Report of an Independent External Review

Impact assessment of WHO Prequalification and Systems Supporting Activities

June 2019

DISCLAIMER:

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Impact assessment for prequalification streams (1/3)

Quantitative
Qualitative

Impact theme	Stakeholder impacted[1]	Description of impact	Type of impact	Impact metric
1 Access to donor funded procurement markets	▪ *Manufac-turers*	▪ Provides unrivalled access for manufacturers to participate in Donor-funded as well as pool-procurement of key Rx, Vx and Dx	▪ Economic impact ▪ Critical access barrier (supply)	A Total size of PQ-enabled market in the three streams B Ratio of developing to developed country manufacturers participating
2 Quality assur-ance system for safe, efficacious products	▪ Patients ▪ *Manufac-turers* ▪ *Donors/ procurers* ▪ *NRAs*	▪ Ensure that known quality products that are safe and efficacious are entering the developing markets	▪ Critical access barrier (Quality; Supply)	A # of major donors requiring PQ for procurement B Manufacturer, procurer/donor, NRA perception of safety, quality, efficacy due to PQ
3 Ensuring products are developed in an LMIC context	▪ Patients ▪ *Manufac-turers* ▪ *Donors/ procurers* ▪ *NRAs*	▪ Provide the technical guidance to ensure LMIC context drives innovation and product development	▪ Critical access barrier (innovation)	A Case studies of WHO driven value-add to ensure LMIC appropriate product development (incl. case study of rejected product) B Manufacturer, procurer/donor, NRA perception of PQ-led innovation in LMIC context
4 Economic return on investment (RoI)	▪ *Donors* ▪ Procurers	▪ Direct economic return for investors in this program due to increased competition / reduced prices	▪ Economic impact ▪ Critical access barrier (affordability)	A RoI (resultant savings over investments) for donor money invested in PQ B Case studies of price drop due to increased competition
5 Contribution to lives saved	▪ *Patients*	▪ Increased affordability due to PQ has enabled gains in access that have saved many more for the given resources	▪ Public Health	A Patients accessed / lives saved as a result of increased affordability

1 Stakeholder impact measured by metrics marked in italics

Impact assessment for prequalification streams (2/3)

Quantitative
Qualitative

Impact theme	Stakeholder impacted[1]	Description of impact	Type of impact	Impact metric
6 Faster access to prequalified products	▪ Patients ▪ *Manufac-turers* ▪ *NRAs* ▪ *Donors/ procurers*	▪ Setup mechanisms that speed up decisions from NRAs thereby providing patients faster access to products	▪ Critical access barrier (Availability)	A % of products that have obtained NRA approval through collaborative procedure in <90 days B Manufacturer, procurer/donor, NRA perception of value add on streamlining downstream approvals
7 Raising overall standards of manufacturing	▪ *Manufac-turers* ▪ *NRAs* ▪ *Donors/ procurers*	▪ Through PQ reviews and by participating in systems upgrade to meet PQ requirements, manufacturers adopt standards that improve quality for other domestic products as well	▪ Critical access barrier (Quality)	A # of developing country manufacturers that have PQ but no SRA products B Manufacturer, procurer/donor, NRA perception on improvements of overall standards of manufacturing

1 Stakeholder impact measured by metrics marked in italics

Impact assessment for systems supporting activities (3/3)

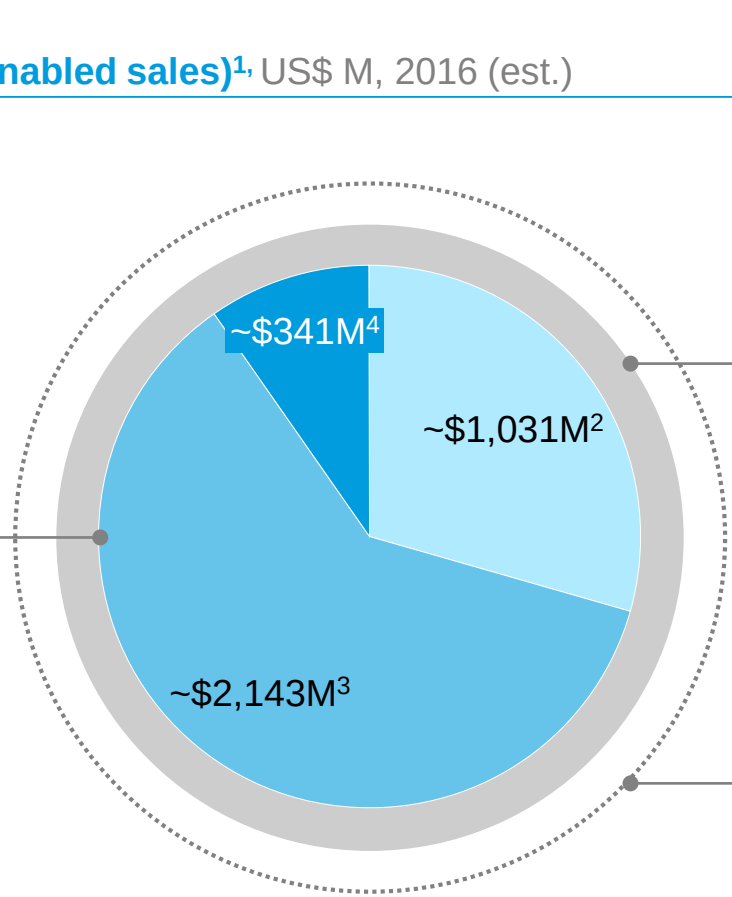
Quantitative
Qualitative

Impact theme	Stakeholder impacted[1]	Description of impact	Type of impact	Impact metric
8 Norms and Standards (N&S)	▪ *Manufac-turers* ▪ *NRAs*	▪ Norms and standards set clear guidance and thresholds to meet in-order to assure quality, safe, efficacious products	▪ Critical access barrier (Quality)	A Manufacturer, procurer/donor, NRA perception of utility of norms & standards published in last 5 years as well as areas for improvement
9 Regulatory Systems Strengthening (RSS)	▪ Patients ▪ *NRAs*	▪ Assistance to NRAs in the form of training, support and tools has enabled increased capacity of NRAs to perform as a regulator	▪ Critical access barrier (Quality)	A Level of activity indicating RSS B NRAs & procurers/donors scoring and perception on utility of the Global Benchmarking Tool C More broadly, perception of NRAs & procurers/donors on: – Most value-added support currently – Future expectations
10 Safety and Vigilance (SAV)	▪ *Manufac-turers* ▪ *NRAs* ▪ Donors/ procurers ▪ HCPs ▪ Patients	▪ Guidance and support to stakeholders that ensures products remain of good quality, safety and efficacy / performance once on the market	▪ Critical access barrier (Quality)	A Level of activity indicating SAV B Mfrs, procurers/donors, NRAs perception of utility of SAV activities

1 Stakeholder impact measured by metrics marked in italics

1A PQ enables a core market of ~$3.5 billion with the majority coming from vaccines

Sales of PQ products (PQ-enabled sales)[1], US$ M, 2016 (est.)



Large donors and procurers (based on detailed PQ market sizing by each disease area and procurer)

Sales: ~$ 3,515M

National markets[5] (based on LMIC market estimation for each disease area and manufacturer perspective on access enabled by PQ)

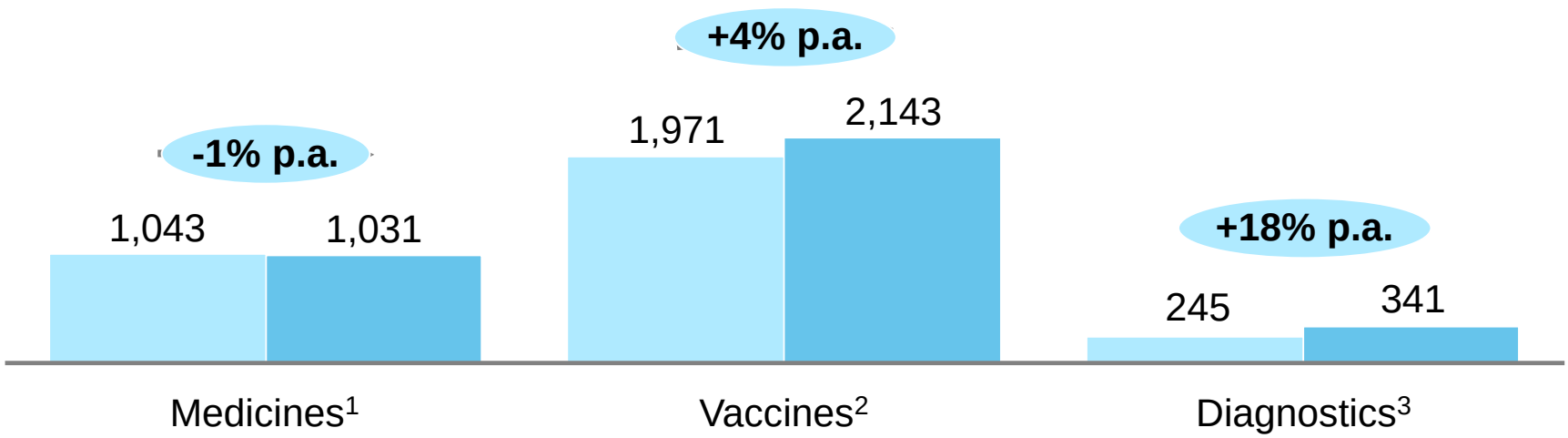
Private market[5] Minimal benefit of PQ approval on private - markets *(except Rx-Malaria)*

1 Includes PQ or SRA+PQ products 2 Estimation based on average 2014-2016 increase in procurement by largest 1-2 donors in HIV, Malaria, TB, RH
3 Based on 2014 vs 2016 vaccine procurement value of UNICEF and assuming fixed PAHO supply of $500 million 4 Based on 2016 donor market size for HIV, Malaria size estimated based on HIV vs Malaria sales ratio in 2014 5 Refers only to Low and Lower Middle Income Markets

SOURCE: Market sizing based on: GPRM, Global Fund Price & Quality Reporting database; RH Interchange database; Unitaid market landscape reports; Unitaid vaccine supply, demand, and pricing data; WHO World Malaria Report

1A PQ enabled spend flat for medicines and vaccines but significant increase for diagnostics

PQ-enabled spend by product type, US$ M



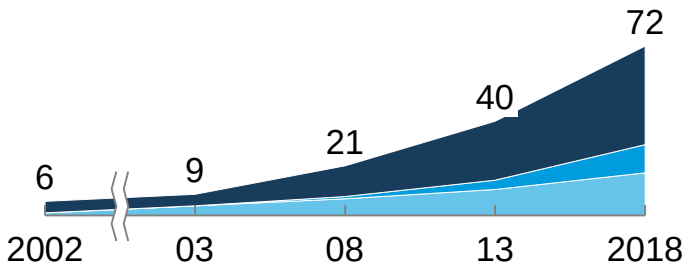
1 Estimation based on average 2014-2016 increase in procurement by largest 1-2 donors in HIV, TB, Malaria, RH
2 Based on 2014 vs 2016 vaccine procurement value of UNICEF and assuming fixed PAHO supply of $500 million
3 Based on 2016 donor market size for HIV, Malaria size estimated based on HIV vs Malaria sales ratio in 2014

SOURCE: Market sizing based on: Global Fund Price & Quality Reporting database; RH Interchange database; Institute of Health Metric and Evaluation

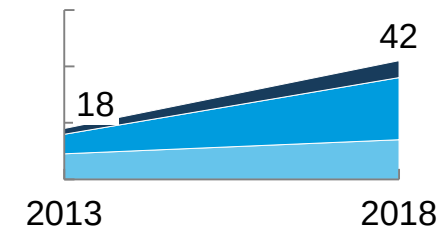
1B Share of DCMs has increased since start of program for FPPs

of manufacturers with ≥1 prequalified product by country class

FPPs

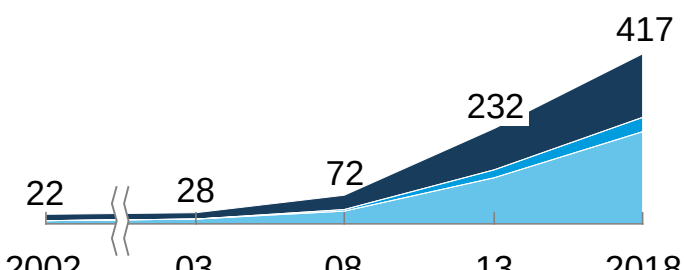


APIs

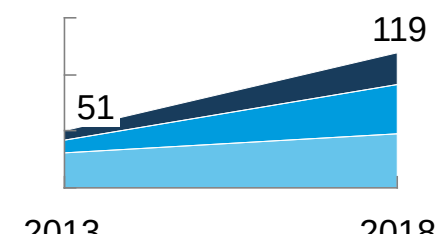


of prequalified products by country class

FPPs



APIs



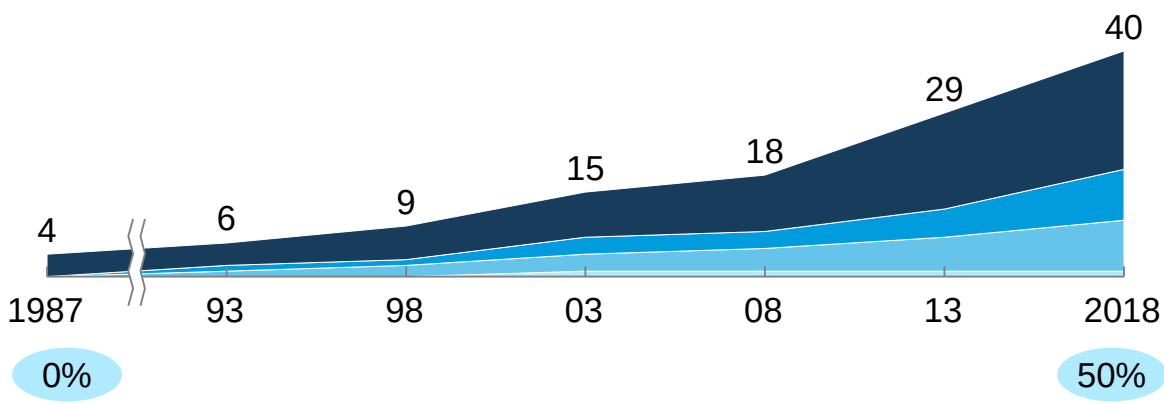
High income
Lower middle income
Upper middle income
Low income
x Share of LMIC (Upper, Lower, Low)

