ Yes ☐ No

10. Human Drug/Biosimilar Biological Products (Applicant)

Does the Applicant have drug products approved under a human drug or biosimilar biological product application by the FDA that have been introduced or delivered for introduction into interstate commerce? ☐ Yes ☐ No

11. Small Business Waiver (Applicant)

Has the Applicant previously received a Small Business Waiver for a human drug or biosimilar biological product? *(See instructions for details.)* ☐ Yes ☐ No

Section II: Affiliate Information *(Enter information for each entity affiliated with the Applicant)*

Provide information for each of the Applicant's domestic and foreign affiliates. For multiple affiliates, click the "Add Affiliate" button for each additional entry. Refer to Instructions, Section II for additional information.

The Applicant does NOT have any Affiliates *(Check if applicable)***:** ☐

12. Affiliate Name

13. Affiliate Address *(No P.O. boxes allowed)*		14. DUNS Number
Address 1 *(Street address)*		15. Number of Employees
Address 2 *(Apartment, suite, unit, building, floor, etc.)*		
City	State/Province/Region	
Country	ZIP or Postal Code	

16. Name of Affiliate's Point of Contact	17. E-mail Address	18. Telephone Number

19. Small Business Waiver (Affiliate)

Has the Affiliate previously received a Small Business Waiver for a human drug or biosimilar biological product application? *(See instructions for details.)* ☐ Yes ☐ No

20. Human Drug/Biosimilar Biological Product Applications (Affiliate)

Has the Affiliate ever submitted a human drug or biosimilar biological product application? ☐ Yes ☐ No

Click for an additional set of Section II affiliate entries (includes items 12 through 20). May be repeated. Add Affiliate

Section III: Refund

21. Did the Applicant pay a fee for this application for _____ prior to requesting this Small Business Waiver?
Product Name

Yes ☐ ☐ No

NDA or BLA Number	Payment Amount	PIN/Invoice Number	Payment Reference Number	Refund Amount Requested

Section IV: Certification

Review, sign, and date the following certification statement:

I certify that _____
Applicant Name (must be identical to item 1)

BsUFA:

i Has fewer than 500 employees, including employees of Affiliates;

ii. Does not have a drug product that has been approved under a human drug application or biosimilar biological product application by the FDA and introduced or delivered for introduction into interstate commerce;

iii. Requests a Small Business Waiver for the first biosimilar biological product application that the Applicant or its Affiliate has submitted.

PDUFA:

i Has fewer than 500 employees, including employees of Affiliates;

ii. Does not have a drug product that has been approved under a human drug application by the FDA and introduced or delivered for introduction into interstate commerce;

iii. Requests a Small Business Waiver for the first human drug application that the Applicant or its Affiliate has submitted.

I further certify that, to the best of my knowledge, the information I have provided in this form is complete, accurate and has been verified. I understand that submission of a false certification may subject me to criminal penalties under 18 U.S.C. § 1001 and other applicable federal statutes.

22. Name of Applicant's Responsible Official	23. Title
24. Telephone Number	25. Email Address

26. Responsible Official's Address		
Address 1 *(Street address)*		
Address 2 *(Apartment, suite, unit, building, floor, etc.)*		
City	State/Province/Region	
Country	ZIP or Postal Code	

27. Signature	28. Date *(mm/dd/yyyy)*
To enable the signature field, please fill out all prior required fields. For a list of required fields which have not yet been filled out, please click here.	

Send Completed Form FDA 3971 to FDA via

Email (preferred): *CDERCollections@FDA.HHS.GOV* **or** **Physical Mail:** Division of User Fee Management and Budget Formulation
Food and Drug Administration 10001 New Hampshire Ave. Silver Spring, MD 20993-0002

FDA Use Only

Date Received: _____ ☐ **Approved** ☐ **Denied**

Privacy Act Notice: This notice is provided pursuant to the Privacy Act of 1974, 5 U.S.C. § 552a. The collection of this information is authorized by 21 U.S.C. § 379h and 21 U.S.C. § 379j-52. FDA will use the information to assess, collect and process user fee payments, and, facilitate debt collection under the Debt Collection Improvement Act. FDA may disclose information to courts and the Department of Justice in the context of litigation and requests for legal advice; to other Federal agencies in response to subpoenas issued by such agencies; to HHS and FDA employees and contractors to perform user fee services; to the National Archives and Records Administration and General Services Administration for records management inspections; to the Department of Homeland Security and other Federal agencies and contractors in order to respond to system breaches; to banks in order to process payment made by credit card; to Dun and Bradstreet to validate submitter contact information, and to other entities as permitted under the Debt Collection Improvement Act. Furnishing the requested information is mandatory unless otherwise indicated. Failure to supply the information could prevent FDA from processing user fee payments and waivers. Additional detail regarding FDA's use of information is available online: Privacy Act and Website Policies.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 40 minutes per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human
Services Food and Drug Administration
Office of Operations
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

PDUFA Waivers, Reductions, and Refunds for Fixed-Combinations and Single-Entity Versions of Previously Approved Antiretrovirals under PEPFAR

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Division of User Fee Management 301-796-7900.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2023
User Fees

PDUFA Waivers, Reductions, and Refunds for Fixed-Combinations and Single-Entity Versions of Previously Approved Antiretrovirals under PEPFAR

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353;
Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2023
User Fees

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PDUFA Waivers, Reductions, and Refunds for Fixed-Combinations and Single-Entity Versions of Previously Approved Antiretrovirals under PEPFAR
Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance describes circumstances in which an applicant may be eligible for a barrier-to-innovation waiver under the Prescription Drug User Fee Act (PDUFA)[2] for certain new drug applications (NDAs) for single-entity (SE) antiretroviral (ARV) and fixed-combination (FC)[3] ARV drug products for the treatment or prevention of human immunodeficiency virus-1 (HIV-1 or HIV). FDA expects that most of the application fees for SE and FC ARV drug products proposed for use in the President's Emergency Plan for AIDS Relief (PEPFAR) will qualify for a waiver under the barrier-to-innovation waiver provision.[4]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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[1] This guidance has been prepared by the Division of User Fee Management in the Center for Drug Evaluation and Research (CDER) in cooperation with the Division of Antivirals, CDER, and the Office of Global Policy and Strategy, Office of the Commissioner.

[2] Sections 735 and 736 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 379g and 379h). Unless otherwise specified, all references to "user fees" in this guidance mean user fees assessed under these sections of the FD&C Act, and not fees assessed under other provisions in the FD&C Act or the Public Health Service Act (PHS Act).

[3] For the purposes of this guidance, a *fixed-combination antiretroviral drug product* is one in which two or more antiretroviral drugs are combined in a single dosage form and the contribution of the individual drugs has been demonstrated to contribute to the effect(s) of the fixed-combination consistent with the requirements of 21 CFR 300.50. For the purposes of this guidance, the term *drug product* will be used to refer to human prescription drugs, under section 505 of the Federal Food, Drug, and Cosmetic (FD&C) Act.

[4] Section 736(d)(1)(B) of the FD&C Act.

II. BACKGROUND

PEPFAR is a U.S. Government initiative to help save the lives of those suffering from HIV/AIDS (acquired immunodeficiency syndrome) around the world. It was originally announced in President George W. Bush's State of the Union address in 2003 and was reauthorized in 2008, 2013, and 2018. To date, this historic commitment is among the largest by any nation to combat a single disease internationally. As of 2012, ARV drug products are also available for HIV prevention, and as of 2015, the World Health Organization recommends the use of these drug products to reduce the risk of HIV-1 acquisition. ARV drug products for treatment and prevention play a major role in this relief plan, and it is important that resources are spent on products that have been demonstrated to be safe and effective. ARV drug products for treatment or prevention of HIV must conform to regulatory standards of safety, efficacy, and quality to maximize the success of treatment or prevention and to reduce the emergence and spread of resistant virus. Of note, FDA-approved or tentatively approved ARV drug products are eligible for procurement under PEPFAR.

In October 2006, to encourage applicants to submit applications for HIV combination therapies that can be used in PEPFAR, FDA issued a final guidance *Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV* (2006 Fixed-Combination Guidance). Attachment A of the 2006 Fixed-Combination Guidance described some scenarios for the approval of fixed-combination and co-packaged products for the treatment of HIV that might be eligible for the PEPFAR program at that time, and Attachment B provided examples of drug combinations that FDA expected could be developed without conducting new clinical efficacy and safety studies. In 2023, FDA issued a draft guidance, *Fixed-Combinations and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment or Prevention of HIV-1 Under PEPFAR* (2023 Fixed-Combination Guidance),[5] which, when finalized, will revise and replace the 2006 Fixed-Combination Guidance to reflect updated information regarding the PEPFAR program. To replace Attachment B, previously attached to the 2006 Fixed-Combination Guidance, the Agency published a separate list, *Antiretroviral Drug Products Needed for Use Under PEPFAR*,[6] which includes single-entity ARV and FC ARV drug products supported by clinical data and currently needed for PEPFAR procurement. Applicants should refer to this list when considering submission of applications for ARV drugs intended for use under PEPFAR. The 2023 Fixed-Combination Guidance provides recommendations for applications for SE and FC ARV drug products for the treatment or prevention of HIV infection that are intended for use under PEPFAR.

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[5] FDA updates guidances periodically. To ensure you have the most recent version of a guidance, check the FDA Guidances (Drugs) web page available at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs.

