Optimizing Regulatory Processes for Quality Global Health Products for Low and Middle Income Countries:

Working with the EU to Enhance Global Health – Article 58

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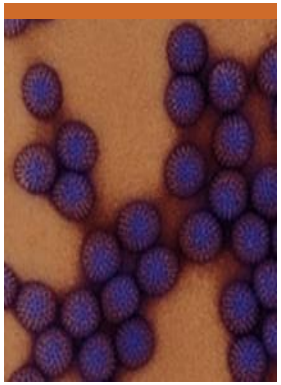
Our history

1994

Bill Gates Sr. starts a small philanthropic foundation at his son's request.

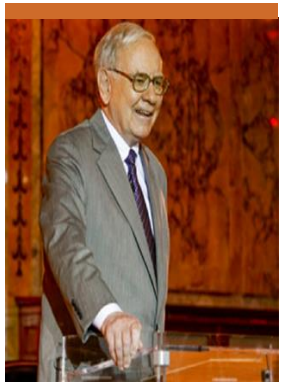


1997

Bill and Melinda read an article about rotavirus and are inspired to act.

2000

The Bill & Melinda Gates Foundation is created, with a focus on health, education, and libraries.



2006

Warren Buffett pledges Berkshire Hathaway stock valued at $31 billion.

2008

Bill joins Melinda full-time at the foundation.

2011

The foundation moves to its new permanent home in Seattle.


EVERY PERSON
DESERVES THE
CHANCE TO LIVE
A HEALTHY,
PRODUCTIVE LIFE
BILL & MELINDA
GATES foundation
VISITOR CENTER
ENTER
CURIOUS