- WHO prequalification of medicines / Finished Pharmaceutical Products (FFPs) launched in 2001 / the first products received PQ label in 2002
- WHO prequalification of Active Pharmaceutical Ingredients (APIs) launched in 2013
- Share of developing country manufacturers has been flat since start of program for FPPs and APIs
- FPP manufacturers from lower middle income countries have higher # of PQ products in portfolio on average

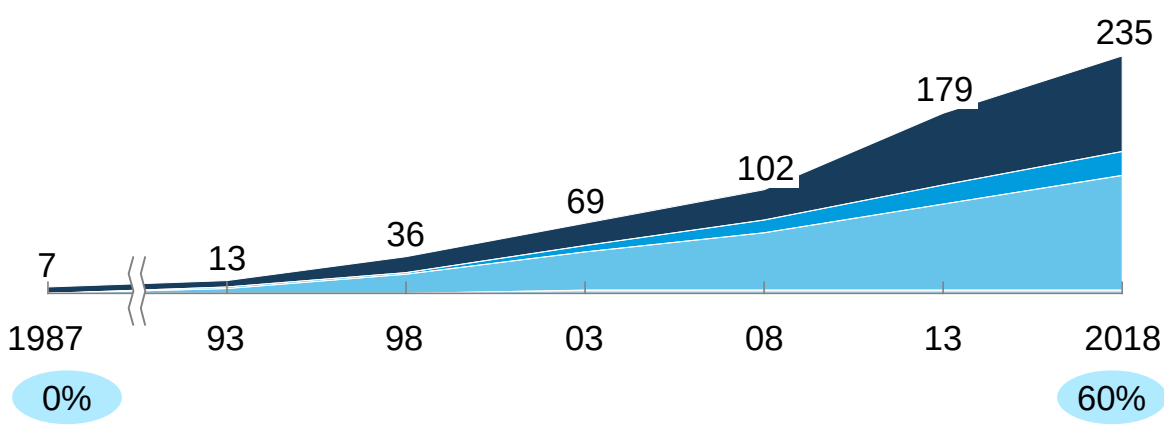
SOURCE: WHO list of prequalified medicines/Finished Pharmaceutical Products; WHO list of prequalified Active Pharmaceutical Ingredients; World Bank country classification (status 2018)

1B Share of DCVMs relatively constant, with majority coming from HI countries

of vaccine manufacturers with ≥1 prequalified product by country class



of vaccines prequalified by country class



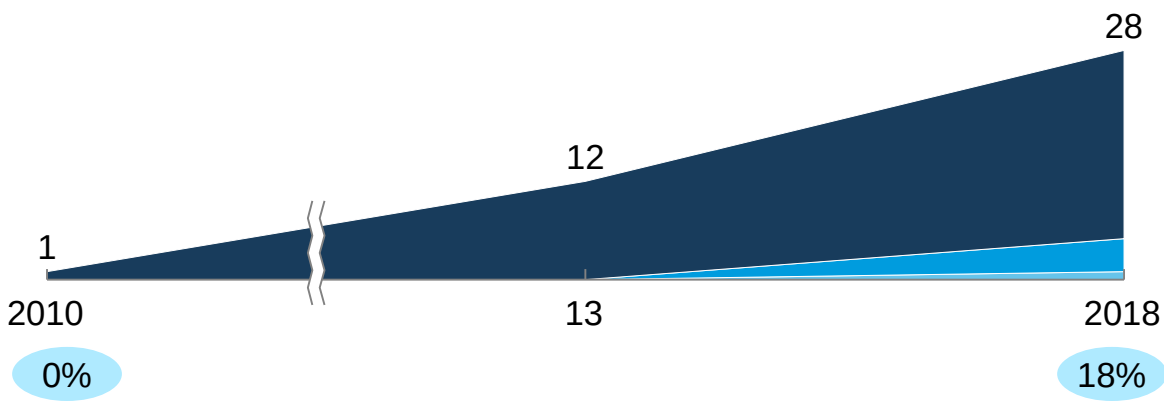
High income
Lower middle income
Upper middle income
Low income
x Share of LMIC (Upper, Lower, Low)

- First vaccine pre-qualified in 1987
- Sharp increase of # of products since 2008
- LMIC manufacturers have higher # of products / manufacturer than high income country manufacturers partially due to more presentation modes and # of doses per package offered for each vaccine

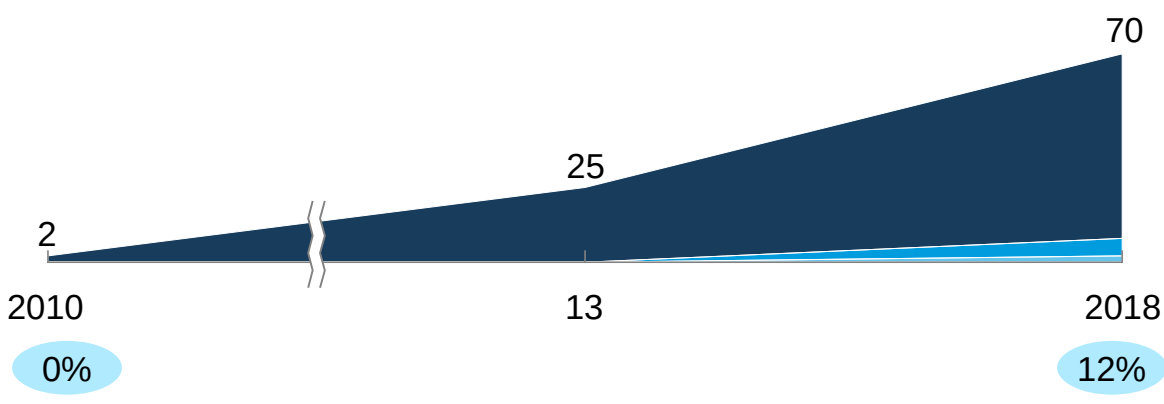
SOURCE: WHO prequalified vaccines list; World Bank country classification (status 2018)

1B Share of DCMs has moderately increased from zero since start of program for Dx

of Dx manufacturers with ≥1 prequalified product by country class



of Dx products prequalified by country class



High income
Lower middle income
Upper middle income
Low income

x Share of LMIC (Upper, Lower, Low)

- First diagnostic product prequalified in 2010
- Diagnostics products pre-qualified for one of following disease areas: HIV, HBV, HCV, HPV and Malaria
- Majority of manufacturers and products from high income countries (IC), including United States, EU countries, Japan and Republic of Korea
- Remaining manufacturers are from middle IC
  - China and Russian Federation from upper middle IC with PQ products
  - India only lower middle IC with PQ products

SOURCE: WHO list of prequalified in vitro diagnostics; World Bank country classification (status 2018)

2A Most donors and procurers view PQ approval as equivalent to SRA approval for medicines

Organization	Donor/ procurer perspective on PQ				Contingency approval process
	HIV/AIDS	TB	MALARIA	RH	
PEPFAR	tFDA[1] (NDA/ANDA)	-	-	-	-
PMI	-	-	PQ or SRA approval	-	-
USAID FROM THE AMERICAN PEOPLE	tFDA (NDA/ANDA)	-	PQ or SRA approval	PQ or SRA approval	UNFPA ERP[2] (for RH only)
UNFPA	-	-	-	PQ or SRA approval	UNFPA ERP
Unitaid	PQ or SRA approval	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 To Fight AIDS, Tuberculosis and Malaria	PQ or SRA approval	PQ or SRA approval	PQ or SRA approval	-	ERP
Stop TB Partnership GLOBAL DRUG FACILITY	-	PQ or SRA approval	-	-	ERP

1 Tentative FDA
2 Expert Review Panel

SOURCE: Donor/procurer publications; web search; expert interviews

2A Major procurers rely on PQ exclusively for vaccines

	Donor/ procurer perspective on PQ	Contingency approval process
Gavi The Vaccine Alliance	Only PQ accepted	Specific exemption to procure non Prequalified products possible under defined criteria
unicef supply	Only PQ accepted	-
Pan American Health Organization	PQ or SRA approval (PQ preferred)	Internal PAHO processes for the assurance of quality
MEDECINS SANS FRONTIERES	PQ or SRA approval	
ICRC	PQ or SRA approval	

SOURCE: Donor/procurer publications; web search; expert interviews

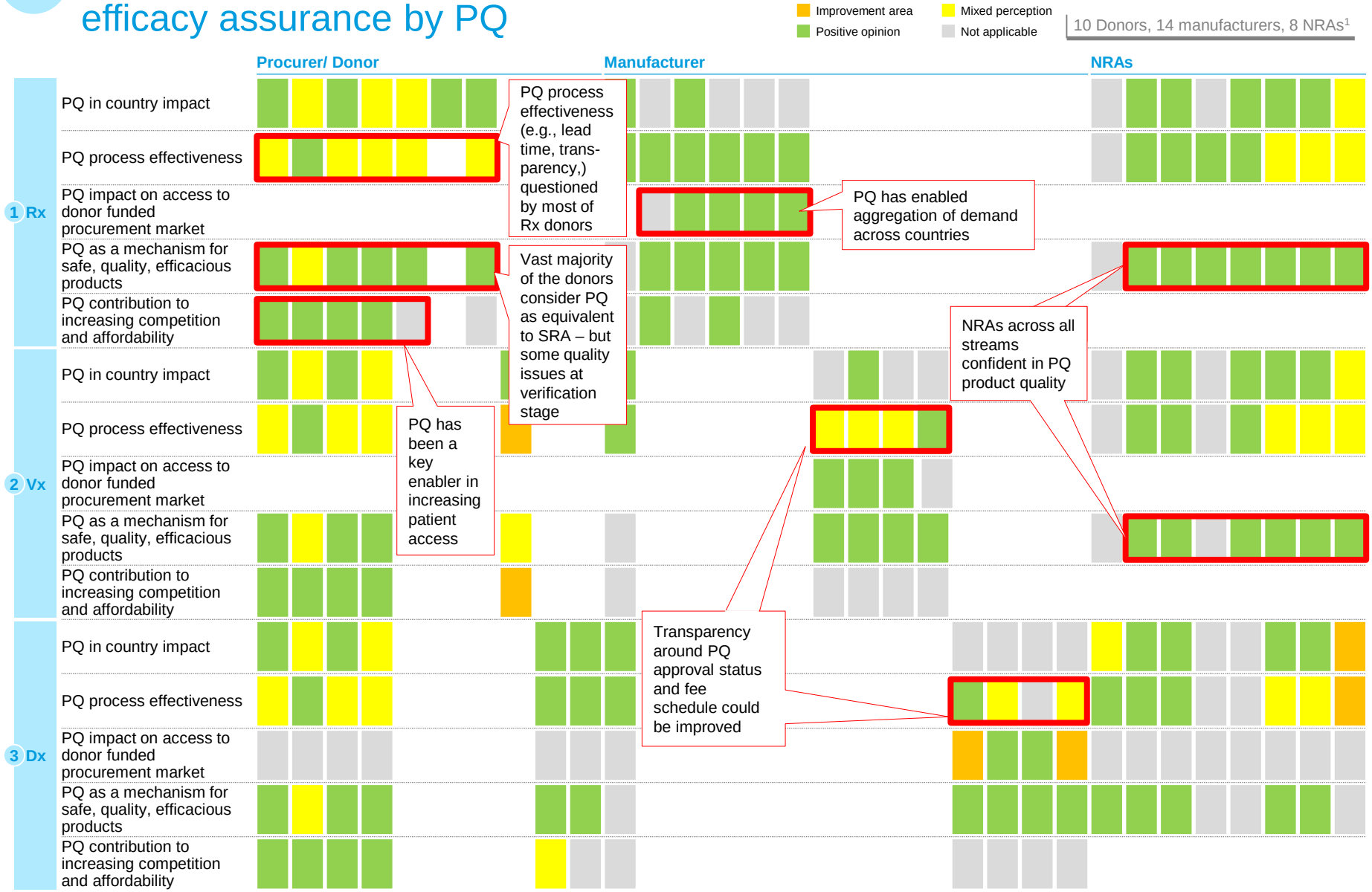
2A Similarly to Rx, most implementing partners view PQ approval as equivalent to SRA approval for diagnostics