[6] The separate list of ARV drug products, *Antiretroviral Drug Products Needed for Use Under PEPFAR*, can be found under question 6, *What PEPFAR products can companies submit for FDA review?*, at FDA's PEPFAR Database on the Frequently Asked Questions web page: available at https://www.fda.gov/international-programs/presidents-emergency-plan-aids-relief-pepfar/pepfar-database-frequently-asked-questions. This list is revised periodically to address current public health needs.

When final, this guidance will supersede the guidance for industry *User Fee Waivers for FDC and Co-Packaged HIV Drugs for PEPFAR*, issued February 2007. In this guidance, FDA provides information about circumstances under which certain applications for ARV drug products for the treatment or prevention of HIV infection that are proposed for use under PEPFAR may be eligible for a user fee waiver under the barrier-to-innovation waiver provision.[7]

III. BASIS FOR ASSESSING PDUFA USER FEES

The Prescription Drug User Fee Act of 1992 (PDUFA I) directed FDA to assess user fees to certain applicants for a five-year period. Beginning in 1997, PDUFA has been reauthorized by Congress every five years. Under the Prescription Drug User Fee Amendments of 2022 (PDUFA VII), which includes the reauthorization of PDUFA through September 2027, FDA generally assesses application fees to an applicant when it submits a human drug application (defined by statute to include certain new drug applications under section 505(b) of the FD&C Act and certain biologics license applications under section 351(a) of the Public Health Service Act (PHS Act) [8]), subject to limited statutory exceptions.[9] FDA also assesses prescription drug program fees annually, subject to limited exceptions, to applicants of approved drugs whose applications were submitted under section 505(b) of the FD&C Act or section 351(a) of the PHS Act.[10, 11] The PDUFA user fee authorities are in sections 735 and 736 of the FD&C Act.

The amount of the application fee assessed for a human drug application depends on whether clinical data[12] (other than bioavailability or bioequivalence studies) with respect to safety or effectiveness are required for approval of the application.[13] Specifically, a human drug application for which such data are not required is assessed one-half the fee of an application that requires such data for approval.[14]

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[7] Section 736(d)(1)(B) of the FD&C Act.

[8] Section 735(1) of the FD&C Act.

[9] Section 736(a)(1) of the FD&C Act.

[10] PDUFA user fee waivers, reductions, and refunds are discussed in FDA's guidance for industry *Prescription Drug User Fee Act Waivers, Reductions, and Refunds for Drug and Biological Products* (Oct. 2019). FDA updates guidances periodically. To ensure you have the most recent version of a guidance, check the FDA Guidances (Drugs) web page available at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs.

[11] In this guidance, the terms *prescription drug program fee* and *program fee* have the same meaning.

[12] For purposes of assessing user fees, FDA's interpretation of clinical data can be found in the guidance for industry *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees* (Dec. 2004).

[13] Section 736(a)(1) and (b) of the FD&C Act (21 U.S.C. 379h(a)(1) and (b)).

[14] Section 736(a)(1)(A) of the FD&C Act (21 U.S.C. 379h(a)). Information on application and program fees, including fee rates, PDUFA goals, and other various user fee related issues can be found on FDA's PDUFA website: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

IV. PDUFA USER FEE WAIVERS, REDUCTIONS, AND REFUNDS

A. Application Fees

Applicants may qualify for a waiver or refund of their application fee under section 736(d) of the FD&C Act. FDA encourages applicants to request a waiver no later than 45 calendar days in advance of submission of an application so that the request can be evaluated before the fee is due.[15] If the applicant pays the fee upon submission of the application and seeks a refund (rather than waiting to submit the application until such time as the waiver is granted), under the statute, a written request for refund *must* be submitted to FDA not later than 180 calendar days after the fee due date.[16, 17] Applicants who pay the fee but believe they will be eligible for a refund are encouraged to request a refund simultaneously with payment of the fee. Instructions for the submission of waiver and refund requests are found in FDA's guidance for industry *Prescription Drug User Fee Act Waivers, Reductions, and Refunds for Drug and Biological Products*.[18]

Section 736(d) of the FD&C Act contains three waiver or reduction provisions under which an applicant may request a waiver or reduction in user fees based on public health necessity, to remove a barrier to innovation, or if the applicant qualifies as a small business submitting its first application. FDA's guidance for industry *Prescription Drug User Fee Act Waivers, Reductions, and Refunds for Drug and Biological Products* describes FDA's interpretation of each of these waiver provisions.[19]

Although the Agency determines whether to grant requests for waivers under the statute on a case-by-case basis, at this time FDA expects that PEPFAR participants will generally be eligible for a ***barrier-to-innovation waiver*** under section 736(d)(1)(B) of the FD&C Act, which provides a waiver of an application fee when the assessment of the fee would present a significant barrier to innovation because of the limited resources available to such person or other circumstances. The agency considers the following two questions in deciding whether to grant a barrier-to-innovation waiver:

1. Is the product or other products or technologies under development by the applicant innovative?
2. Would the fee(s) be a ***significant barrier*** to the applicant's ability to develop, manufacture, or market innovative products or to pursue innovative technology?

As to the first question, at this time FDA generally intends to consider ARV drug products for the treatment or prevention of HIV on the *Antiretroviral Drug Products Needed for Use Under*

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[15] Normally, FDA encourages the submission of requests for waivers 3 to 4 months in advance of the submission of an application. To further reduce the burden on applicants interested in making products available under PEPFAR, FDA will expedite the processing of waiver requests and will aim to process such requests within 45 calendar days.

[16] Sections 736(a)(1)(B) and 736(i) of the FD&C Act (21 U.S.C. 379h(a)(1)(B) and 379h(i)).

[17] See footnote 10.

[18] See footnote 10.

[19] See footnote 10.

PEPFAR list[20] to be an innovative product because simplified regimens that will facilitate distribution and patient compliance, particularly in treatment-naïve patients, are needed in developing countries. Accordingly, the Agency would expect to answer the first question in the affirmative. At some point, as alternative options for treatment or prevention become available, FDA may reevaluate whether the listed ARV drug products remain innovative and may find that an application fee waiver is no longer appropriate for a drug to be procured under the PEPFAR program. For example, a user fee waiver may not be appropriate if, after consultation with the agencies that administer the PEPFAR program,[21] FDA determines that there are already sufficient alternatives available to fulfill the needs of the PEPFAR program.

As to the second question, a fee may be a significant barrier because of limited resources available or other circumstances. FDA generally intends to consider the development of drugs for PEPFAR to be classified as "other circumstances" that would justify a waiver of PDUFA user fees under the barrier-to-innovation waiver provision where:

- The applicant is submitting an application for an ARV drug product for the treatment or prevention of HIV on the *Antiretroviral Drug Products Needed for Use Under PEPFAR* list;[22]
- The applicant is submitting an application that seeks only a tentative approval[23] in the United States, and at the date of submission the application is not expected to become eligible for a final approval as of the user fee goal date;[24]
- The applicant certifies by letter[25] to The U.S. Agency for International Development (USAID) that upon receipt of tentative approval, the applicant will make the product available at competitive prices suitable for procurement under PEPFAR in one or more of the designated PEPFAR countries, with a copy of the letter included in the waiver request; ***and***

- Certifications are supported with evidence that the product will be offered for procurement by PEPFAR, ***and*** either: (1) evidence that the product for which the application is being submitted has been approved for use by the government of one or more PEPFAR countries, ***or*** (2) if such approval has not been obtained, the ARV drug product is listed on an HIV

[20] See footnote 6.

[21] The PEPFAR program is led by the Office of the U.S. Global AIDS Coordinator and Health Diplomacy at the U.S. Department of State with support and collaboration from other United States Government agencies, including principally the Office of HIV/AIDS within the Global Health Bureau at U.S. Agency for International Development.

[22] The separate list on the FDA's PEPFAR Database is not meant to be comprehensive and is expected to evolve as HIV clinical research continues and program needs change. Applicants who have access to data supporting the efficacy and safety of drugs or regimens not included in the list of needed ARV drug products are encouraged to contact the Division of Antivirals (DAV) within CDER's Office of New Drugs to discuss the available support for ARV drug products not on the list. The DAV PEPFAR Project Manager may be contacted about these questions at 301-796-1500.

[23] In the PEPFAR context, applicants who are seeking tentative approval have almost always submitted a Paragraph III [21 CFR 314.94(a)(12)(i)(A)(3)] certification to patents listed in the FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (also known as the Orange Book) at the time of submission of the application.

[24] See, *e.g.*, 21 CFR 314.107(b) and (d).

[25] Applicants should contact USAID at SCH.HIV.Pharma@usaid.gov with the following subject line: "Request for barrier-to-innovation waiver under PDUFA NDA# (product name)".

guideline for one or more of the PEPFAR countries and the applicant provides a plan and schedule for the submission of an application for approval in one or more of the countries.

B. Annual Prescription Drug Program Fees

PDUFA requires the collection of annual prescription drug program fees for certain FDA-approved prescription drug products. Annual prescription drug program fees are not assessed for drug products that are:

1. Listed on the "Discontinued Drug Product List" in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly known as the "Orange Book"),[26] or
2. Tentatively approved.