Our global reach and presence

1,200
2012 active grantees

$3.4B
2012 grant payments

1,100
2012 employees worldwide

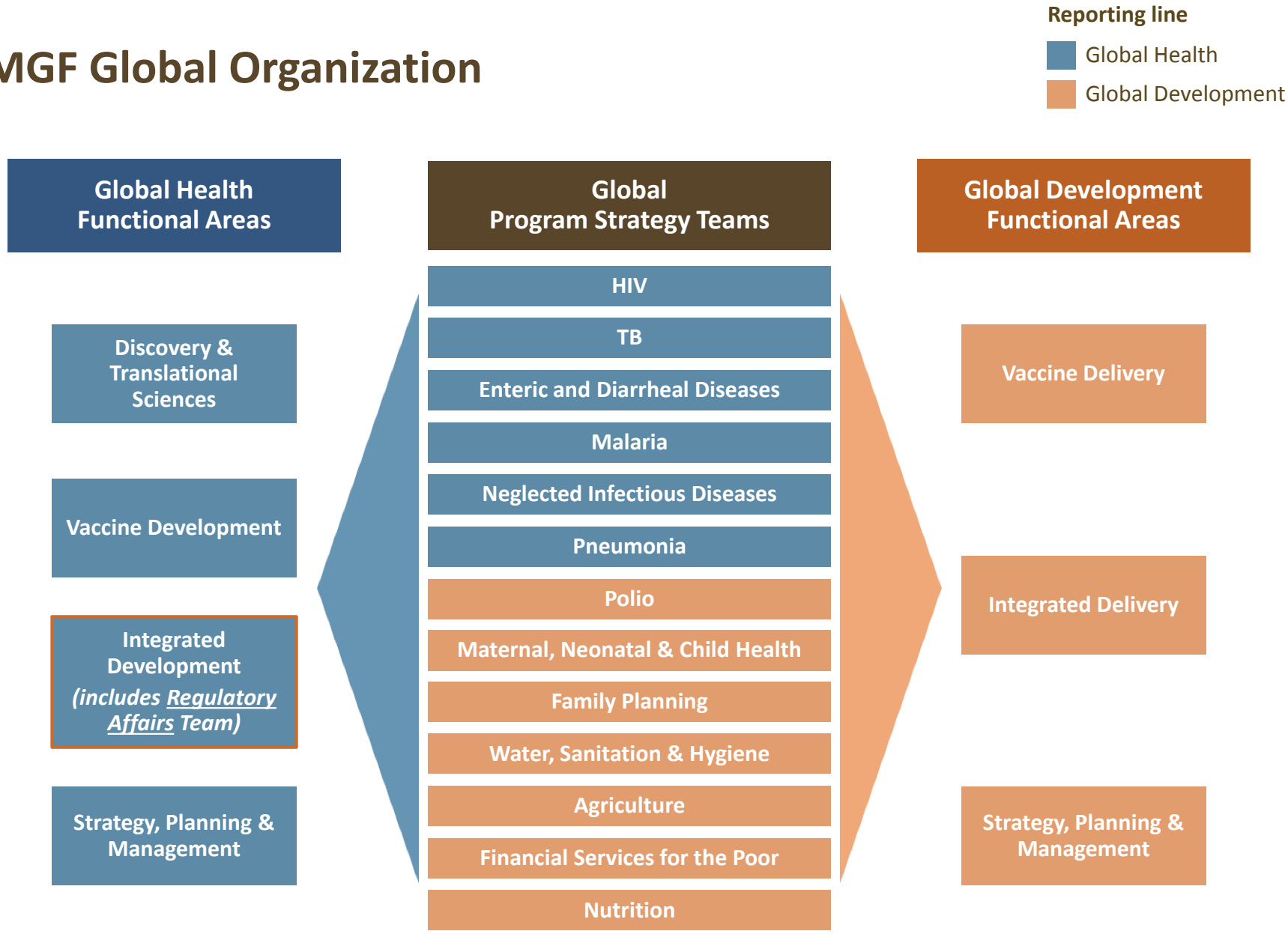
What we do

GLOBAL HEALTH

GLOBAL DEVELOPMENT

UNITED STATES PROGRAM

BMGF Global Organization



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Challenges along the three main steps of the regulatory landscape

Role of regulation

- **Approval and oversight** of pre-clinical experiments and clinical trials for demonstration of product efficacy and safety and quality of clinical trial supplies
- **Approval for distribution** in own jurisdiction through the evaluation of
  - product **safety, efficacy, quality,**
  - **manufacturing** and **distribution** facilities
  - **Benefit-to-risk ratio** in the intended population
- **Monitoring** to learn about quality, safety, and efficacy profiles and act on potential **adverse effects (pharmacovigilance)**
- Monitoring of **product marketing practices**
- On-going **manufacturing quality assessments**

Lack of adequate capacity for value added regulatory activities (and definition/agreement on those)

Key regulatory challenges in LMIC landscape

- **Insufficient funding** to support the clinical development regulatory activities
- **Long approval timelines**, related to **systemic redundancies and complexity, long "down times"**
- **Limited diagnostics regulation** with a **complex landscape for manufacturers**
- **Limited infrastructure** to support pharmaco-vigilance, methodologic challenges
- Increased inflow of **counterfeit and substandard** medicines

Registration activities are key steps in global health product access

Illustrative example for medicines and vaccines

- To introduce a vaccine or drug in many SSA countries
- The product must be registered with the country's NRA
- The product typically needs WHO-PQ to meet quality requirements of donors and procurers
- Before that, the product generally needs a first registration, usually in the country of origin, or a recognized SRA (often needs CMP/CPP)
- R&D phase for product development

Strategy development for registration component informed by robust fact base and extensive expert engagement

Current progress:

Vector control

Diagnostics

Drugs & Vaccines

	From "beliefs" to facts	Proposed strategy	"Making it happen"
Drugs and Vaccines *70% of portfolio[1]*	▪ Data collected: registration time data for 200+ products ▪ Stakeholders interviewed: product developers (20), regulators and policy makers (11), and procurers (4)	Strategy developed and approved: ▪ Near-term and long-term vision ▪ Strategic actions ▪ Risks/mitigation ▪ Support requested	*Implementation and stakeholder outreach in progress (investments and advocacy efforts)*
Diagnostics *20% of portfolio[1]*	▪ Data collected: WHO PQ, FDA CBER, 510K approval times & application volumes; select mfg case studies; RDT quality assessments ▪ 42 stakeholders interviewed: Manufacturers (9), Country regulators and policy makers (11), Regulatory experts (13), Procurers (4), Quality assurance mechanisms (5)	▪ Stakeholder engagement on vision and strategy ▪ Internal leadership approval on high-level vision and strategy	*Recently started*
Vector *10% of portfolio*	*Recently started*		

Summary of factbase of challenges in medicines and vaccines registration (data through end of 2012)