Organization	Donor/ procurer perspective on PQ				
	HIV/AIDS	MALARIA	RH	Contingency approval process	TB[4]
unicef[1]	Only PQ accepted	Only PQ accepted	PQ or SRA approval	-	-
UNDP					
UNFPA					
The Global Fund To Fight AIDS, Tuberculosis and Malaria	PQ or SRA approval	PQ or SRA approval	-	ERP[2]	WHO endorsement
PEPFAR	Only PQ accepted	-	-	PEPFAR Formal review process	-
PMI	-	PQ or other USAID/ CDC approval[3]	-	-	-
MEDECINS SANS FRONTIERES[5]	PQ or SRA approval	PQ or SRA approval	PQ or SRA approval	MSF's own qualification scheme	-
Unitaid	PQ or SRA approval	PQ or SRA approval	PQ or SRA approval	ERP	WHO endorsement
Clinton Health Access Initiative	PQ or SRA approval	Only PQ accepted	Only PQ accepted	ERP	-
Elizabeth Glaser Pediatric AIDS Foundation	PQ or SRA approval	-	-	ERP	-

1 For projects with Unitaid and CHAI, SRA approval or ERP are also used
2 Expert Review Panel
3 PQ is accepted, but other products based on USAID/CDC requirements can be accepted too. CDC will soon start malaria RDT performance evaluations for PQ
4 Dx TB is not covered by PQ but by TB WHO guidelines (and associated standards) on tuberculosis
5 PQ is preferred, but SRA approval is also accepted

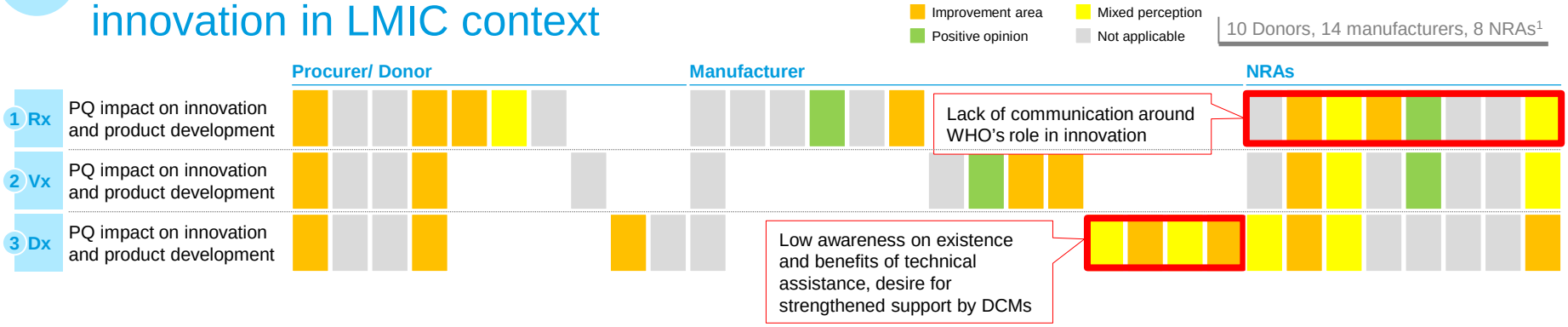
SOURCE: Donor/procurer publications; web search; expert interviews

2B Manufacturer, procurer/donor, NRA perception of safety, quality, efficacy assurance by PQ



1 Only stakeholders that provided scores listed

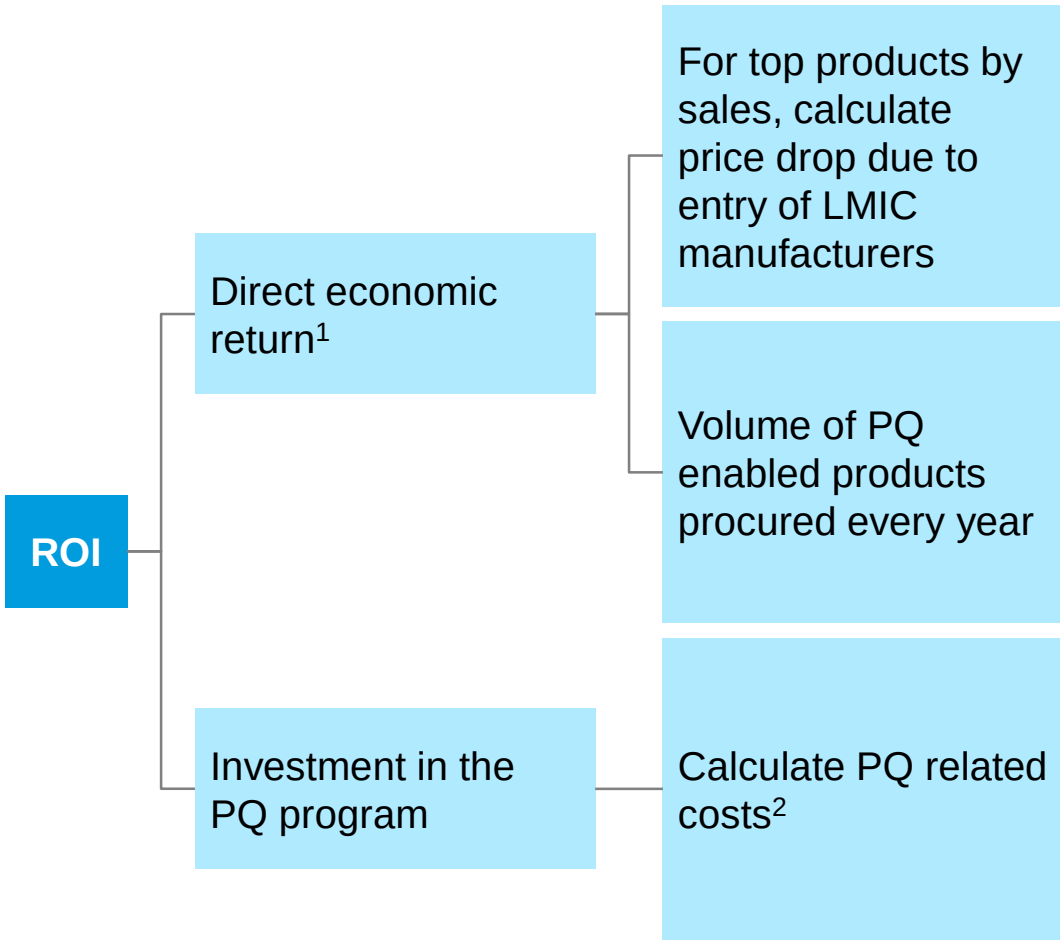
3B Manufacturer, procurer/donor, NRA perception of PQ-enabled innovation in LMIC context



1 Only stakeholders that provided scores listed.

4A General approach for Return on Investment calculation (1/2)

Methodology overview



Detailed method

- For each product/dosage strength, establish price drops between price when 1st major LMIC entered the market and latest price in the database
- Calculate donor procured volume of top products by disease areas / dosage strength
- Scale up to total market

Savings

- Variable PQ costs
- Fixed PQ costs
- Indirect PQ costs

RoI

1 Not considering other benefits such as benefits to economy/productivity, value of life saved,…

2 Non PQ RHT costs are excluded

4A General approach for Return on Investment calculation (2/2)

Calculate savings for product dosage strength

1. Calculate weighted average unit price per dosage strength for top 3 products by donor-funded sales
   - Top 2 product types[1] for Rx-RH and diagnostics
   - Top 5 products for vaccines
2. For each product / dosage strength, establish price differential post-prequalification and before
3. Multiply with volume of sales to obtain total savings for selected products

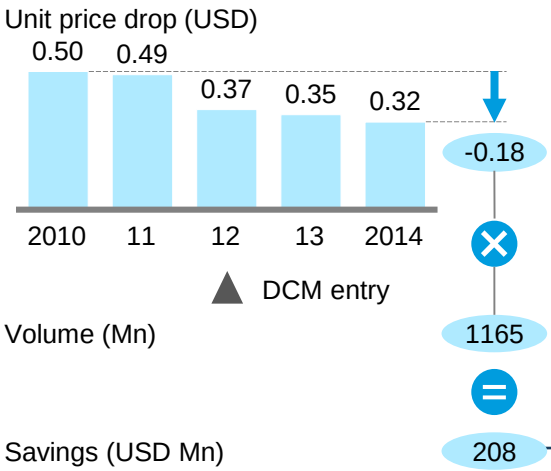
Scale up to total savings for product stream / disease area

1. Sum savings of all dosage strengths for top 3 products
   - Top 2 product types[1] for Rx-RH and diagnostics
   - Top 5 products for vaccines
2. Scale up savings of top products of disease area to total donor funded PQ approved LMIC market (based on 2014 market share)
   - Higher bound: savings to sales ratio of top products considered equal for other products
   - Lower bound: no savings for non-top products considered

Calculate RoI for PQ program & PQ related activities

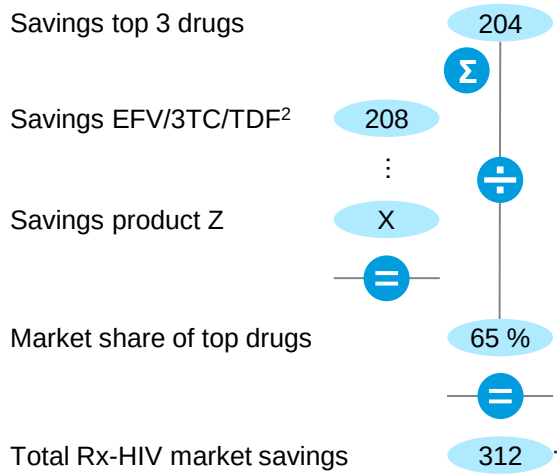
1. Sum savings across all product streams
2. Calculate PQ related costs
   - Variable PQ costs
   - Fixed PQ costs
   - Indirect PQ costs
   - Non-PQ RHT costs are excluded
3. Determine Return on Investment

Example: Rx-HIV: EFV/3TC/TDF[2] (600 mg + 300 mg + 300 mg)



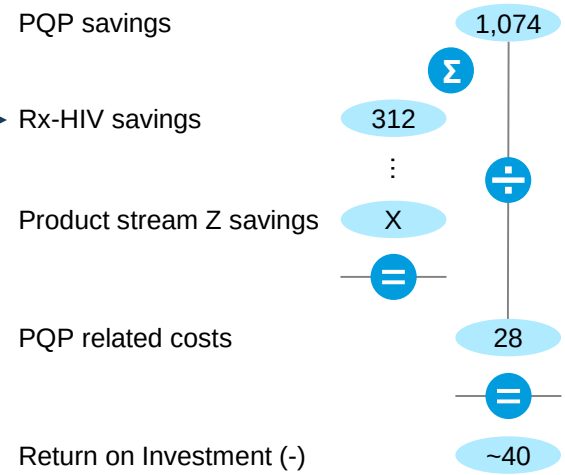
Example: Rx-HIV – Higher bound

USD Mn



PQ program – Higher bound

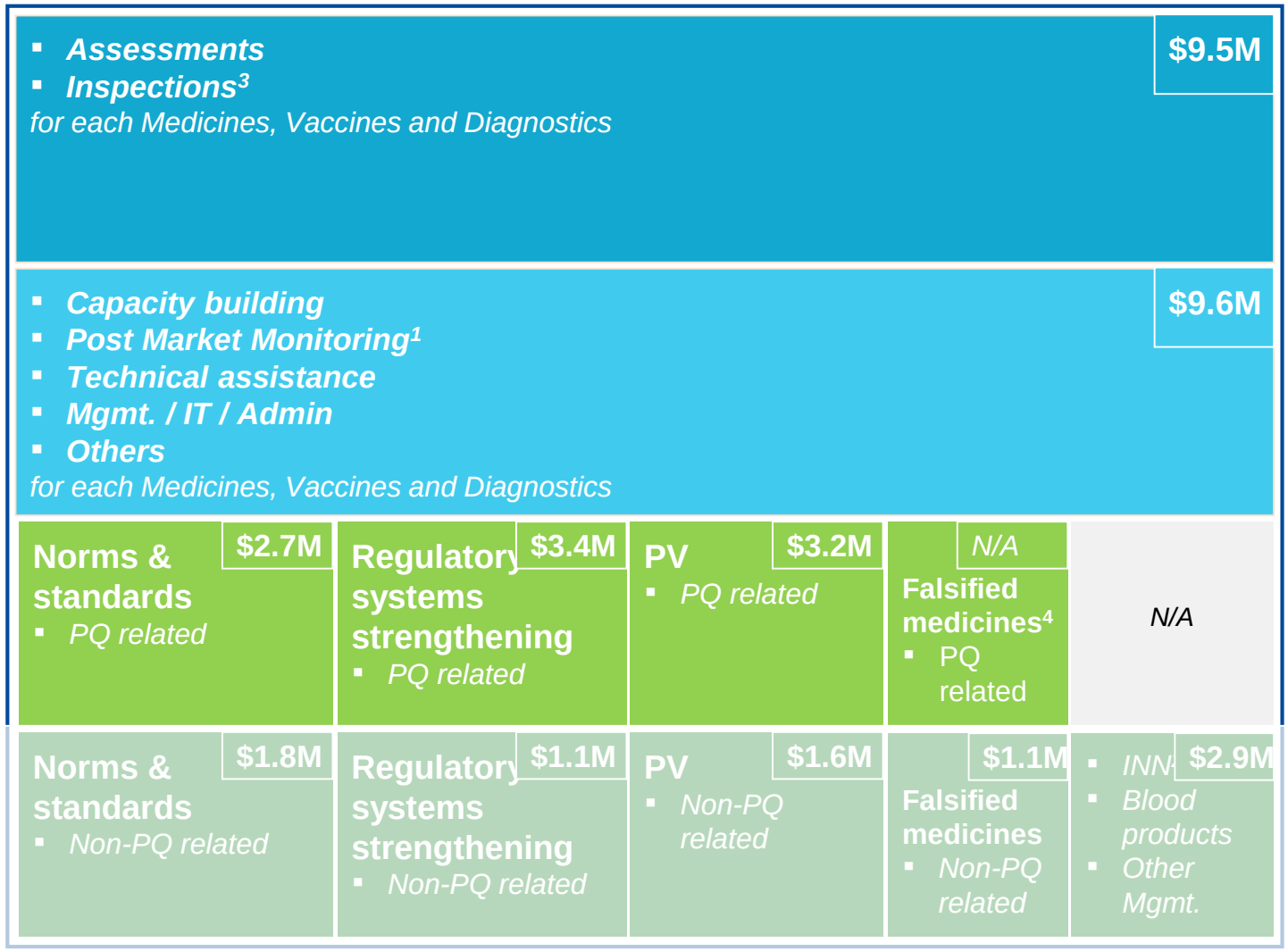
USD Mn



1 Product types for Rx-RH are injectables and orals - combined, product types for Dx are rapid tests and CD4 technologies; 2 Efavirenz-Lamivudine-Tenofovir Disoproxil Fumarate