Because a drug product that is either listed as discontinued in the Orange Book or is tentatively approved will not be assessed annual prescription drug program fees, a request for a waiver for program fees is not necessary.[27]

If a drug product is listed in the Orange Book as an approved prescription drug product and is not listed as discontinued, an annual prescription drug program fee would be assessed unless the product qualifies for a waiver, exception, or exemption. Waiver requests are evaluated on a case-by-case basis. FDA does not anticipate that program fees would generally constitute a barrier to innovation under the "other circumstances" criterion because their Orange Book listing indicates that the drug product is marketed in the United States, making other marketing opportunities available.

V. SUBMITTING REQUESTS FOR WAIVERS, REDUCTIONS, AND REFUNDS

Further guidance for applicants regarding the submission of requests for waivers, refunds, and reductions of fees assessed under sections 735 and 736 of the FD&C Act can be found in FDA's guidance for industry *Prescription Drug User Fee Act Waivers, Reductions, and Refunds for Drug and Biological Products Guidance for Industry*.[28] Among other things, the guidance discusses where to submit requests and what information to include.

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[26] The Orange Book is available at https://www.accessdata.fda.gov/scripts/cder/ob/. Prescription drug program fees are assessed under section 736(a) of the FD&C Act for certain "prescription drug products." Section 735(3) of the FD&C Act defines a "prescription drug product" to exclude, among other things, drug products in the discontinued section of the Orange Book.

[27] If a tentatively approved product receives final approval, it would be added to the "Prescription Drug Product List" of the Orange Book and, therefore, would be subject to the annual prescription drug program fee at the beginning of the fiscal year following final approval.

[28] See footnote 10.

VI. FDA RESPONSES TO REQUESTS FOR WAIVERS, REDUCTIONS, AND REFUNDS

FDA will review waiver, reduction, and refund requests, consulting with relevant Agency officials as appropriate. If needed to support an applicant's assertions that the applicant qualifies, FDA may request additional information and documentation from the applicant during its review of a waiver, reduction, or refund request. Failure to provide the requested information or documentation may result in a denial of a waiver, reduction, or refund request. The Agency will respond to requests for waivers, reductions, and refunds in a timely fashion based on available resources and collection time for additional information.

VII. DISCLOSURE OF PUBLIC INFORMATION

FDA may disclose information publicly about its actions granting or denying waivers, refunds, and reductions. Any such disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

Fixed-Combinations and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment or Prevention of HIV-1 Under PEPFAR

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Division of Antivirals at 301-796-1500.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

Procedural
August 2023

Revision 1

Fixed-Combinations and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment or Prevention of HIV-1 Under PEPFAR

Guidance for Industry

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Fixed-Combinations and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment or Prevention of HIV-1 Under PEPFAR
Guidance for Industry[1]

I. INTRODUCTION

This guidance provides recommendations for applications for single-entity (SE) antiretroviral (ARV) and fixed-combination (FC) ARV drug products for the treatment or prevention of human immunodeficiency virus-1 (HIV-1 or HIV) infection that are intended for distribution outside of the United States under the President's Emergency Plan for AIDS Relief (PEPFAR).[2] Specifically, this guidance addresses versions of previously approved SE and FC ARV drug products and FC ARV drug products for which the individual drug product components of the combination are already FDA-approved (i.e., for which substantial evidence of safety and efficacy of the specific individual drug product components or combination already exists).

This guidance discusses regulatory procedures relevant to such applications and makes recommendations on how to identify and address common issues.

This guidance revises the guidance for industry *Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV* issued in October 2006. When finalized, this guidance will replace the October 2006 guidance. Significant changes from the 2006 final guidance include, but are not limited to, the following:

- Addition of information about ARV drug products for prevention of HIV infection.

[1] This guidance has been prepared by the Division of Antivirals (DAV) in cooperation with the Office of Pharmaceutical Quality, Office of Clinical Pharmacology, and Office of Generic Drugs (OGD) in the Center for Drug Evaluation and Research (CDER).

[2] For the purposes of this guidance, a *fixed-combination antiretroviral drug product* is one in which two or more antiretroviral drugs are combined in a single dosage form and the contribution of the individual drugs has been demonstrated to contribute to the effect(s) of the fixed-combination consistent with the requirements of 21 CFR 300.50. For the purposes of this guidance, the term *drug product* will be used to refer to human prescription drugs under section 505 of the Federal Food, Drug, and Cosmetic (FD&C) Act.

- Deletion of references to co-packaged products and focus on SE ARV and FC ARV drug products currently most needed under PEPFAR.

- Inclusion of a subsection that describes the processes for making changes to applications after tentative approval.

- Addition of updated descriptions of regulatory requirements and procedures in the main text of the guidance and deletion of Attachment A, which provided hypothetical scenarios.

- Reference to other FDA guidances for industry for common regulatory topics instead of repeating information.

- Addition of updated information in the section on chemistry, manufacturing, and controls to be consistent with other guidances for industry published after 2006.

- Deletion of Attachment B, which listed examples of two and three drug FCs supported by clinical data. Instead, the guidance refers applicants to a separate list[3] for ARV drug products supported by clinical data and needed for PEPFAR procurement. This list is published in conjunction with the FDA's PEPFAR database.

- Deletion of Attachment C, which listed combinations that were not acceptable for FC or co-packaging.

This guidance is not an exhaustive document on FDA's current thinking regarding the development and review of ARV drug products eligible for procurement under PEPFAR. Applicants can refer to other guidances cited in this document or seek advice from FDA when questions arise regarding specific drug development programs.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[3] The separate list of ARV drug products, Antiretroviral Drug Products Needed for Use Under PEPFAR, can be found under question 6, What PEPFAR products can companies submit for FDA review?, at FDA's PEPFAR database on the Frequently Asked Questions web page available at https://www.fda.gov/international-programs/presidents-emergency-plan-aids-relief-pepfar/pepfar-database-frequently-asked-questions. This list is revised periodically to address current public health needs.

II. BACKGROUND ON HIV TREATMENT, HIV PREVENTION, AND PEPFAR

A. HIV Treatment

ARV drug products are essential for the treatment of HIV/AIDS (acquired immunodeficiency syndrome). The goals of HIV treatment are to maximally and durably suppress HIV to allow recovery of the immune system, reduce adverse clinical outcomes associated with HIV, reduce the emergence of resistance, and reduce HIV transmission to others. In the United States and developing countries, simplified HIV regimens in the form of FC ARV drug products improve patient adherence and facilitate distribution. For patients initiating ARV drug product therapy, preferred regimens are listed in the U.S. Department of Health and Human Services (DHHS) treatment guidelines,[4] the International AIDS Society guidelines,[5] and the World Health Organization (WHO) guidelines.[6]

B. HIV Prevention

ARV drug products that are safe and effective for HIV prevention are important for people who are negative for HIV but are at substantial risk of HIV acquisition. The goal of using ARV drug products to prevent HIV acquisition is to reduce the morbidity, mortality, and cost to individuals and society associated with HIV infection. Recommendations for initiating HIV prevention, including recommended ARV drug products for prevention, are presented in the U.S. Public Health Service guidelines[7] and the WHO guidelines.[8]

C. PEPFAR

PEPFAR is a U.S. Government initiative to help save the lives of those with HIV/AIDS around the world, outside the United States. It was originally announced in President George W. Bush's State of the Union address in 2003 and was reauthorized in 2008, 2013, and 2018. This historic

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[4] See the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council, available at https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv.

[5] See Saag MS, Benson CA, Gandhi RT, et al., 2018, Antiretroviral drugs for Treatment and Prevention of HIV Infection in Adults: 2018 Recommendations of the International Antiviral Society-USA Panel, JAMA, 320(4):379–396.

[6] See the WHO's Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring: Recommendations for a Public Health Approach. Geneva: World Health Organization; 2021, available at https://www.who.int/publications/i/item/9789240031593.

[7] See the Centers for Disease Control and Prevention's U.S. Public Health Service: Preexposure Prophylaxis for the Prevention of HIV Infection in the United States — 2021 Update, available at https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf.

[8] See the WHO's Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery, and Monitoring: Recommendations for a Public Health Approach, available at https://www.who.int/publications/i/item/9789240031593.

commitment is among the largest by any nation to combat a single disease internationally. As of 2012, ARV drug products are also available for HIV prevention, and as of 2015, WHO recommends the use of these drug products to reduce the risk of HIV acquisition. ARV drug products for treatment and more recently prevention play a major role in PEPFAR, and it is important that resources are spent on products that have been demonstrated to be safe and effective. ARV drug products for treatment or prevention of HIV must conform to regulatory standards of safety, efficacy, and quality[9] to maximize the success of treatment or prevention and to reduce the emergence and spread of resistant virus. Of note, FDA-approved or tentatively approved ARV drug products are eligible for procurement under PEPFAR.

D. ARV Drug Products Needed for PEPFAR

The FDA's PEPFAR database[10] includes a list of ARV drug products that have been tentatively approved or approved and are eligible for procurement under PEPFAR, and a separate list[11] of ARV drug products that are currently most needed for HIV treatment or prevention in the developing world and countries supported by PEPFAR. An applicant should refer to the list of needed ARV drug products when considering submitting an ARV drug product application for HIV treatment and when evaluating whether to submit a user fee waiver request.[12] The list of needed ARV drug products for treatment is expected to evolve as HIV research continues and program needs change. An applicant that has access to data supporting the efficacy and safety of ARV drug products for treatment that are not included in the list of needed ARV drug products is encouraged to discuss with the Division of Antivirals (DAV)[13] its rationale for why the ARV drug product is important for PEPFAR and may qualify for a new drug application (NDA) user fee waiver. Similarly, an applicant is encouraged to consult DAV when considering submitting

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[9] Section 505 of the FD&C Act.