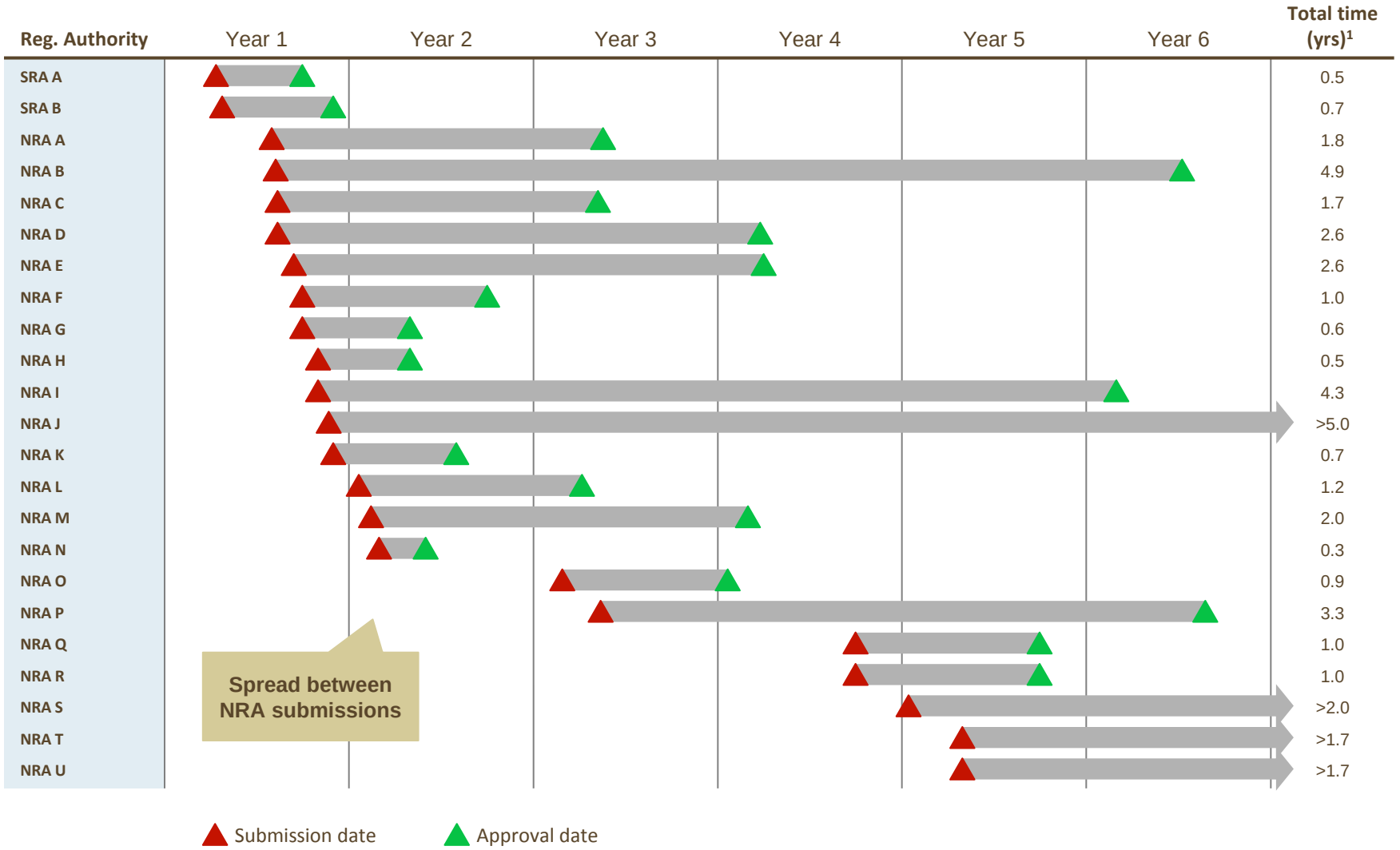
Registration pathway		Typical duration in months, median				
		1st RA approval time	PQ approval time	Gap from 1st approval to 1st SSA NRA submission	Spread from 1st NRA submission to last NRA submission[1]	Sub-Saharan Africa NRA approval time
Drug	Novel, SRA first	10 months	4	9	52 (D)	11 (C)
	Generic, NRA first	~12	27 (B)	~3-6	~24	~18
Vaccine	SRA first	15	16 (A)	5	78	16
	NRA first	~12	16	~3-6	N/A	N/A