4A Overview of WHO PQT cost components in scope for ROI

Overall PQT costs - $28.4M (excluding Non-PQ RHT cost)



1 Excluding Pharmacovigilance costs associated with PQ products; 2 INN is self-funded through its activities
3 Does not include cost of vaccine inspection activities (per DM, Travel, APWs) that are directly covered by manufacturers on an actual basis
4 Falsified medicine costs may include some cost of follow-up of relevant complaints involving potential counterfeits

SOURCE: WHO Prequalification team

4A WHO PQP has a Return on Investment of 30-40 to 1

USD Mn

VISUALIZATION NOT TO SCALE

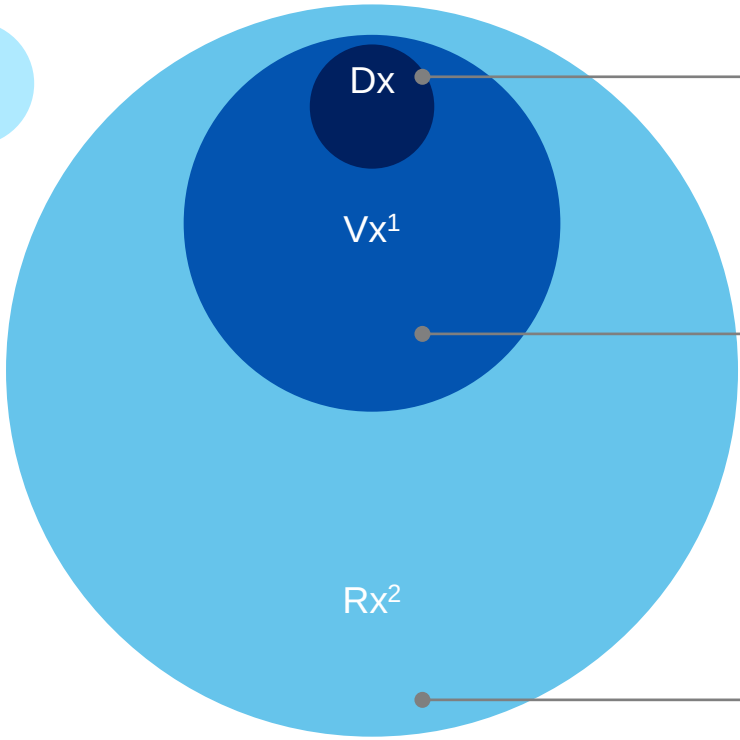
PQ costs

28

PQ savings

826 – 1,074

- PQ costs include direct (variable and fixed) and indirect RHT PQ costs



- Limited unit price drop given each diagnostics method has 1 MNC with > 50% market share
- Conservative value as a limited time interval (2012-2014[2]) and only HIV diagnostics is considered

- Key driver is high volume
- DTP-HepB-Hib[3] accounts for majority of savings

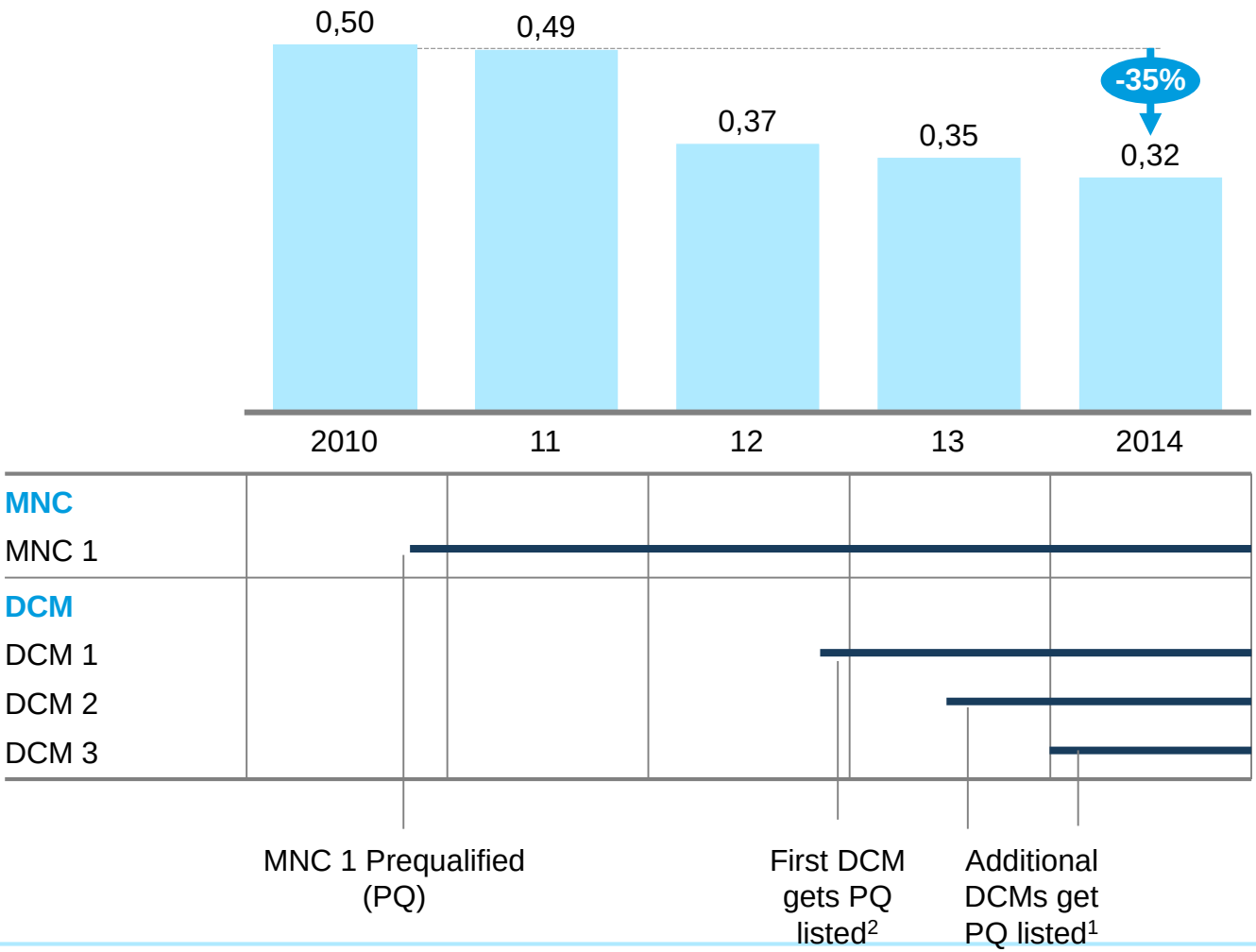
- Rx-HIV and Rx-Malaria comprises > 80% of savings
  - Rx-HIV key driver is high volume
  - Rx-Malaria key driver is large unit price drop
- No savings Rx-RH considered despite injectables price drop, however these are mostly supplied by MNCs (90%+)

RoI 30-40 to 1

1 Not including PCV and Rotavirus despite price drop, because price drop attribution to PQ is questionable 2 Due to the lack of a reliable dataset, for other products the time interval 2004-2014 is considered 3 Also referred to as Pentavalent vaccine

4B Largest ARV drug by market share in 2014 saw sharp price decrease in 2012 when first DCM entered market with PQ-listed product

Weighted average ex works unit price of EFV/3TC/TDF[1] (600 mg + 300 mg + 300 mg), USD/unit



- Sharp price drop after DCM 1 entered LMIC market with PQ-listed product in 2012
- Price dropped continuously over a series of years when additional products got PQ listed[2]
  - DCM 3 received PQ in 2015 and DCM 1 received PQ in 2017
- DCM 1 only DCM to achieve a market share of >20% (35%)
  - MNC 1 adjusted pricing to the same level as DCMs from 2012 onwards
  - All manufacturers have an average price between $ 0.30-0.35/unit

1 Efavirenz + Lamivudine + Tenofovir;

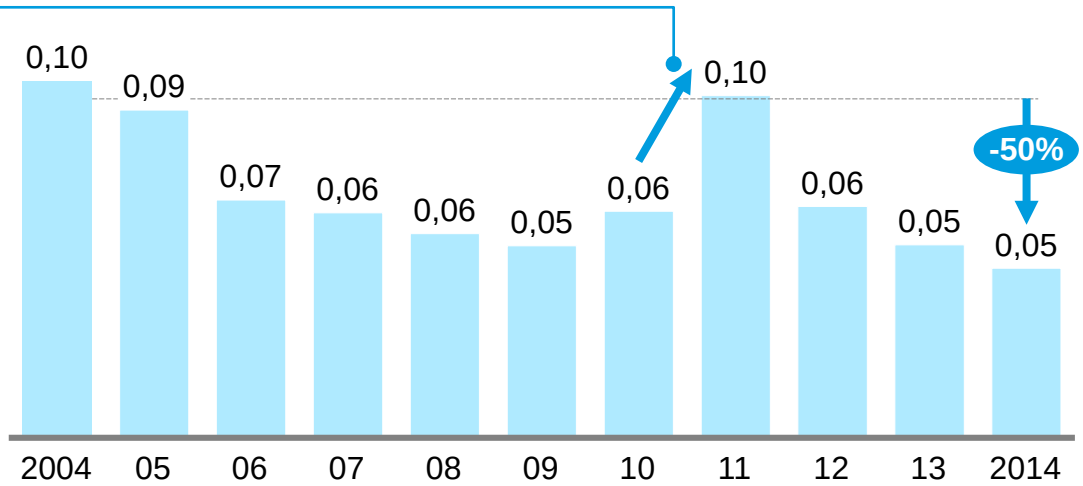
2 PQ listed, i.e. drug has tentative US FDA approval (applies to all ARVs);

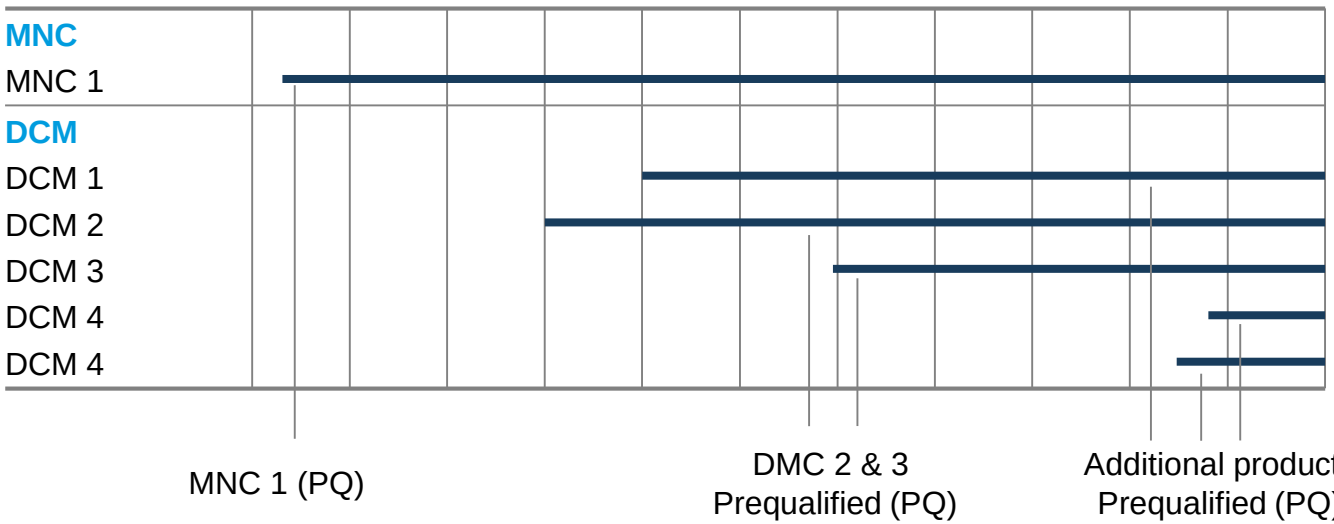
SOURCE: WHO's GPRM database

4B Anti-Malaria drugs experienced price increase in 2010/11 due to Artemisinin shortage, but prices have dropped again since