[10] The FDA's PEPFAR database is available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=pepfar.page.

[11] The separate list of ARV drug products, Antiretroviral Drug Products Needed for Use Under PEPFAR, can be found under question 6, What PEPFAR products can companies submit for FDA review?, at FDA's PEPFAR Database on the Frequently Asked Questions web page available at https://www.fda.gov/international-programs/presidents-emergency-plan-aids-relief-pepfar/pepfar-database-frequently-asked-questions. This list is revised periodically to address current public health needs.

[12] Under certain circumstances, FDA is authorized to waive user fees assessed under the Prescription Drug User Fee Act (PDUFA) for new drug applications (NDAs) and biological license applications (BLAs). In 2006, FDA issued a guidance for industry regarding certain user-fee waiver provisions of special relevance to PEPFAR products, *User Fee Waivers for FDC and Co-Packaged HIV Drugs for PEPFAR* (February 2007). In 2023, FDA published a new draft guidance for industry *PDUFA Waivers, Reductions, and Refunds for Fixed-Combinations and Single-Entity Versions of Previously Approved Antiretrovirals under PEPFAR* (August 2023). When final, the new user-fee guidance will replace FDA's 2006 guidance and represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[13] For more information on contacting DAV, see the Office of Infectious Diseases web page at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-new-drugs.

an ARV drug product application for HIV prevention and when evaluating whether to submit a user fee waiver request.[12]

III. GENERAL CONSIDERATIONS

This guidance focuses on tentative approval of ARV drug products for HIV-1 treatment or prevention, particularly of those submitted in an abbreviated new drug application (ANDA) under section 505(j) of the Federal Food, Drug, and Cosmetic (FD&C) Act or in a section 505(b)(2) of the FD&C Act.[10,12] Because ARV drug products submitted as 505(b)(1) NDAs are usually eligible for approval rather than tentative approval, these applications are generally not discussed in this guidance.

A tentative approval may be granted for ARV drug products that cannot be marketed in the United States because of existing patents and/or exclusivity.[14] Drug products that receive tentative approval meet the same substantive requirements (e.g., safety, efficacy, and quality standards) as drug products that receive final marketing approval.

FDA will not grant a tentative approval action in lieu of final marketing approval when there are no patent and exclusivity barriers to final approval.[15]

A. Submitting ARV Drug Product Applications Eligible for Procurement Under PEPFAR Through the Appropriate Abbreviated Approval Pathway

An applicant should determine whether its application should be submitted as an ANDA or a 505(b)(2) NDA as discussed briefly in this section and as addressed in detail in the guidance for industry *Determining Whether to Submit an ANDA or a 505(b)(2) Application* (May 2019).[16] That guidance highlights statutory and regulatory criteria for submitting applications under the abbreviated approval pathways described in section 505(j) and 505(b)(2) of the FD&C Act, identifies considerations to help potential applicants determine which pathway is most appropriate, and provides recommendations to potential applicants on requesting assistance from FDA in making this determination.

1. ANDAs

Like all ANDAs, an ANDA for an ARV drug product is submitted and approved under section 505(j) of the FD&C Act (commonly referred to as a *generic* drug application). An ANDA relies on FDA's finding that the previously approved drug product, i.e., the reference listed drug

[14] See 21 CFR 314.3(b) and 21 CFR 314.105. If one or more active moiety in an ARV drug product is protected by new chemical entity exclusivity, acceptance of an ANDA or 505(b)(2) NDA containing that active moiety for review could be delayed. See sections 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the FD&C Act; 21 CFR 314.108(b).

[15] See 21 CFR 314.105.

[16] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

(RLD), is safe and effective. An RLD is defined as the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA[17] and is listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book).[18] An ANDA generally must contain information to show that the proposed drug product (1) is the same as the RLD with respect to the active ingredient(s), conditions of use, dosage form, strength, route of administration, and labeling (with certain permissible differences), and (2) is bioequivalent to the RLD.[19] FDA's review process ensures that generic drug products perform the same way in the human body and have the same intended use as the RLD. All generic drug products approved by FDA have the same high quality, strength, purity, and stability as brand-name drug products. In addition, FDA inspects facilities to make certain the generic manufacturing, packaging, and testing sites pass the same quality standards as those of brand-name drug products.

ANDAs are reviewed in FDA's Office of Generic Drugs (OGD). If an applicant has questions about its proposed ARV drug product, the applicant can submit a controlled correspondence to FDA's OGD.[20]

2. 505(b)(2) NDAs

A 505(b)(2) NDA for an SE or FC ARV drug product must contain full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use[21] (e.g., the Agency's finding of safety and/or effectiveness for a listed drug, published literature). A 505(b)(2) NDA applicant may rely on FDA's finding of safety and/or effectiveness for a listed drug only to the extent that the proposed product in the 505(b)(2) application shares characteristics (e.g., active ingredient, dosage form, route of administration, strength, indication or other conditions of use) in common with the relied-upon listed drug(s). The applicant is expected to establish a *bridge* (e.g., by using comparative bioavailability data) between the proposed drug product and each listed drug that the applicant seeks to rely upon to demonstrate that reliance on the listed drug is scientifically justified. To the extent that the listed drug and the drug proposed in the 505(b)(2) NDA differ (e.g., a product with a different dosage

[17] 21 CFR 314.3(b). See also the guidance for industry *Referencing Approved Drug Products in ANDA Submissions* (October 2020).

[18] Available at https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book.

[19] See section 505(j)(2) and 505(j)(4) of the FD&C Act; 21 CFR 314.94, 21 CFR 314.127, and 21 CFR 320.21(b). See also the guidance for industry *Determining Whether to Submit an ANDA or a 505(b)(2) Application*.

[20] See the draft guidance for industry *Controlled Correspondence Related to Generic Drug Development* (December 2022) for information on the types of inquiries appropriate for controlled correspondence and on how to submit controlled correspondence to OGD. When final, this guidance will represent the FDA's current thinking on this topic.

[21] See 21 CFR 314.3(b).

form or a product that is intentionally more bioavailable than the listed drug), the 505(b)(2) NDA must include sufficient data to support those differences.[22] For drug products included in the list of needed drug products[23] on the FDA's PEPFAR database,[24] submission of a 505(b)(2) NDA that relies on FDA's findings of safety and effectiveness for approved SE or FC ARV drug products may be appropriate if the applicant does not have a right of reference to data establishing the safety and efficacy of the SE or FC ARV drug product.

505(b)(2) NDAs for ARV drug products are reviewed in DAV, which is part of FDA's Office of New Drugs.[25] If an applicant has questions about submission of an application through the 505(b)(2) pathway, the applicant should contact DAV for assistance.

B. Changes Made After Tentative Approval of an Application

An applicant can submit amendments to a tentatively approved application that propose changes to the application, request final approval, or both propose changes and request final approval. This section describes appropriate data to submit in an amendment to the application when changes (including significant changes, e.g., addition of new manufacturing sites or important new safety information) are made after tentative approval, but before final marketing approval.

1. Amendments: Before Final Marketing Approval Request

While a drug product that is granted tentative approval is not an approved drug and may not be marketed in the United States until final approval,[26] a tentatively approved ANDA or NDA for an ARV drug product may be eligible for procurement and distribution outside the United States under PEPFAR. Accordingly, an applicant may determine that changes (e.g., manufacturing, labeling) to its tentatively approved application eligible for procurement under PEPFAR may be appropriate or necessary as a scientific matter. In general, these changes are processed as amendments to tentatively approved applications. Although the administrative and regulatory procedures for handling changes to these tentatively approved applications may differ from the procedures for changes to ANDAs and NDAs after final approval, the scientific principles that guide the evaluation of these changes generally remain the same. In other words, FDA considers

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[22] See 21 CFR 314.93.

[23] The separate list of ARV drug products, Antiretroviral Drug Products Needed for Use Under PEPFAR, can be found under question 6, What PEPFAR products can companies submit for FDA review?, at FDA's PEPFAR Database on the Frequently Asked Questions web page available at https://www.fda.gov/international-programs/presidents-emergency-plan-aids-relief-pepfar/pepfar-database-frequently-asked-questions. This list is revised periodically to address current public health needs.

[24] The FDA's PEPFAR database is available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=pepfar.page.

[25] For guidance on the content and format of or the submission process for an NDA, see the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents and search using the term *NDA* and select either the Administrative/Procedural or Clinical/Medical topic in the filter.

[26] See 21 CFR 314.3(b) and 21 CFR 314.105. See also 505(j)(5)(B)(iv)(II)(dd) of the FD&C Act.

the assessment of risk and type of change for such ANDA and NDA amendments similarly to supplements to approved applications. Therefore, when proposing changes to these tentatively approved applications, FDA recommends that an applicant indicate in a cover letter its view of whether the changes are considered a major, moderate, or minor potential to have an adverse effect on the quality of the drug product. FDA expects to review PEPFAR change amendments for tentatively approved NDAs as shown in the timelines in Table 1. FDA classifies amendments to tentatively approved ANDAs as unsolicited, and in general, FDA will set a review goal consistent with the recommendations outlined in section IV of the guidance for industry *ANDA Submissions—Amendments to Abbreviated New Drug Applications Under GDUFA* (July 2018) (see Table 2).