1. Excludes those with data available for only 1 NRA submission
Note: "Relevant SSA submission" defined as top-20 disease-burden country or all countries for contraceptives and certain vaccines
Source: Data from CEO Roundtable member registration data received as of 1/7/2013; PQ approval times from WHO PQ data, NRA/SRA data from FDA/EMA databases, CIRS, WHO PARs, and online research; BCG analysis

Main challenges and root causes in medicines and vaccines

	Key challenge	Root causes
A	**PQ of SRA-approved vaccines takes 1-2 years following prior SRA approval**	▪ Vaccine PQ repeats full assessment for SRA-approved vaccines ▪ Programmatic suitability issues for developing-country use (e.g., vaccines lack needed thermostability properties) ▪ Manufacturers prioritize commercial market over PQ (~12 mos. response)
B	**PQ of generic drugs from emerging markets typically takes >2 years**	▪ Manufacturers run into hurdles because they are used to local standards (e.g., ~45% of dossiers lack required clinical data like bioequivalence) ▪ PQ is often a 2nd priority for these manufacturers
C	**Sub-Saharan Africa NRA approval takes 1-2+ years for products that have SRA approval or PQ**	▪ NRAs repeat assessments (e.g., plant inspections) performed by SRA or PQ ▪ Limited technical and HR capacity results in slow review
D	**Registration submission to NRAs across all relevant SSA countries often spreads over several years**	▪ Manufacturers don't prioritize registration for all endemic countries ▪ No harmonization of dossier requirements limits manufacturer ability to apply to many NRAs at once

Example of large spread between submissions to NRAs



1. Time from submission to approval

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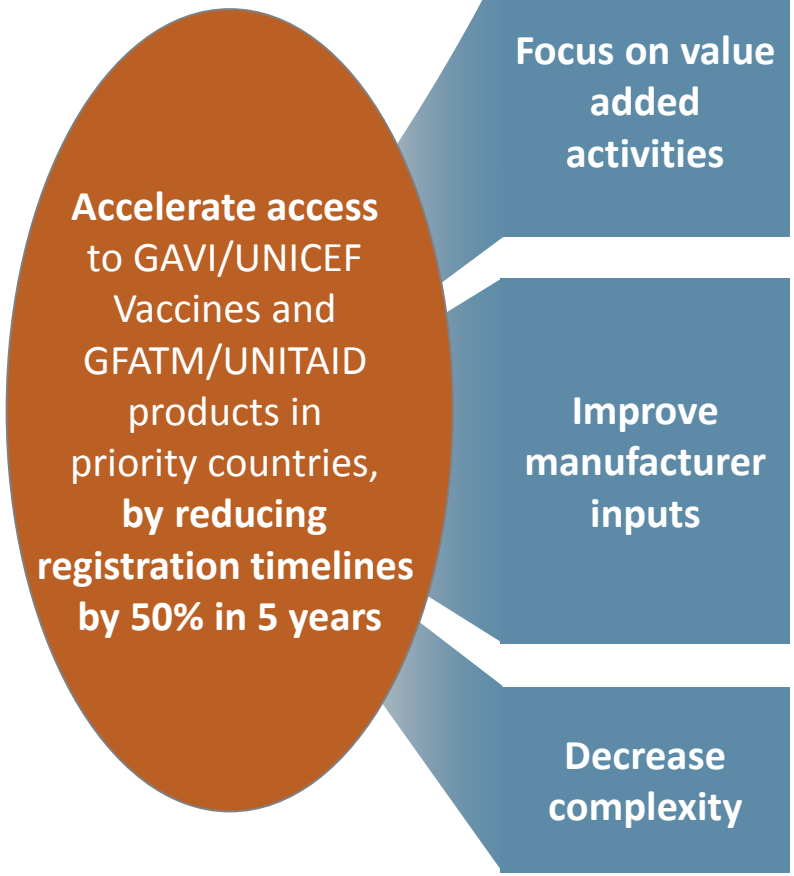
Future vision and strategic actions

● Problems addressed



Key strategic actions

- **Maximize focus on value added activities** by all stakeholders — A
- **Maximize efficiency of WHO PQ program**, including increased reliance on SRAs and NRAs — B, C
- **Expand WHO accelerated NRA review programs**

- **Raise enforced standards for generics and vaccines regulation in India and China**
- **Directly encourage manufacturers to improve inputs** (e.g. programmatic suitability, regulatory planning, early regulator engagement) — B
- **Advocate for donors/procurers to reward quality**