Weighted average unit ex works price of Artemether + Lumefantrine (20 mg + 120 mg), USD/unit

End of Memorandum of Understanding between WHO and MNC 1 for the supply of treatment at cost price to malaria endemic countries





- MNC 1 first decreased prices in 2006, 1 year before Cipla entered the market
- All manufacturers were forced to increase prices in 2010 and 2011 due to global Artemisinin shortage, a key ingredient of Artemether
- Prices again dropped significantly after 2011

Sidenote:

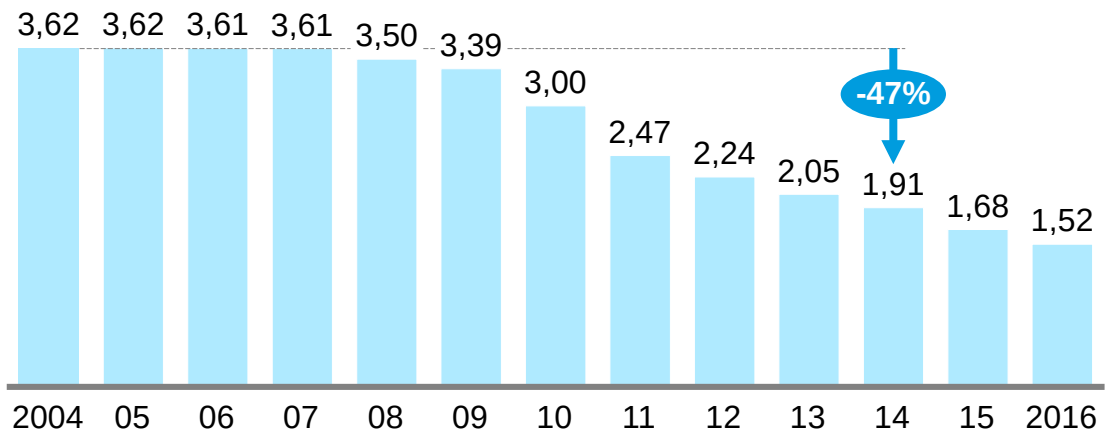
- Manufacturers that have recently entered the market have not been able to have sales before prequalification
- DCM 1 and 2, who entered earlier, managed to achieve only limited sales before obtaining PQ status (DCM 2's sales increased by a factor 46 upon obtaining PQ)

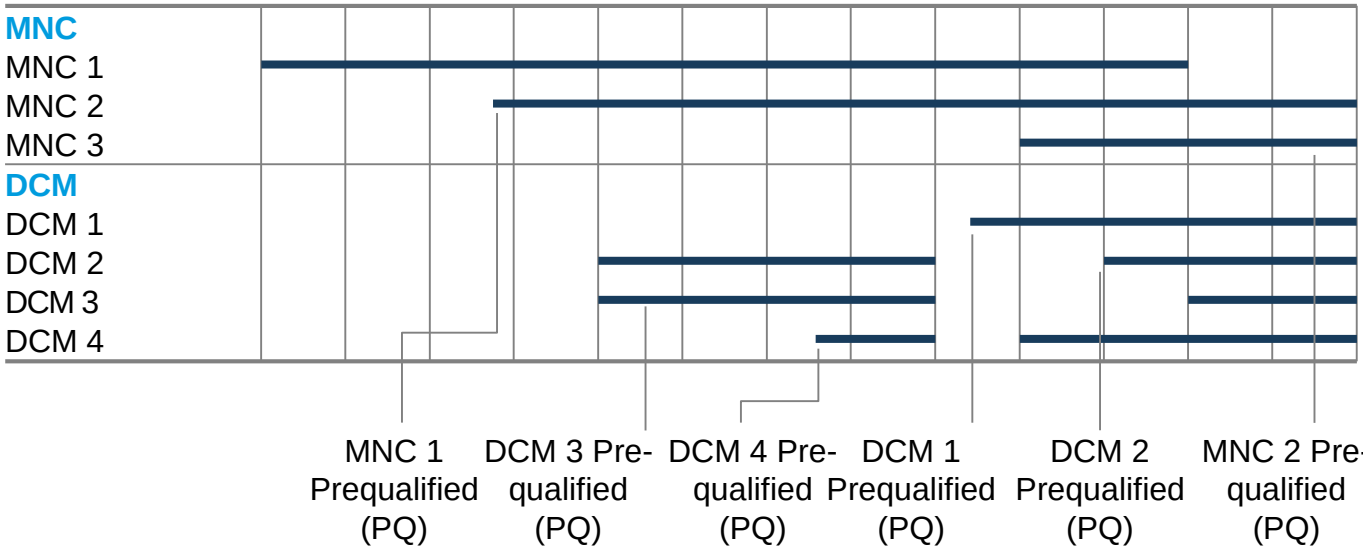
SOURCE: WHO's GPRM database

4B Pentavalent vaccine (DTP-HepB-Hib) prices dropped by 47 % following entry of developing country vaccine manufacturers

Weighted average price of Pentavalent vaccine dose

USD/unit





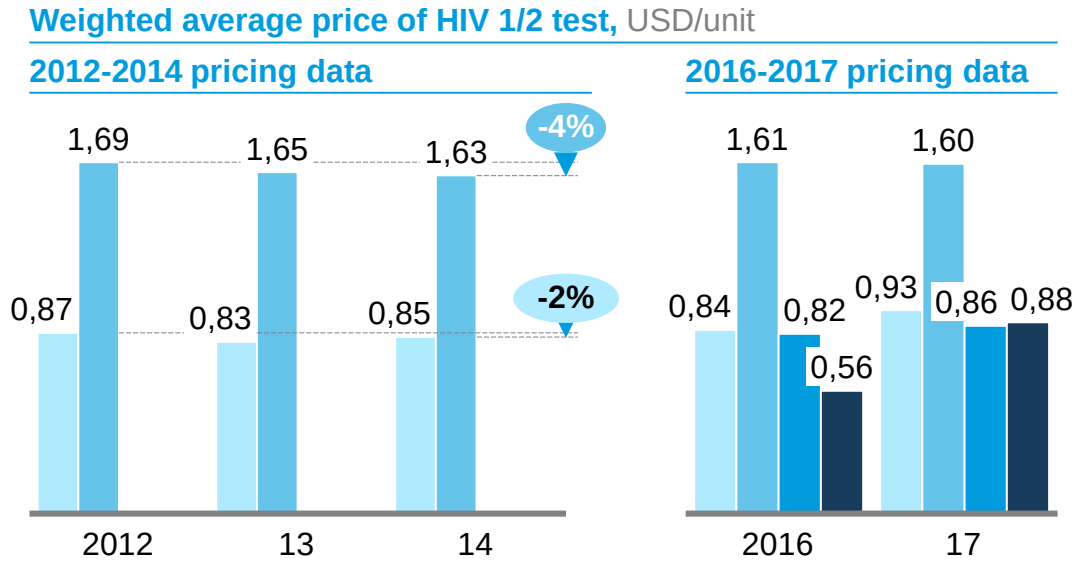
- New suppliers have constantly driven down prices
- Sharp price decrease started with entry of DCM 4 in 2010
- Delisting and re-entry of DCM 2, 3 and 4 highlights fragility of the supply chain
- MNC 1 has no sales after 2014, when their dose price was 54% above market average

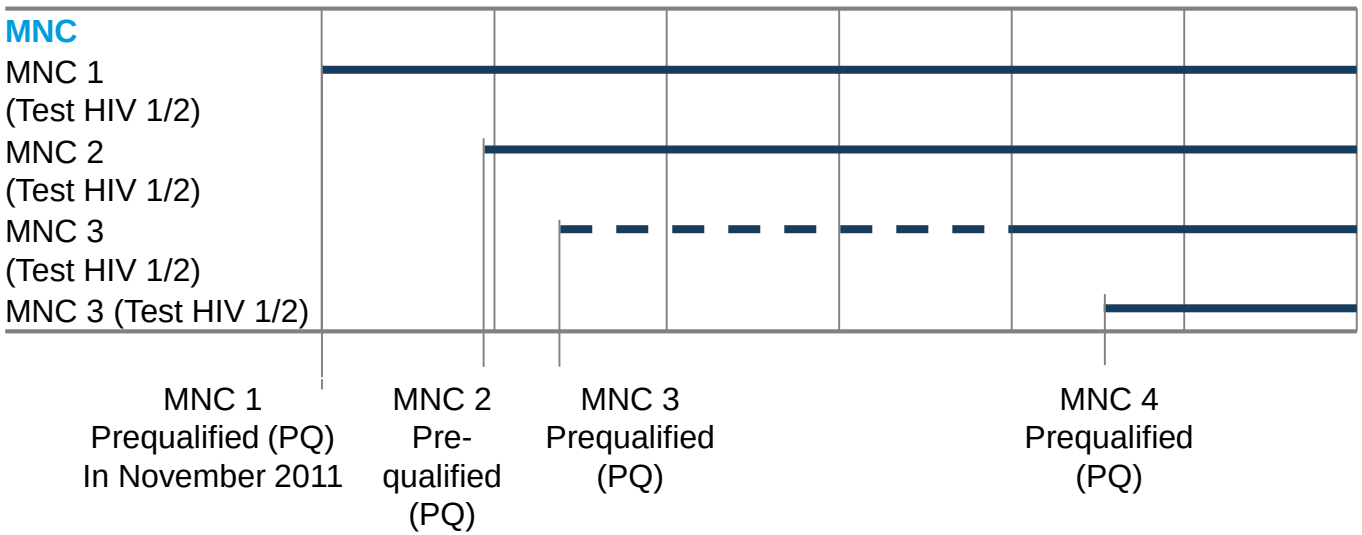
SOURCE: UNICEF

4B Rapid HIV serology tests have not seen a price drop upon entrance of competitors

2 different datasets have been used for this case study

- 2012-2014 data is sorted on a mix of purchase date and delivery date
- 2016-2017 data is sorted on delivery date





- HIV rapid tests detect anti-bodies and a positive diagnosis consists of 3 tests, assay 1, 2 & 3
- No price drop due to:
  - Fixed pricing agreements
  - Less competitive dynamics due to market split into A1, A2, A3
  - Reputation an important consideration
- MNC 1 is market leader in A1 market (screening tests)
- MNC 2, which offers highest specifity) competes for A2 and A3 market (confirmatory assays)
  - Lower volume as only (false)positive A1 test subset uses Trinity to confirm A1

SOURCE: WHO; UNICEF; Unitaid; GFATM

5A 340-400 million more patients are accessible thanks to resources freed up by PQ

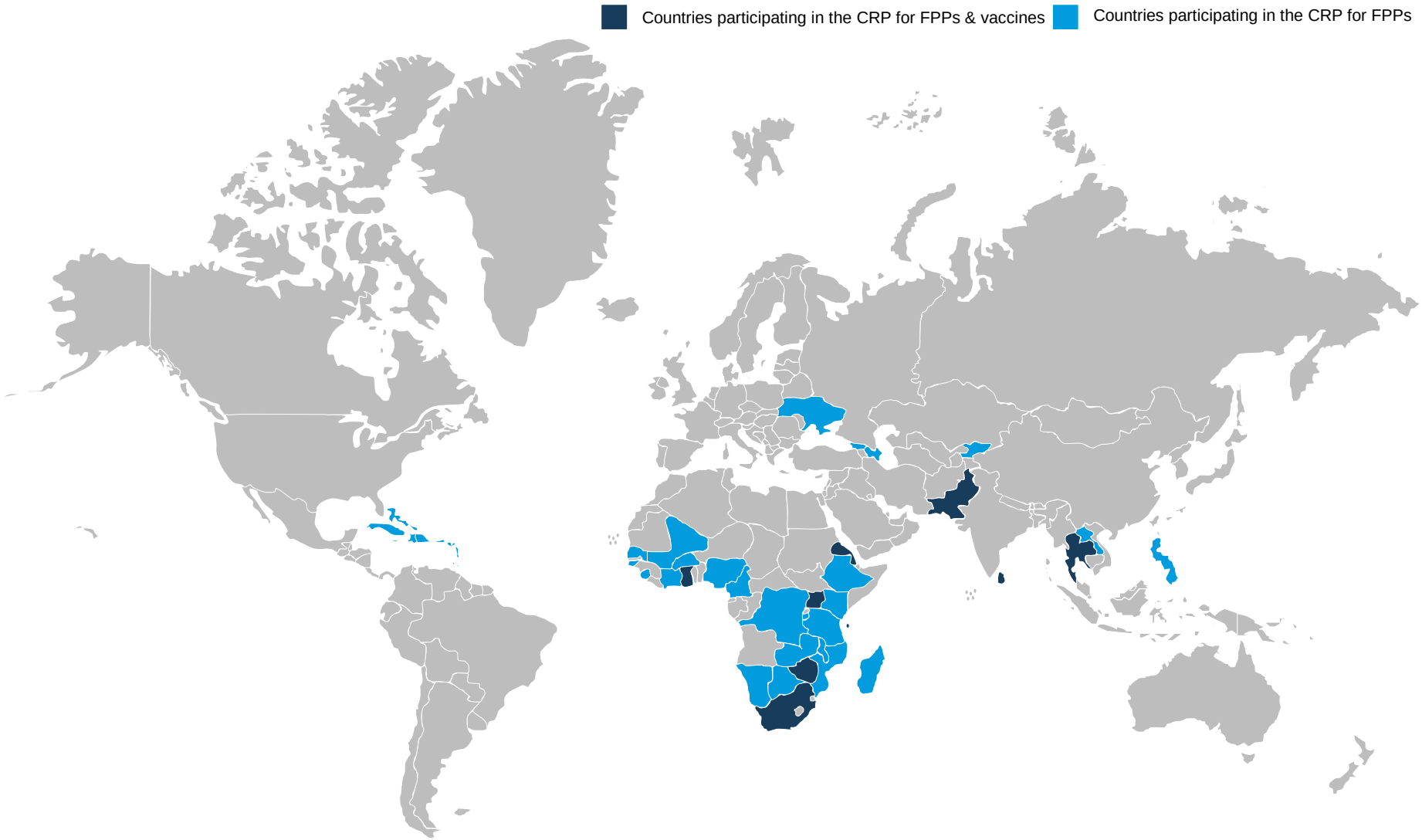
Product stream	Freed up budget[1] USD Mn (% of market[2])	÷	Treatment cost/year USD	=	Additional patients accessible[1], Mn	Methodology
Rx-HIV	147 - 196 28 - 37%		93.35		1.6 - 2.1	▪ Treatment cost per year = Total sales / total # treatments ▪ Most ARVs require daily pills ▪ CHAI estimates 94 USD/year in 2016
Rx-Malaria	124 - 145 39 - 45%		0.68		183 - 213	▪ Based on GF reference treatment pricing for largest product in 2018 ▪ Considered 1 adult dose treatment per year (twice daily for 3 days)
Rx-TB	13 - 19 9 - 14%		662		0.0	▪ Treatment cost per year is weighted average of FLDs and SLDs[3] cost ▪ Based on Global Drug Facility sales in 2017
Rx-RH	0 0		3.60		0	▪ CHAI RH 2018 report for treatment pricing, using market value to determine average cost
Vx	337 - 382 17 - 19%		2.19		154 - 174	▪ # doses for each of top 5 drugs according to WHO recommendation used to determine vaccination cost
Dx	3.4 – 7.7 1 - 3%		1.33		2.5 – 5.8	▪ 1 unit is equal to 1 diagnosis ▪ Considered 1 diagnosis per year ▪ Average price of HIV diagnosis