Table 1. Types of PEPFAR Change Amendments and Review Timelines for Tentatively Approved NDAs [*]

	Type of Change	**FDA Review Timelines**	**Change Amendment Implementation**	
	Amendment – Major Change	4 months	Requires submission of change and decisional action by FDA before implementation	
	Amendment – Moderate Change	6 months	Requires submission of change, but the change can be implemented 30 days after FDA officially receives the submission	
	Amendment – Minor Change[a]	6 months		

PEPFAR = President's Emergency Plan for AIDS Relief; NDA = new drug application.

[a] Includes changes that, for approved applications, would be submitted in annual reports per 21 CFR 314.70(d).

Table 2. Review Performance Goals for ANDA* Amendments[27]

Submission Type	Goal
Standard Major ANDA Amendments	90% within 8 months of submission date if preapproval inspection not required
	90% within 10 months of submission date if preapproval inspection required
Priority Major ANDA Amendments	90% within 6 months of submission date if preapproval inspection not required
	90% within 8 months of submission date if preapproval inspection required and applicant meets requirements described in the GDUFA III Commitment Letter[b]
	90% within 10 months of submission date if preapproval inspection required and applicant meets limitations described in the GDUFA III Commitment Letter[b]
Standard Minor and Priority Minor[a] ANDA Amendments[a]	90% within 3 months of submission date

* ANDA = abbreviated new drug application.
[a] Includes changes to ANDAs for ARV drug products eligible for procurement under PEPFAR that are recommended as moderate type change amendments.
[b] See the Generic Drugs User Fee Act (GDUFA) Reauthorization Performance Goals and Program Enhancement Fiscal Years 2023–2027 https://www.fda.gov/industry/generic-drug-user-fee-amendments/gdufa-iii-reauthorization.

To make a risk assessment of a proposed change amendment (e.g., determine whether a change has a major, moderate, or a minor potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product) and to determine what information or data should be submitted to support the proposed change amendment, FDA recommends that applicants refer to the following guidances for industry:

- *Changes to an Approved NDA or ANDA* (April 2004)
- *Changes to an Approved NDA or ANDA: Questions and Answers* (January 2001)
- *Immediate-Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (November 1995)
- *PAC-ATLS: Postapproval Changes — Analytical Testing Laboratory Sites* (April 1998)

After review of a change amendment for an NDA or an ANDA, FDA generally sends the applicant one of two types of notifications noted below. In either case, the original application remains tentatively approved.

[27] See the guidance for industry *ANDA Submissions—Amendments to Abbreviated New Drug Applications Under GDUFA*. Note that review goal percentages refer to all ANDAs, not just those for drug products eligible for procurement under PEPFAR.

The possible types of notifications are:

- A PEPFAR Permitted letter, if the change is found acceptable
- A PEPFAR Denied letter, if the change is found unacceptable

Implementation of a change submitted as a minor or moderate change amendment before issuance of a PEPFAR Permitted letter is at the risk of the applicant. If FDA determines that a change submitted as a minor or moderate change amendment is a major change amendment, FDA will notify the applicant not to implement the change until a PEPFAR Permitted letter is issued for the major change to the tentatively approved application.

For approved applications, applicants must submit postmarketing reports (e.g., annual reports);[28] although this requirement does not apply to tentatively approved applications, FDA recommends that applicants submit information related to the distribution outside the United States under PEPFAR of a product described in a tentatively approved ANDA or NDA as an amendment designating the information as an *annual update*. An annual update provides the FDA reviewer with background information that may be useful in reviewing other changes to the application. Information that is useful in an annual update includes distribution data, stability updates (e.g., on original registration batches, commitment batches, and annual batches), a copy of the current labeling (including a representative container label), and a cumulative list of all change amendments submitted through amendments after tentative approval.

Recommended format for the cumulative list of change amendments with their current statuses (e.g., pending, permitted, denied) can be found in the guidance for industry *Format and Content for the CMC Section of an Annual Report* (September 1994).

See section VI.E., CMC Changes After a Tentative Approval, for examples of changes to tentatively approved applications.

2. Amendments: Requesting Final Approval

When the period of patent and exclusivity protection is ending or has ended, the applicant may submit an amendment to a tentatively approved application requesting final approval. The amendment should include final labels and labeling that comply with all applicable U.S. regulations (e.g., uniqueness of drug product appearance in accordance with 21 CFR part 206; child-resistant packaging in accordance with 16 CFR part 1700).[29] The amendment should also

[28] 21 CFR 314.81.

[29] In addition, for ANDAs, if the prescribing information includes reference to the antiretroviral pregnancy registry contact number, then the prescribing information for the generic product must also include the same antiretroviral pregnancy registry reference. See, for example, section 505(j)(4)(G) of the FD&C Act; 21 CFR 314.127(a)(7). Including the pregnancy registry contact in the prescribing information means that a sponsor has joined the antiretroviral pregnancy registry. For 505(b)(2) NDAs, the need to include a reference to the antiretroviral pregnancy registry will be decided on a case-by-case basis depending on what is known about the risk and benefit of the use of the ARV drug(s) in pregnant females.

either describe all significant changes to the drug product and manufacturing processes made since tentative approval or certify that no significant changes have been made. A guidance for industry is available that provides recommendations for seeking final approval of tentatively approved ANDAs.[30]

C. Regulatory Procedures that May Expedite the Availability of ARV Drug Products Submitted in NDAs Eligible for Procurement Under PEPFAR[31]

To facilitate rapid development and review of NDAs for ARV drug products eligible for procurement under PEPFAR, DAV interacts with applicants early in the development stages to discuss the appropriateness of the SE or FC ARV drug product, the dosing strength, and the appropriate nonclinical and chemistry, manufacturing, and controls (CMC) data. In addition, some of the regulatory procedures for expediting review of NDAs may apply to ARV NDAs, such as fast track designation and priority review designation. Applicants should refer to FDA's guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics* (May 2014) for more information on these expedited programs.

IV. CLINICAL CONSIDERATIONS

FDA believes adequate clinical studies confirming safety and efficacy have already been conducted for ARV drug products needed for PEPFAR and listed on the FDA's PEPFAR database;[32] therefore, in general, new clinical studies are not needed to support applications for these drug products when the doses of the approved ARV drug products are unchanged.

Proposed SE and FC ARV drug products should be relatively well tolerated and easy to administer, provide potency and a barrier to the emergence of drug resistance, and have available clinical safety and efficacy data that support use of the drug product. Proposed FC ARV drug products for HIV treatment intended to be eligible for procurement under PEPFAR should contain two or more components of an established fully suppressive ARV regimen that are recommended as a preferred or alternative regimen (or regimen component) for treatment-naïve patients with HIV in treatment guidelines.[33] Proposed ARV drug products for HIV prevention

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[30] See the guidance for industry *ANDA Submissions — Amendments and Requests for Final Approval to Tentatively Approved ANDAs* (September 2020).

[31] These approaches do not apply to potential ANDA submissions.

[32] The FDA's PEPFAR database is available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=pepfar.page. In general, SE and FC ARV drug products listed on the FDA's PEPFAR database were evaluated in at least one study conducted under good clinical practices that evaluated changes in HIV-RNA and CD_4 cell counts for at least 48 weeks and showed statistical noninferiority, or superiority, of the ARV drug product or regimen to an accepted control at the time the study was conducted.

[33] See the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council, available at https://clinicalinfo.hiv.gov/en/guidelines; and the WHO's Consolidated

eligible for procurement under PEPFAR should represent a prevention option as recommended in treatment guidelines.[34]

Proposed drug products that change the dose of an approved ARV drug product could, as a scientific matter, need additional clinical studies to support the change as compared to the relied upon listed drug. Potential applicants should request advice from DAV in this situation.

A. Pediatric Considerations

FDA encourages applicants to review consensus pediatric guidelines and focus development efforts on the types of drug products most needed. Drug products distributed under PEPFAR are used in some countries where liquid drug products may pose significant challenges. Families with pediatric patients may travel long distances to and from a clinic making it difficult to transport bulky, heavy bottles of liquid medication. Many families may not have a place to store liquid formulations, particularly if refrigeration is required. Thus, alternative suitable pediatric formulations are preferred, such as tablets for oral suspension or oral pellets that can be mixed with food. To allow maximum flexibility in dosing, another desirable dosage form is a scored tablet that can be crushed and dispersed in liquid or food vehicle if the patient cannot swallow a solid dosage form. Scored tablets can include a single score that bisects the tablet or multiple score lines, allowing the tablets to be divided into halves, thirds, and/or quarters. Applicants should refer to the guidance for industry *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013).

Dosing instructions for ARV drug products intended for pediatric patients typically include dosing recommendations by weight band. For FC ARV drug products submitted as a 505(b)(2) NDA, it may not be possible to match the U.S. approved dose for each component across all weight bands. If the application proposes doses for weight bands that differ from such previously approved doses, the safety and efficacy of such proposed doses at the limits of weight bands should be supported by clinical study data or scientific literature. Potential applicants should request advice from DAV in this situation.

V. CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

This section describes the types of clinical pharmacology and biopharmaceutical data that are particularly relevant for ARV drug products eligible for procurement under PEPFAR. For additional details, applicants should refer to other guidances for industry cited in this section.

Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring: Recommendations for a Public Health Approach, available at https://www.who.int/publications/i/item/9789240031593.

[34] See the Centers for Disease Control and Prevention's U.S. Public Health Service: Preexposure Prophylaxis for the Prevention of HIV Infection in the United States — 2021 Update, available at https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf.

A. Bioequivalence or Bioavailability Studies[35]

Bioequivalence or bioavailability studies are needed to bridge FDA's finding of safety and efficacy of U.S. approved drug products to the PEPFAR drug product.

For a drug product submitted in an ANDA (under section 505(j) of the FD&C Act), applicants must demonstrate that their drug product is bioequivalent to the RLD. In addition, applicants must use the reference standard (RS), which is selected by FDA, in conducting any in vivo bioequivalence testing required to support approval.[36] The RLD and RS are identified in the Orange Book. Applicants should refer to the guidance for industry *Referencing Approved Drug Products in ANDA Submissions* and the draft guidance for industry *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (August 2021).[37] For additional information on recommended bioequivalence studies to support submission of a particular drug product, ANDA applicants can also access the OGD web page, Product-Specific Guidances for Generic Drug Development, available at: https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.

For an SE or FC ARV drug product submitted as an NDA (under section 505(b)(2) of the FD&C Act), a relative bioavailability study or studies may be necessary as a scientific matter. Applicants should refer to the guidance for industry *Bioavailability Studies Submitted in NDAs or INDs — General Considerations* (April 2022).

All bioanalytical methods should be well characterized, fully validated, and documented. For additional details, applicants should refer to the guidance for industry *Bioanalytical Method Validation* (May 2018).

B. Assessment of the Effect of Food

It is important to evaluate the effect of food on the absorption of the active ingredients of the ARV drug products eligible for procurement under PEPFAR.

For ARV drug products submitted under the ANDA pathway (section 505(j) of the FD&C Act), applicants should refer to the Product-Specific Guidances for Generic Drug Development resources[38] and the draft guidance for industry *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA.*[39]

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[35] See generally 21 CFR part 320, Bioavailability and Bioequivalence Requirements.

[36] See 21 CFR 314.3(b).

[37] When final, this guidance will represent the FDA's current thinking on this topic.

[38] Available at https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development.

[39] When final, this guidance will represent the FDA's current thinking on this topic.

For ARV drug products submitted under the 505(b)(2) NDA pathway), applicants should refer to the draft guidance for industry *Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations* (February 2019)[40] and guidance for industry *Bioavailability Studies Submitted in NDAs or INDs — General Considerations*.

C. Waivers of Bioequivalence or Bioavailability Studies

There are circumstances in which an in vivo bioequivalence or bioavailability study can be waived.[41] For FDA's current thinking on such waivers, applicants should refer to the following guidances for industry:

Draft guidances[42]

- *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*
- *Bioavailability Studies Submitted in NDAs or INDs — General Considerations*

Final guidances

- *M9 Biopharmaceutics Classification System-Based Biowaivers* (May 2021)
- *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (August 1997)
- *Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances* (August 2018)

D. Pediatric Formulations

Results from bioavailability studies should be included in NDA submissions supporting pediatric formulations. Bioavailability studies, which are typically conducted in adult patients, should evaluate the drug product administered under conditions described in the proposed product labeling (e.g., chewed, crushed, dissolved, dispersed, or sprinkled in an appropriate liquid or food vehicle[43]). In some cases, additional administration conditions may need to be evaluated.

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[40] When final, this guidance will represent the FDA's current thinking on this topic.

[41] See, for example, 21 CFR 320.21 and 21 CFR 320.22.

[42] When final, these guidances will represent the FDA's current thinking on these topics.

[43] See the draft guidance for industry *Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments* (July 2018). When final, this guidance will represent the FDA's current thinking on this topic.

VI. CHEMISTRY, MANUFACTURING, AND CONTROLS

This section highlights certain specific topics with respect to CMC submissions in ANDAs and NDAs for ARV drug products eligible for procurement under PEPFAR. Applicants should refer to other guidances for industry cited in this section for additional details on FDA's current thinking regarding submission of CMC information.

A. Drug Master Files

Drug substance manufacturing processes should be well-documented through reference to drug master files (DMFs) of the drug substance manufacturers, if complete data cannot be included in the application. Applicants should ensure that DMFs are submitted to FDA for the processes used in the manufacturing of the drug substance(s) for both the registration batches of the drug product and for the intended commercial drug product.
If reference is made to a DMF, applicants should ensure that the DMF is submitted to FDA and that a Letter of Authorization to refer to this DMF is included in the NDA or ANDA and in the DMF itself.[44]

A single DMF may have multiple manufacturing sites, and each site should be listed in the ANDA or NDA even though the DMF number is the same. Applicants should clarify which of the drug substance manufacturing sites in the DMF will be used to produce drug substance(s) for the drug product. Asking DMF holders, before the ANDA/NDA submission, about any changes planned for the near future may lessen the need for late change amendments to the ANDA or NDA.

When a DMF is changed, the DMF holder should notify applicants to whom Letters of Authorization have been issued. These applicants should submit the appropriate amendment to their application(s) that reference this DMF. For example, notification of a new manufacturing site is generally a major change amendment and can extend the review goal accordingly, particularly if an inspection is needed.[45] When notified of a new manufacturing site by a DMF holder during a review cycle, the applicant should contact the regulatory project manager in either OND or OGD and the regulatory business project manager in the Office of Pharmaceutical Quality immediately.

B. Manufacturing Facilities and Processes

All facilities used in the manufacturing, testing, packaging, and labeling of the drug substance(s) and the drug product are subject to inspection and should be ready and available for inspection before approval to assess compliance with current good manufacturing practice.[46]

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[44] See 21 CFR 314.420 for additional information on referencing DMFs.

[45] See 21 CFR 314.60(b). See also section III.B.1., Amendments: Before Final Marketing Approval Request, and 21 CFR 314.70(b).

[46] See 21 U.S.C. 351(a)(2)(B), 21 CFR parts 210 and 211. See also, guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (September 2016).

The process activities, including actual protocols, sampling plans, and acceptance criteria as well as study outcomes, will be evaluated during a current good manufacturing practice inspection. Process validation should be complete before the release of the drug product intended for distribution. Applicants should refer to the guidance for industry *Process Validation: General Principles and Practices* (January 2011).

C. Drug Substance Issues

Scientific issues related to controls and impurities may arise during FDA review of ARV drug product submissions intended to be eligible for procurement under PEPFAR. Applicants should refer to cited guidances in this section for additional details on FDA's current thinking.

1. Controls

If the drug substance is poorly soluble or is a small percentage of the drug product weight, applicants should consider drug substance particle size control, according to the recommendations described in the guidance for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (December 2000). If the drug substance can exist in different solid-state polymorphic forms, additional controls may be appropriate.

2. Impurities

Batch analyses for at least three lots of drug substance produced by the same process that is to be used for the material used for the exhibit batch of drug product should be included in the DMF, NDA, or ANDA. If impurities exceed the recommended qualification thresholds on drug substance as described by the guidance for industry *Q3A(R2) Impurities in New Drug Substances* (June 2008), additional toxicological justification may be appropriate. If impurities are below the recommended Q3A(R2) qualification thresholds, there is no need for toxicological qualification unless the structure suggests unusual toxicology (e.g., there is a genotoxic substructure). If the residual solvents or elemental impurities in the drug substance exceed the recommendations in the guidances for industry *Q3C Impurities: Residual Solvents* (December 1997) and *Q3D(R2) Elemental Impurities* (September 2022), additional toxicological justification may be appropriate.

D. Drug Product Issues

This section describes scientific issues regarding the drug product that may arise during FDA review of ARV drug product submissions intended to be eligible for procurement under PEPFAR. For more information on pharmaceutical development, applicants should refer to the guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009).

1. Controls and Impurities

Drug products should be formulated using excipients that meet internationally recognized compendial standards. Information should be provided to support the safety of each excipient, particularly those derived from animals. Applicants should justify the use of novel excipients, using animal toxicity data if necessary.[47]

Identification of an impurity is not needed if the guidance for industry *Q3B(R2) Impurities in New Drug Products* (August 2006) identification threshold recommendation is not exceeded. For an FC ARV drug product, in general, the amount of an unknown peak should be calculated as a percentage of the smallest active peak.

2. Water Content

Given the likely exposure to high humidity in countries supported by PEPFAR, applicants should provide a water content specification, or a justification for not providing such a specification, for solid oral dosage forms.

3. Markings and Labeling

There are now a significant number of tentatively approved or approved drug products eligible for procurement under PEPFAR and prequalified by WHO, and FDA expects drug products to be marked and labeled so that they can be identified by medical professionals. Each dosage unit should be marked so that it can be readily identified, and different drugs from the same manufacturer should have distinct labeling.

4. Scored Tablets

If tablets are scored, testing should be performed to show that split tablets are suitable for their intended purpose. More information can be found in the guidance for industry *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013) (Tablet Scoring guidance). An applicant submitting a change amendment[48] to a tentatively approved application should also refer to the Tablet Scoring guidance.