- **Support NRA harmonization and regionalization** through African Regional Medicines Harmonization (AMRH) initiative — C, D

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The Bill & Melinda Gates Foundation: General Overview

Why our interest in regulatory systems

BMGF's strategy to improve GH regulatory landscape for Medicines and Vaccines

The European Union and Article 58

Future vision and strategic actions

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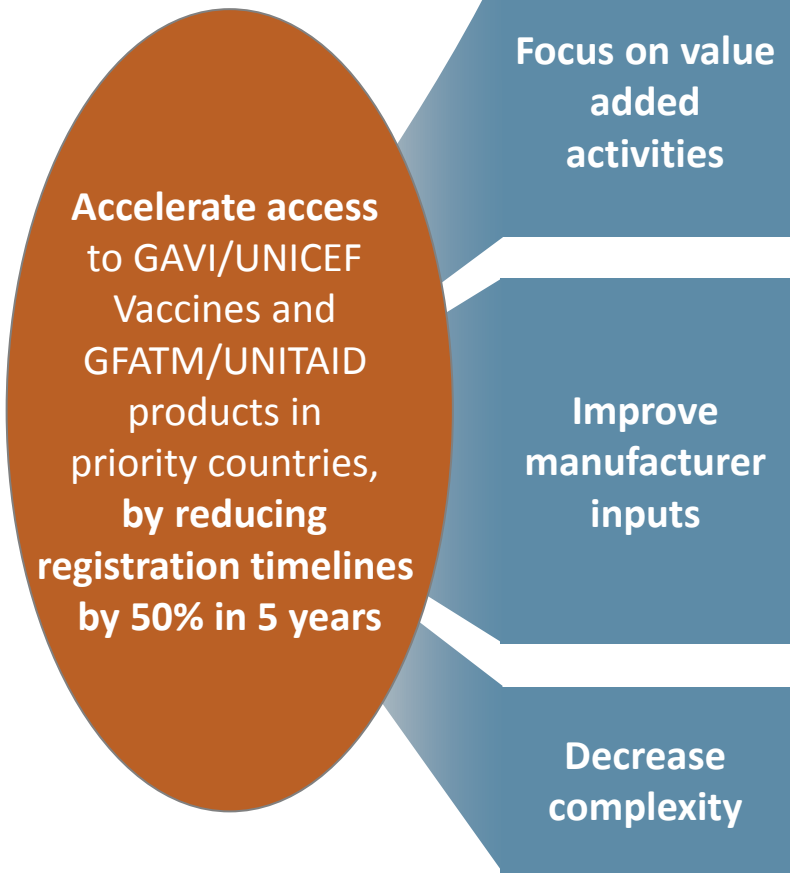

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Article 58

Special provision of EU pharmaceutical law:
Article 58 of Regulation (EC) No 726/2004

Intended to provide access to EU technical expertise (pre-clinical, clinical, and manufacturing quality) for products that will not be marketed in Europe

- **During the development phase**
- **During the marketing dossier assessment phase**
- **During the post-marketing authorisation phase**

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Manufacturer makes decision to employ this route

Applies to be accepted into this programme

- **EMA works with WHO on whether or not to accept product into this programme**

After acceptance

- **Access to scientific advice from EU experts / Sc Adv WG / CHMP**

Fees apply, but in certain cases can be reduced or waived

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During CHMP marketing dossier assessment

- **WHO experts integral part of the process**
- **Can include representatives from NRAs of countries where product may be ultimately used**
- **Does not result in a European marketing authorisation; rather results in a positive CHMP scientific opinion about the benefit/risk profile of the product and about the manufacturing quality of the product**

Manufacturer is responsible to the EMA/Commission for post-positive opinion responsibilities just as if it were a EU marketing authorisation

- **Pharmacovigilance, manufacturing updates, quality defect reports**

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Results: 6 positive opinions

HIV – 3 products
Malaria – 1 product
Vaccines – 2 (multiple antigens)

Why so few?

Non-access to EU market can be disincentive
Lack of knowledge
WHO does not feel a product is critical for LMIC
? Others

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Information on this programme:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000162.jsp&mid=WC0b01ac0580024e9b

www.ema.europa.eu

In Search Engine: Article 58

THANK YOU!