Assuming a fixed donor market size for all products, calculated the share of the market represented by savings (i.e. the freed up budget). Treatment cost/year price only includes price of the product itself.

1 Interval with lower bound only considering top products savings and higher bound considering equal savings to sales ratio of top products for non-top products; 2 share (%) of total donor funded LMIC market; 3 First-line anti-TB drugs and second-line anti-TB drugs (i.e. MDRs: multi drug resistant anti-TB drugs)

SOURCE: Rx-HIV (WHO's GPRM database, CHAI: ARV market report 2017); Rx-Malaria (WHO's GPRM database, Global Fund ACT reference pricing 2018); Rx-TB (Tuberculosis market-shaping strategy, Stop-TB 2017); Rx-RH (RHInterchange); Vx (UNICEF, WHO recommendations for immunization 2018); Dx (Global Fund, USAID, UNICEF, WHO)

6A Overview of countries participating in the WHO Collaborative Registration Procedure for FPPs and vaccines



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization (WHO) concerning the legal status of any country, territory, city or area of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on map represent approximate border lines for which there may be not yet be full agreement.

SOURCE: WHO website, status August 2018

Prior to introduction of CRP, approval timelines were up to 18 months as a median

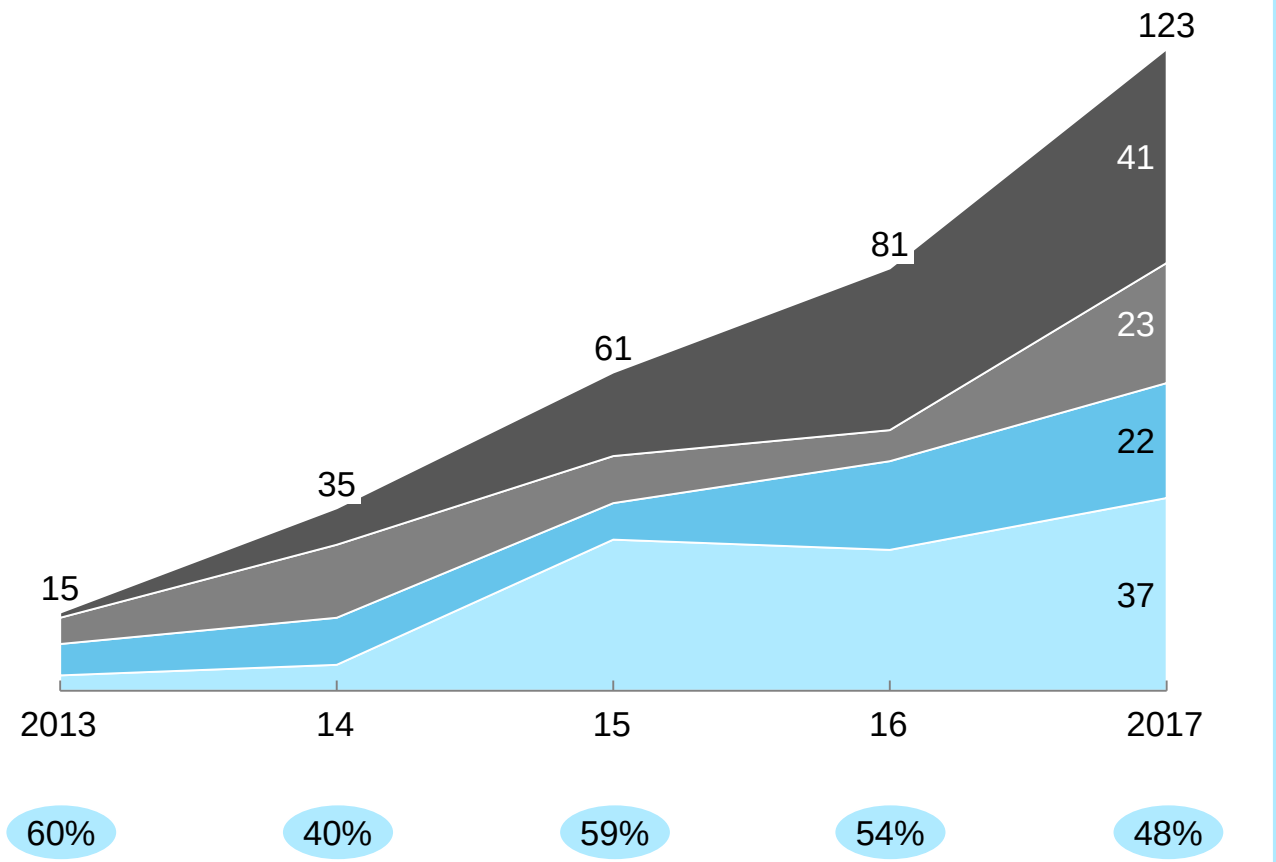
Registration pathway		Typical duration in months, median				
		Step 1	Step 2		Step 3	
		1st regulatory authority (RA) approval time	PQ approval time	Gap from 1st RA approval to 1st SSA NRA submission	Spread from 1st SSA NRA submission to last SSA NRA submission[1]	Sub-Saharan Africa (SSA) NRA approval time
Drug	Novel, SRA first	*10 months* n=44 drugs	*4* n=20	*9* n=12	*52* n=10	*11* n=100 reg. for 10 Rx
	Generic, NRA first	~12	*27* n=131	~3-6	~24	~18
Vaccine	SRA first	*15* n=33	*16* n=26	*5* n=11	*78* n=8	*16* n=61 reg. for 14 Vx
	NRA first	~12	*16* n=23	~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: Gates Foundation: 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

6A The number of CRP registrations has steadily increased…

of CRP registrations[1] by time to registration (FPPs only), *# CRP*



- The number of CRP registrations has steadily increased since the inception of the CRP for FPPs (x8 in 4 years)
- About 50% of the CRP exceed the 90 days time limit set by the WHO CRP guidelines with some fluctuation between 2013 and 2017

1 Single registrations, i.e. counted multiple times per product (separately for each country)

SOURCE: WHO CRP database

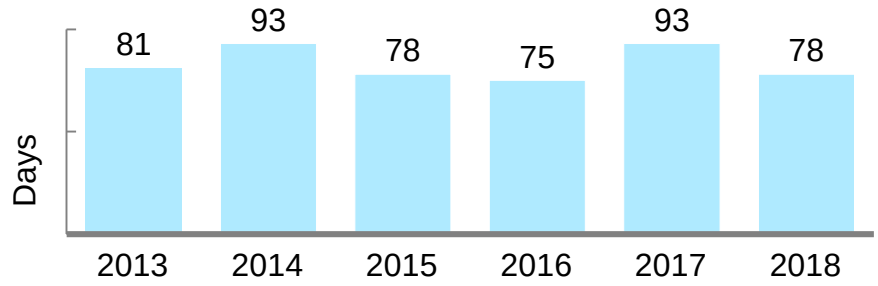
6A NRA relying on CRP have achieved significant acceleration of approval timelines vs pre-CRP registrations

Prior to introduction of CRP...

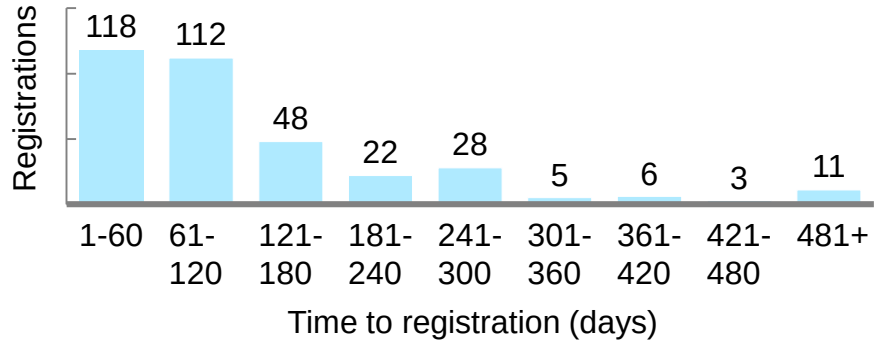
Registration pathway		NRA approval time (Sub-S. Africa)
Drug	Novel, SRA first	*11 months = 330+ days*
	Generic, NRA first	~18 months = ~550 days

...after introduction of CRP

Average time to registration in NRAs using CRP (days)