Some RLD tablets are scored but would not be considered functionally scored tablets as described in the Tablet Scoring guidance. In these situations, versions of these ARV tablets eligible for procurement under PEPFAR should also be manufactured with a score. However, to support labeling claims for splitting these ARV tablets, the tablets should contain appropriate information for functional scoring. The Tablet Scoring guidance recommends a 90-day stability study for split tablets stored in pharmacy dispensing containers (no seal/no desiccant) for a period of 90 days at 25ºC/60 percent relative humidity (RH). However, for ARV drugs products

[47] See the guidance for industry *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients* (May 2005).

[48] See 21 CFR 314.60(b). See also section III.B.1., Amendments: Before Final Marketing Approval Request, and 21 CFR 314.70(b).

intended for use under PEPFAR, such testing should instead occur at 30°C/75 percent RH because of the conditions that may be encountered in climatic zones III and IV.[49]

5. Tablets Intended for Dispersion in Water or Other Liquids

If the labeling indicates that the tablet may be dispersed in water or other liquids, appropriate testing should demonstrate that dispersion is feasible for this specific drug product. The following information should be included in the application:

- Information on how quickly the tablet breaks up in water or other liquids (e.g., typically, 2 teaspoons (10 milliliters) per tablet)

- Appropriate controls on process parameters, in-process tests, or specifications to ensure that the tablet will break up in water in a reasonably quick fashion

- Short-term stability data to show that the active ingredient is chemically stable when dispersed in water or the other liquids (e.g., to support a statement to drink the mixture within a certain time frame)

6. Packaging

In most cases, FDA recommends child-resistant packaging although such a decision should be made after consultation with procuring organizations (e.g., U.S. Agency for International Development, U.S. Department of State's Office of Global AIDS Coordinator and Health Diplomacy) keeping in mind the local laws of the country where the drug product is to be used.

Some applicants have expressed a preference for demonstrating the stability of their drug products in non-child-resistant packaging, such as in bottles and blisters that applicants believe are acceptable to the regulatory authorities of the PEPFAR-supported recipient countries. FDA believes that issues related to special packaging (e.g., child-resistant, senior-friendly) are best approached in the context of the PEPFAR-supported recipient country's regulations and prescribing practices; accordingly, it may be appropriate to grant a tentative approval with this type of packaging. However, when patents and/or exclusivities expire for the referenced drug products, applications for final marketing approval in the United States must comply with all final approval requirements, including relevant U.S. packaging and labeling regulations.[50]

Applicants should refer to the guidances for industry *Container Closure Systems for Packaging Human Drugs and Biologics* (May 1999) and *Container Closure Systems for Packaging Human Drugs and Biologics — Questions and Answers* (May 2002) for recommendations on the information needed for the container closure systems.[51] FDA anticipates that procurement

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[49] See the International Council for Harmonisation (ICH) guidance for industry *Q1A(R2) Stability Testing of New Drug Substance and Products* (November 2003).

[50] See footnote 30.

[51] See also MAPP 5015.5 Rev. 1 *CMC Reviews of Type III DMFs for Packaging Materials*.

organizations, applicants, and regulatory authorities will cooperate to share information on the equivalence of container closure system protection.

The shelf-life specification should be the same for all packaging configurations. Different packaging configurations may have different expiration dating periods to ensure that the drug product meets the specification throughout its shelf life. It is acceptable to have a tighter internal release specification, but the regulatory specification applies throughout the approved expiration dating period to all packaging configurations.

7. Stability[52]

As provided in 21 CFR 314.50(d)(1)(ii)(*a*), applicants must demonstrate the stability of the drug product. Generally, this includes accelerated and long-term stability data; the application should include stability data obtained from the drug product in the commercial packaging.

8. Stability Storage Conditions

Drug products distributed under PEPFAR are likely to be used in several countries with hot and dry or hot and humid conditions (climatic zones III and IV).[53] Given the conditions that may be encountered during distribution and storage under programs such as PEPFAR, applicants should generate data on the stability of their drug products under the conditions specified by regulatory authorities in the recipient countries and WHO.

At present, long-term studies at 30°C/75 percent RH and 6-month accelerated studies at 40°C/75 percent RH will cover use and registration in all climatic zones. If the data obtained at 30°C/75 percent RH are satisfactory, data obtained at 25°C/60 percent RH are not generally needed.

FDA recommends in-use stability studies for ARV drug products containing amorphous dispersions (e.g., products containing ritonavir) and/or tenofovir prodrugs (e.g., products containing tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF)). These ARV drug products have a sensitivity to moisture, and studies could support bottles that are intended to be dispensed to patients and then opened daily for 90 days or 180 days. By combining results from long-term and in-use stability studies at 30°C/75 percent RH, applicants can predict the amount of a particular degradant by summing the following values:

- The amount of degradant present in freshly manufactured drug product

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[52] For more information, see the guidances for industry *ANDAs: Stability Testing of Drug Substances and Products* (June 2013) and *ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers* (May 2014) and the ICH guidances for industry *Q1A(R2) Stability Testing of New Drug Substance and Products* and *Q1C Stability Testing for New Dosage Forms* (November 1996).

[53] Deitz, R, K Feilner, F Gerst, and W Grimm, 1993, Drug Stability Testing — Classification of Countries According to Climatic Zone, Drugs Made in Ger, 36:99–103.

- The amount of degradant likely to be formed as the sealed bottle sits in storage (rate of degradation (percent degradation per month) times expiration dating period (in months))

- The amount of degradant that is formed during the in-use study

The amount of degradation (or reduction in assay) predicted at the end of expiration can be compared to the acceptance criteria for stability. Depending on the outcome of these studies, it may be appropriate to tighten the release acceptance criteria for major degradants (or assay) to ensure that the acceptance criteria for stability are met. If desiccant is included in the bottle and retained during the in-use study, FDA in general would recommend a labeling statement such as, *"Store and dispense in original bottle, protect from moisture, and keep bottle tightly closed. Do not remove desiccant."* for NDAs for ARV drug products eligible for procurement under PEPFAR.

FDA recommends a storage labeling statement such as *"Store below 30°C (86°F)"* for NDAs for ARV drug products eligible for procurement under PEPFAR if supported by data obtained at 30°C/75 percent RH. In general, ANDAs for ARV drug products eligible for procurement under PEPFAR will follow storage recommendations for the RLD.

These recommendations apply to the drug product. Because the drug substance is generally held at more controlled conditions (e.g., at the manufacturing site) it is typically tested under less stressful conditions (e.g., 25°C/60 percent RH).

9. Amount of Stability Data

Currently, FDA recommends that at least 6 months of stability data obtained under long-term (e.g., 30°C/75 percent RH) and accelerated (e.g., 40°C/75 percent RH) conditions be submitted with the initial application. These data should be obtained for at least three batches of drug product manufactured by a process representative of the intended commercial process.[54] At least two of these batches should be a minimum of 10 percent of the intended commercial scale, unless otherwise justified. When appropriate, the design of stability studies can incorporate bracketing and matrixing.[55] Additional stability data may be requested by FDA during the review cycle. If a 24-month expiration date is desired, 12 months of stability data should be submitted by the middle of the review cycle.

10. Assessment of Stability Data

Assessment of stability should include assaying each active ingredient to meet acceptance criteria of 90 to 110 percent of labeled strength, determining individual and total impurity levels,

[54] See the guidances for industry *ANDAs: Stability Testing of Drug Substances and Products* and *ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers* and the ICH guidances for industry *Q1A(R2) Stability Testing of New Drug Substance and Products* and *Q1C Stability Testing for New Dosage Forms*.

[55] See the ICH guidance for industry *Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substance and Products* (January 2003).

and measuring dissolution rates. Applicants should submit data on moisture uptake in the dosage form, which is important if the drug product is to be packaged in polymer/foil blisters that are not as impervious to moisture as high-density polyethylene bottles or foil/foil blisters.

11. Expiration Dating Period

Applicants should provide justification of the proposed expiration dating period based on actual stability data for the drug product in the application, supportive stability data for pilot batches or similar drug products, qualitative or statistical analysis of trends, etc. Applicants should include sufficient time points on the stability protocol to cover any anticipated future extension of expiration. To facilitate the effective delivery of drug products distributed outside of the U.S. under PEPFAR, FDA encourages applicants to extend the expiration dating period to 36 or 48 months, once sufficient supporting stability data have been acquired. An applicant could acknowledge its commitment to submit amendments after tentative approval for extension of expiration in a timely manner by including a statement in the original application (section 3.2.P.8.2, Postapproval Stability Protocol and Stability Commitment, of the common technical document is recommended). Once sufficient stability data have been obtained (typically 24 or 36 months of data), FDA encourages applicants to submit an amendment after tentative approval to extend the expiration. Applicants should include the wording "Priority Review Requested" in the submission and the cover letter and should not include other changes in the expiration-extension amendment. See section VI. E., CMC Changes After a Tentative Approval, for recommended approaches to extending the expiration dating period.

E. CMC Changes After a Tentative Approval

This section addresses some of the common CMC changes after tentative approval of ARV drug products eligible for procurement under PEPFAR.

1. Addition of a New Drug Substance Manufacturer or Manufacturing Site, Drug Product Manufacturer, or Manufacturing Site or Testing Site

A new manufacturer (supplier) of the drug substance should be submitted as a major change amendment. A new manufacturing site for an existing manufacturer that has not been previously inspected by FDA should also be submitted as a major change amendment. In contrast, a new manufacturing site for an existing manufacturer that has been previously inspected by FDA should be submitted as a moderate change amendment. An inspection may take place, even if previously inspected, depending on review of the submission. Note that the manufacturing process needs to be validated at the new manufacturing site, regardless of previous manufacturing experience at other sites. A Letter of Authorization to allow an applicant to reference the DMF should be submitted to the DMF, with copies submitted to the relevant application(s).

2. Extension of Expiration Dating Period

Depending on the data available to justify the extension, the two following approaches are examples of what may be appropriate:

a. Submitting a major change amendment proposing to extend the expiration dating period for the drug product on the basis of real-time data plus extrapolation using acceptable statistical methods,[56] for example, extrapolating to a 36-month expiration dating period based on statistical analysis of 24-month stability data on the original three registration batches.

b. Proposing extension of the expiration dating period through a minor change amendment based on real-time stability data from pilot-scale or larger/commercial-scale batches following the acceptable stability protocol for an application that has already received a tentative approval action, for example, proposing a 36-month expiration dating period based on 36-month stability data on the original three registration batches.

3. Changes in Excipient Specifications

Applicants should submit a change made to comply with U.S. Pharmacopeia/National Formulary (USP/NF) that adds a new test or tightens existing acceptance criteria in an excipient specification in a minor change amendment. Applicants should submit deletions of tests or relaxation of limits as a moderate change amendment if the relaxation or deletion is in compliance with an updated USP/NF monograph. Applicants should submit other deletion of tests or relaxations of limits as major change amendments.

4. Changes to the Stability Testing Program

Applicants should submit any changes to the stability testing protocol after tentative approval as major change amendments, except the addition of time points or deletion of time points beyond the approved expiration dating period, which may be submitted as a minor change amendment.

VII. LABELING AND PRESCRIBING INFORMATION

ARV drug products eligible for procurement under PEPFAR must comply with all applicable labeling requirements.[57] This section highlights certain labeling considerations specific to ARV drug products eligible for procurement under PEPFAR. For pediatric dosage forms, the proposed labeling for the drug product should provide clear instructions so that the patient's caregiver can administer the appropriate dose of the drug product.[58] In some cases, it may be appropriate for written and pictorial Instructions for Use intended for caregivers to be included in the prescribing information.[59]

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[56] See the ICH guidance for industry *Q1E Evaluation of Stability Data* (June 2004).

[57] See generally section 502 of the FD&C Act; 21 CFR part 201, Labeling.

[58] See, for example, 21 CFR 201.57(c)(9)(iv) and 201.80(f)(9).

[59] See the guidance for industry *Instructions for Use — Patient Labeling for Human Prescription Drug and Biological Products — Content and Format* (July 2022).

The inclusion of product-identifying information (e.g., National Drug Code (NDC) numbers), if relevant, on the labeling (e.g., container labels, carton labeling, prescribing information) of tentatively approved drug products eligible for procurement under PEPFAR can assist with drug product differentiation. .

For tentatively approved 505(b)(2) NDA drug products eligible for procurement under PEPFAR, it is not necessary to revise the product labeling whenever there are minor updates in the labeling for the listed drug(s) (on which the 505(b)(2) NDA relied upon for safety and efficacy). Applicants must submit updated labeling amendments for the drug products if the following scenarios apply (21 CFR 201.57(a)(5)):

- When submitting a chemistry change amendment that affects the labeling

- There is a significant update in the labeling for the listed drug(s) on which the 505(b)(2) NDA relied upon for safety and efficacy (e.g., new information for Limitations of Use, the BOXED WARNING section, the DOSAGE FORMS AND STRENGTHS section, the CONTRAINDICATIONS section, or the WARNINGS AND PRECAUTIONS section that is applicable to the ARV drug product eligible for procurement under PEPFAR).

For tentatively approved 505(j) ANDA drug products eligible for procurement under PEPFAR, labeling must be the same as the last approved labeling for the RLD, except for differences as provided for in section 505(j)(2)(v) of the FD&C Act and 21 CFR 314.94(a)(8)(iv) .

VIII. OTHER REGULATORY CONSIDERATIONS

This section briefly discusses other considerations for ARV drug products intended to be eligible for procurement under PEPFAR.

A. User Fees

1. NDAs

By law, FDA must assess a user fee on human drug applications and an annual prescription drug program fee, subject to certain exceptions.[60] However, the law provides that under certain circumstances FDA can grant a waiver or reduction in fees.[61] Potential waivers for ARV drug products eligible for procurement under PEPFAR (for NDAs but not ANDAs) are addressed in the draft guidance for industry *PDUFA Waivers, Reductions, and Refunds for Fixed-Combinations and Single-Entity Versions of Previously Approved Antiretrovirals under*

[60] Section 736(a) of the FD&C Act; 21 U.S.C. 379h(a). The application fee is the most significant of the fees. Application reviews do not begin until user fees are paid.

[61] Section 735(d) of the FD&C Act.

PEPFAR.[62] Drug products that are included in the list of needed ARV drug products[63] on the FDA's PEPFAR database[64] may be considered for potential NDA user fee waivers as appropriate.

2. ANDAs

For ANDAs, application and facility fees are assessed according to the Generic Drugs User Fee Act (GDUFA). Applicants should refer to information found on the FDA's Generic Drug User Fee Amendments web page available at https://www.fda.gov/industry/fda-user-fee-programs/generic-drug-user-fee-amendments for additional information on fee structure and amounts.

B. Pediatric Requirements

The Pediatric Research Equity Act (PREA)[65] requires that any NDA[66] or BLA, or supplement to such application, for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration contain pediatric assessments, unless the requirement is waived, deferred, or inapplicable. Such assessments "shall contain data, gathered using appropriate formulations for each age group for which the assessment is required, that are adequate (i) to assess the safety and effectiveness of the drug . . . for the claimed indications in all relevant pediatric subpopulations; and (ii) to support dosing and administration for each pediatric subpopulation for which the drug . . . is safe and effective."[67] Pediatric studies may be deferred if (1) the drug product is ready for approval for use in adults before pediatric studies are complete, (2) additional safety or effectiveness data need to be collected, or (3) there is another appropriate reason for the deferral; and if the applicant submits required information[68] to support the deferral.[69] Pediatric studies will be waived if (1) the studies are impossible or highly

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[62] When final, this guidance will represent the FDA's current thinking on this topic.

[63] The separate list of ARV drug products, Antiretroviral Drug Products Needed for Use Under PEPFAR, can be found under question 6, What PEPFAR products can companies submit for FDA review?, at FDA's PEPFAR Database on the Frequently Asked Questions web page available at https://www.fda.gov/international-programs/presidents-emergency-plan-aids-relief-pepfar/pepfar-database-frequently-asked-questions. This list is revised periodically to address current public health needs.

[64] The FDA's PEPFAR database is available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=pepfar.page.

[65] Public Law 108-155 (2003), codified at section 505B of the FD&C Act (21 U.S.C. 355c). Although section 505B has been amended since the passage of PREA, by convention, that section is often referred to as PREA, and we adopt that convention in this guidance.

[66] PREA does not apply to drug products submitted in an ANDA under section 505(j) of the FD&C Act.

[67] 21 U.S.C. 355c(a)(2)(A).

[68] Described in 21 U.S.C. 355c(a)(4)(A)(ii).

[69] See 21 U.S.C. 355c(a)(4)(A). See also 21 U.S.C. 355c(a)(4)(C) and (D).

impracticable, (2) there is evidence strongly suggesting that the drug product would be ineffective or unsafe in all pediatric age groups, or (3) the drug product does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of pediatric patients.[70] In certain cases, as appropriate, FDA will grant a partial waiver with respect to a specific pediatric age group(s).[71]

PREA, as described above, applies to NDAs for ARV drug products eligible for procurement under PEPFAR. Generally, most ARV drug products indicated for pediatric populations are labeled by weight-band dosing, and DAV recommends designing the PREA assessments accordingly. For some SE or FC ARV drug products submitted under section 505(b)(2) of the FD&C Act, available information for the reference drug product may provide sufficient information to support pediatric use for at least some part of the pediatric population. For ARV drug products not intended for use in specific pediatric age (or weight) groups, FDA encourages applicants to contact DAV about the possibility of a waiver or deferral.

Submission of NDAs for ARV drug products discussed in this guidance are usually not preceded by end-of-phase 2 meetings or pre-NDA meetings. Sometimes, sponsors seek pre-investigational new drug application (pre-IND) advice regarding design of relative bioavailability studies. Sponsors seeking pre-IND advice should consider providing an initial pediatric study plan (iPSP) at that time.[72] A sponsor that has not met with FDA or sought advice before submission of an application should provide an iPSP, submitted to a pre-IND, to DAV when the sponsor submits a request for a user fee waiver.

C. Adverse Event Reporting

For approved ANDAs or NDAs, applicants must comply with adverse event reporting requirements (i.e., reports of serious and unexpected adverse events within 15 days of receipt of the information by the applicant or its affiliates).[73] For tentatively approved ARV drug products to be distributed in PEPFAR-partner countries, a system of collecting and reporting adverse drug events by the distributor is encouraged (e.g., through governmental or nongovernmental agencies distributing the drug products).

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[70] See 21 U.S.C. 355c(a)(5)(A). See also 21 U.S.C. 355c(a)(4)(C) and (D).

[71] See 21 U.S.C. 355c(a)(5)(B).

[72] For more information on iPSPs, see the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (July 2020).

[73] 21 CFR 314.80 and 314.81.