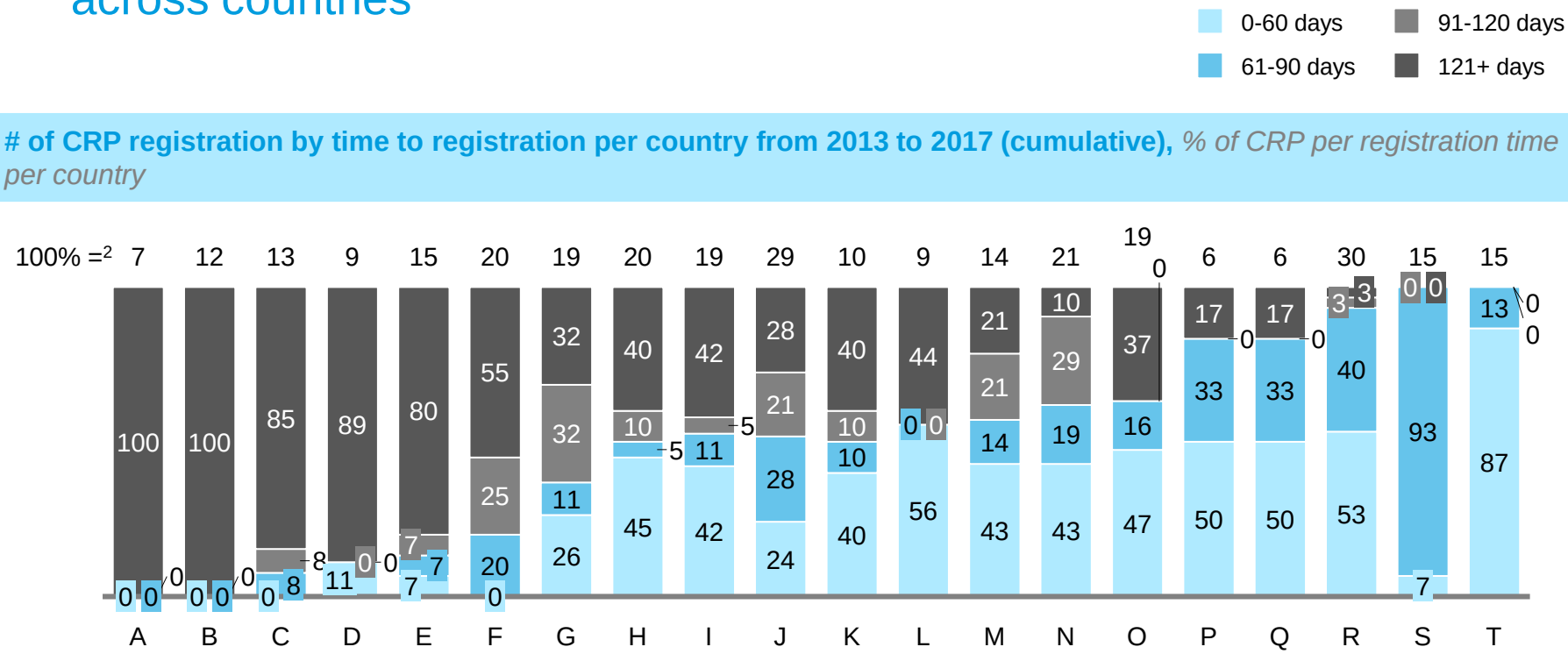


Distribution of CRP registrations based on time to registration



SOURCE: Gates Foundation: 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

6A …but there are high variations in terms of speed to approval across countries

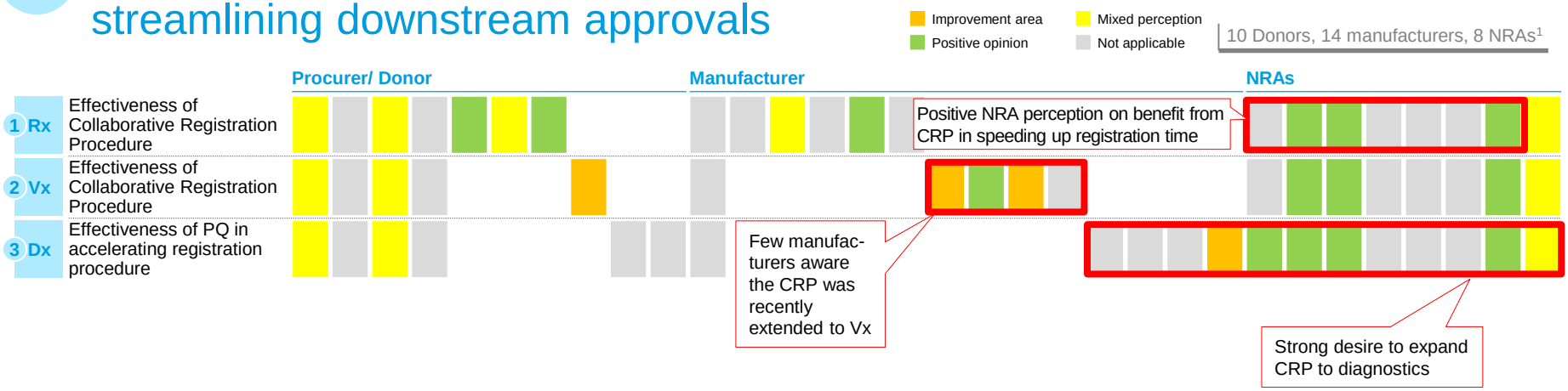


- High variation in terms of speed of approval across LMIC
- Some countries extensively use the CRP and stay below 90-day limit (e.g., CARICOM, Philippines, Malawi), others use the CRP less frequently and do not meet their 90-day commitment (e.g., DRC, Burundi)

1 Single registrations, i.e. counted multiple times per product (separately for each country)

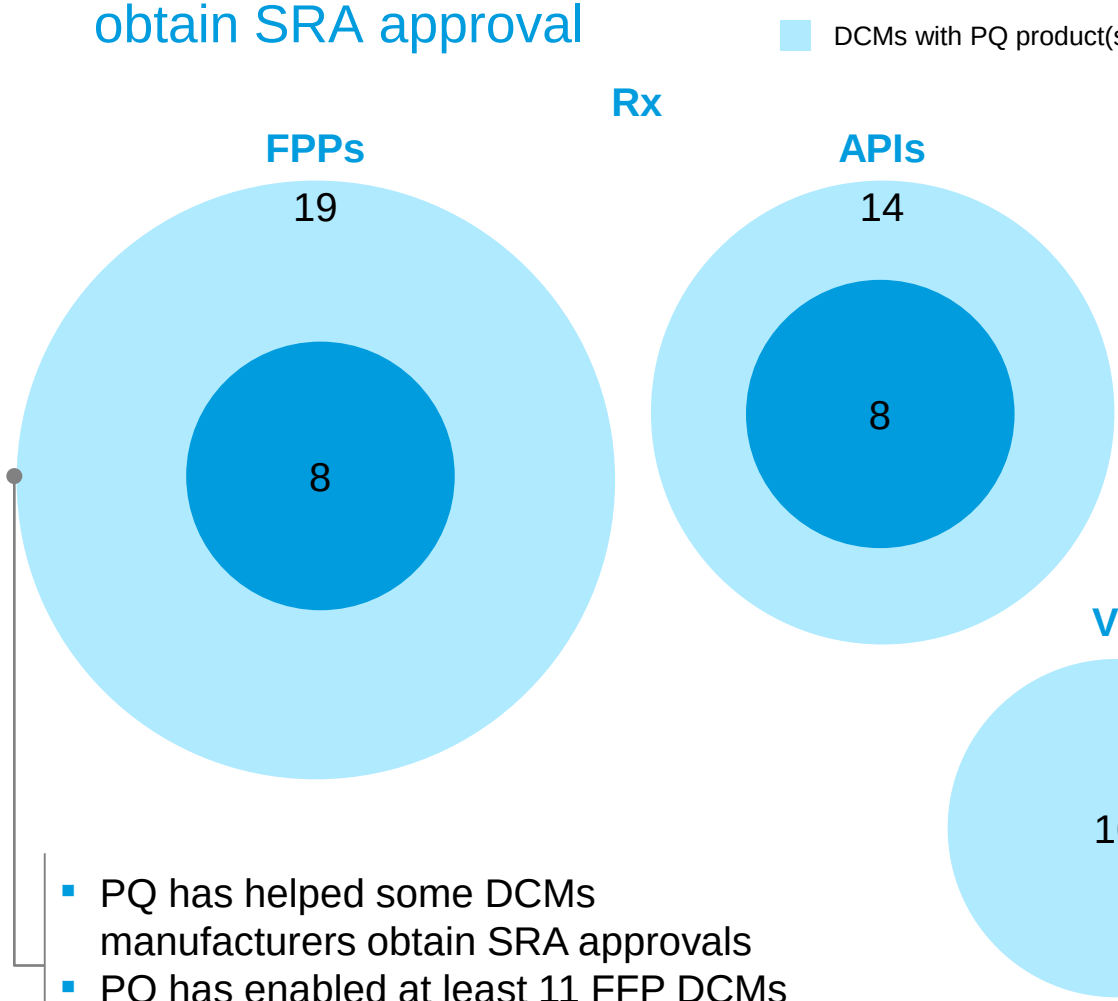
SOURCE: WHO PQ team, CRP database

6B Manufacturer, procurer/donor, NRA perception of value add on streamlining downstream approvals



1 Only stakeholders that provided scores listed.

7A PQ has enabled some medicines manufacturers from LMIC[1] obtain SRA approval



- PQ has helped some DCMs manufacturers obtain SRA approvals
- PQ has enabled at least 11 FFP DCMs to enter donor funded market

- Only 1 DCM managed to have PQ products
- 9 DCMs had products withdrawn or rejected by PQ
- For Diagnostics, CE-mark often easier to obtain than PQ (unlike SRA approval for Rx / Vx)

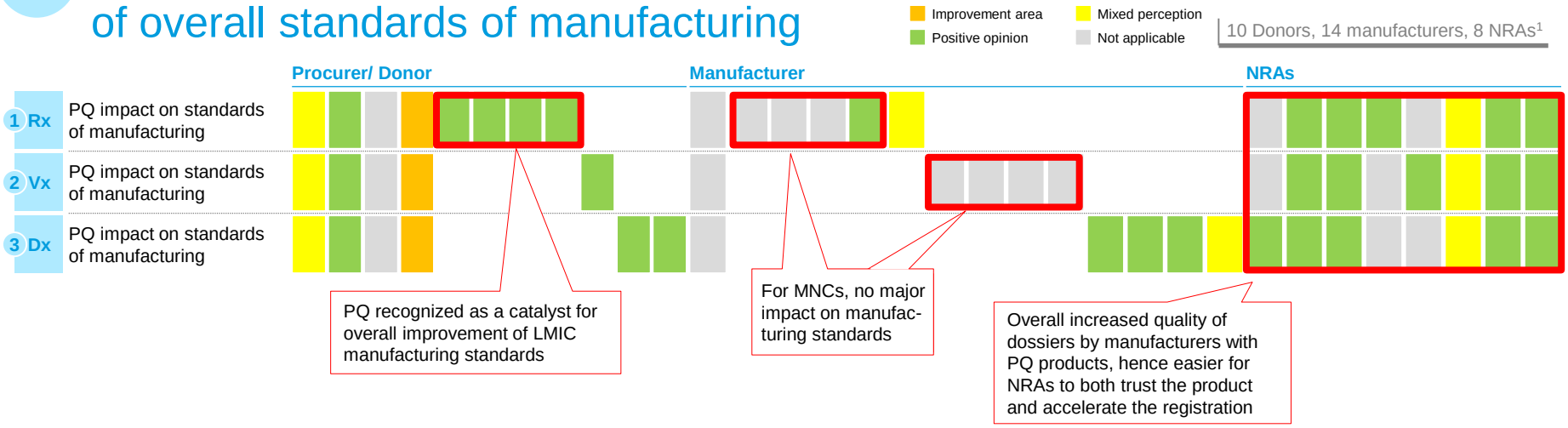
- PQ has enabled 10 DCVMs to enter donor funded market
- None of the DCVMs has products with SRA approval

NB: FDA approval (Rx/Vx) or CE-mark (Dx) used as proxy for SRA

1 Only considering DCMs from low income and lower middle income countries according to World Bank classification

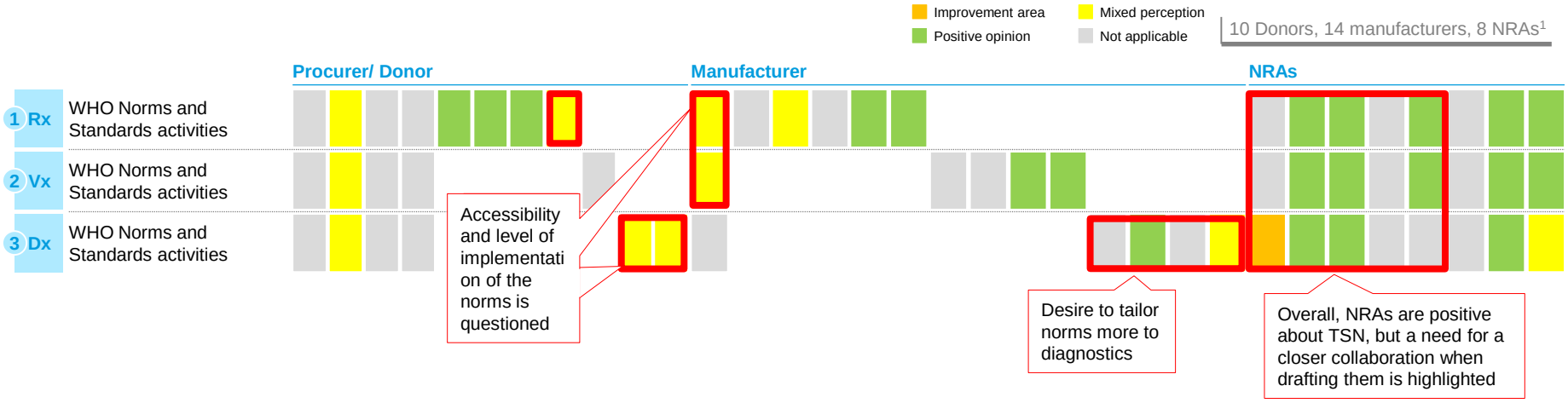
SOURCE: WHO PQ lists for FPPs, APIs, Vaccines and IVDs (as of 2018)

7B Manufacturer, procurer/donor, NRA perception on improvements of overall standards of manufacturing



1 Only stakeholders that provided scores listed.

8A Manufacturer, procurer/donor, NRA perception of utility of technical norms & standards

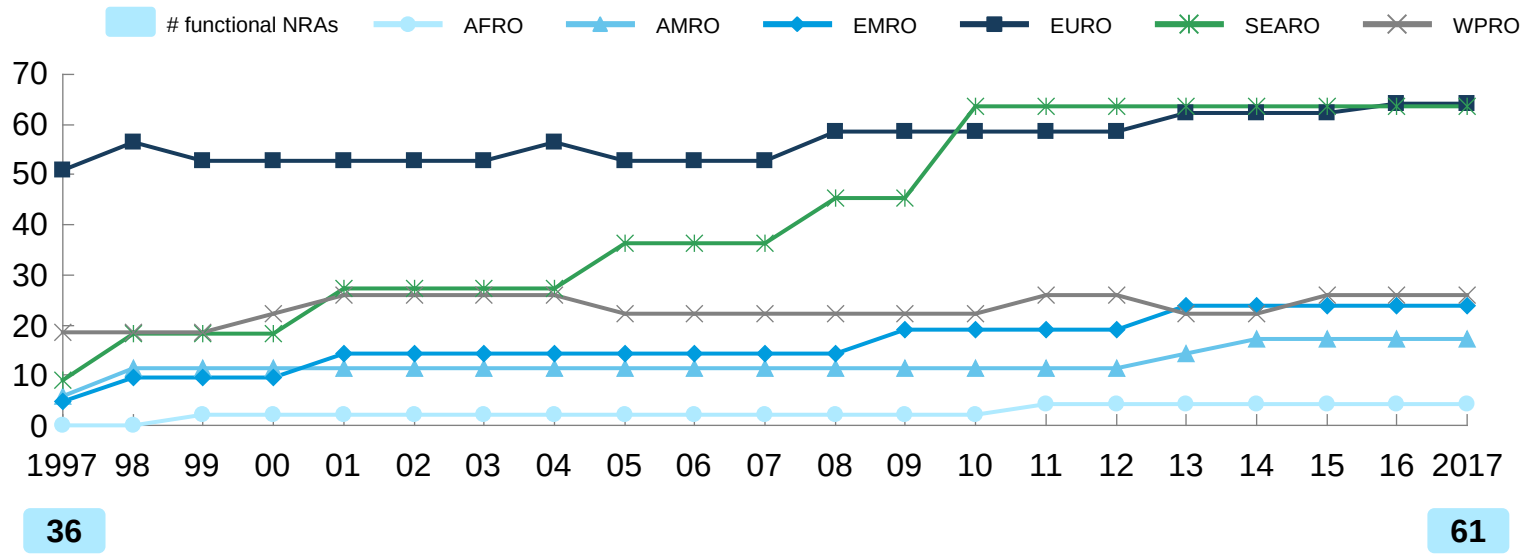


1 Only stakeholders that provided scores listed.

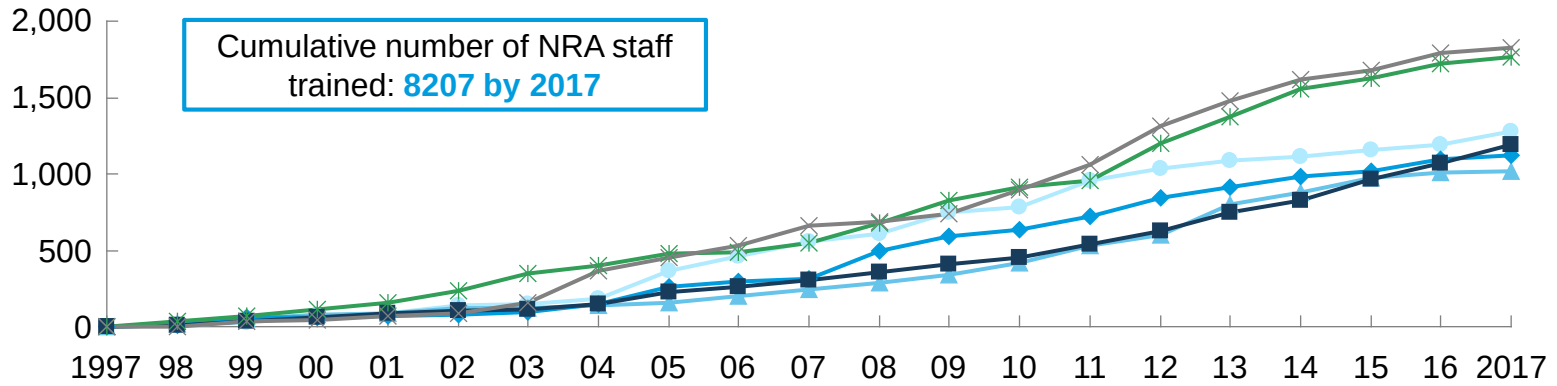
9A Since 1997, WHO trained more than 8000 NRA staff worldwide and number of functional NRAs increased by 70%

PRELIMINARY

Number of countries with functional NRAs 1997 to 2017, % by region[1]



Number of NRA staff trained from 1997 to 2017, by region

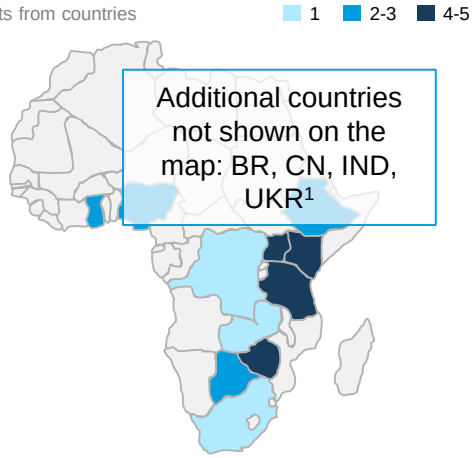


1 Majority of NRAs were assessed with respect to their vaccines regulatory system

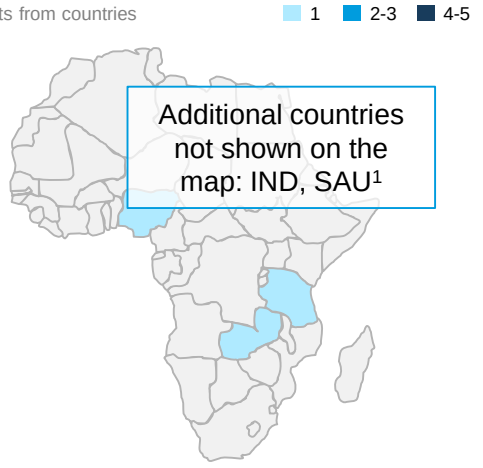
SOURCE: WHO RSS team

9A NRA capacity building through trainings by PQ Rx, Vx, Dx teams

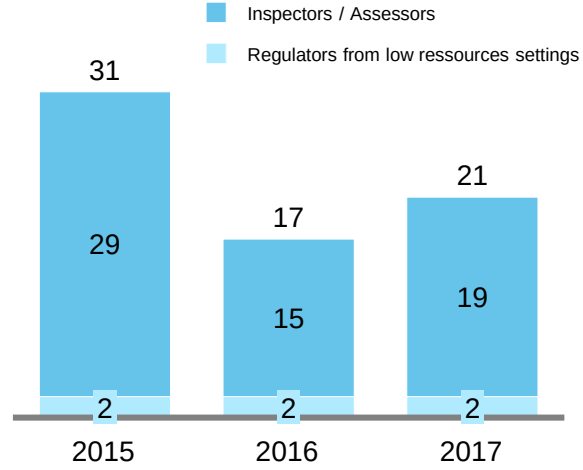
Rx: *Countries that participated on the 3 month rotational program*



Vx: *Countries that participated on the 3 month rotational program*



Dx: *NRA staff trained on assessment/inspection*



Additional activities

- Since 2001, a total of **1983 assessor-visits** (43% coming from LMIC).
- **6 CPH sessions per year** (more than 100 sessions since 2001)
- On average, **37 assessors attended each Copenhagen session** (over the last 54 sessions)
- Countries with the highest number of assessors[2]:
  - Uganda
  - Tanzania
  - Ghana
  - Zimbabwe
  - Kenya

Additional activities

- Experts from listed countries below are **actively contributing** to the activities conducted by the Vx team (e.g., 3 session of review of dossiers per year, post PQ activities).
  - **AMRO** (Argentina, Brazil, Canada, Cuba, Venezuela)
  - **WPRO** (Australia)
  - **EURO** (Belgium, France; Germany, Netherlands)
  - **SEARO** (China[3], India[3], Indonesia[3], Republic of Korea[3], Thailand, Vietnam[3])
  - **AFRO** (Ghana, Nigeria; South Africa)

Additional activities

- **Annual assessors/inspectors** meetings:
  - 22 people in 2015
  - 22 people in 2016
  - 19 people in 2017

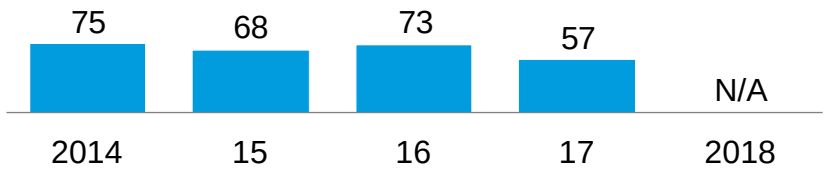
1 One participant from each of the countries mentioned
2 Around 25% of all assessor participation since 2010
3 Country where NRAs participate in briefing workshop to manufacturers on a regular basis

9A Four types of inspection-related capacity building activities are held to support local NRAs

Participation over time, # of participants

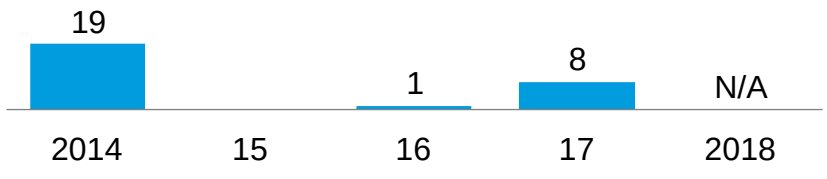
Description

Training of local in-country NRA inspectors



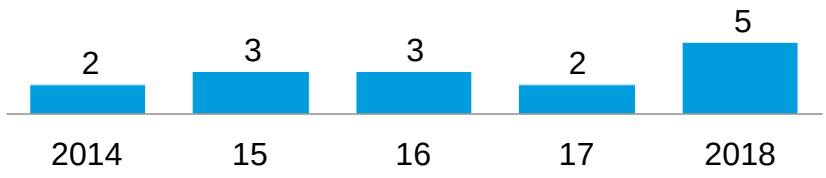
- Local NRAs, invited by WHO, send inspectors as observers to attend local inspections; local observers present in ~80% of inspections

Participation of NRA inspectors in WHO inspect-ions as observer inspectors



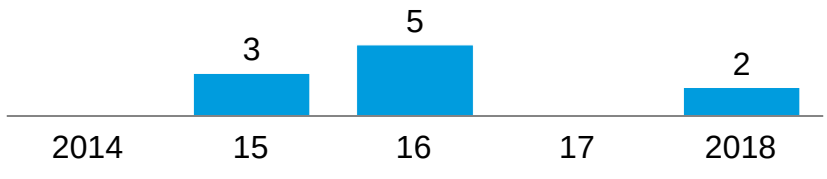
- NRAs invited to nominate inspectors to participate
- 1 Asian and 11 African countries represented

Rotational inspector program



- NRA inspectors spend 3-4 months at WHO HQ as rotational inspectors
- 2 Asian (7 inspectors), 7 African (7), and 1 South American (1) countries represented
- 1 diagnostics inspector participated

Invitation of ex-rotational NRA inspectors as co-inspector



- NRA inspectors get opportunity to further their training with WHO

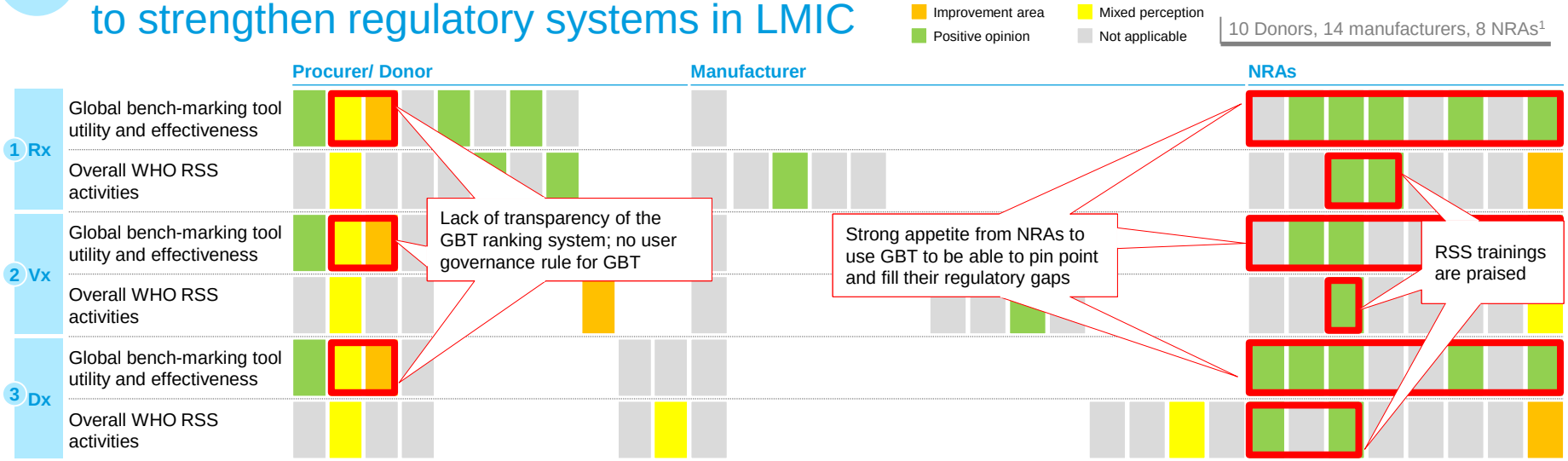
In addition to these training programs, WHO organizes training and workshop seminars including: data integrity trainings (South Africa and Switzerland), joint workshops (e.g. Brazilian Ministry of Health, PAHO and UNFPA workshop), bioequivalence training for Ethiopia in 2015 on inspection of a clinical trial site

9B WHO GBT Performance Maturity Levels

WHO GBT Performance Maturity Levels

	1	2	3	4
ISO 9004	*No formal approach*	*Reactive approach*	*Stable formal system approach*	*Continual improvement emphasized*
WHO GBT	Some elements of regulatory system exist	Evolving national regulatory system that partially performs essential regulatory functions	Stable, well-functioning and integrated regulatory system	Regulatory system operating at advanced level of performance and continuous improvement
	Can be considered as functional if rely on other regulators for some specific functions		Target of WHA Resolution 67.20	Advanced/reference Regulatory Authorities

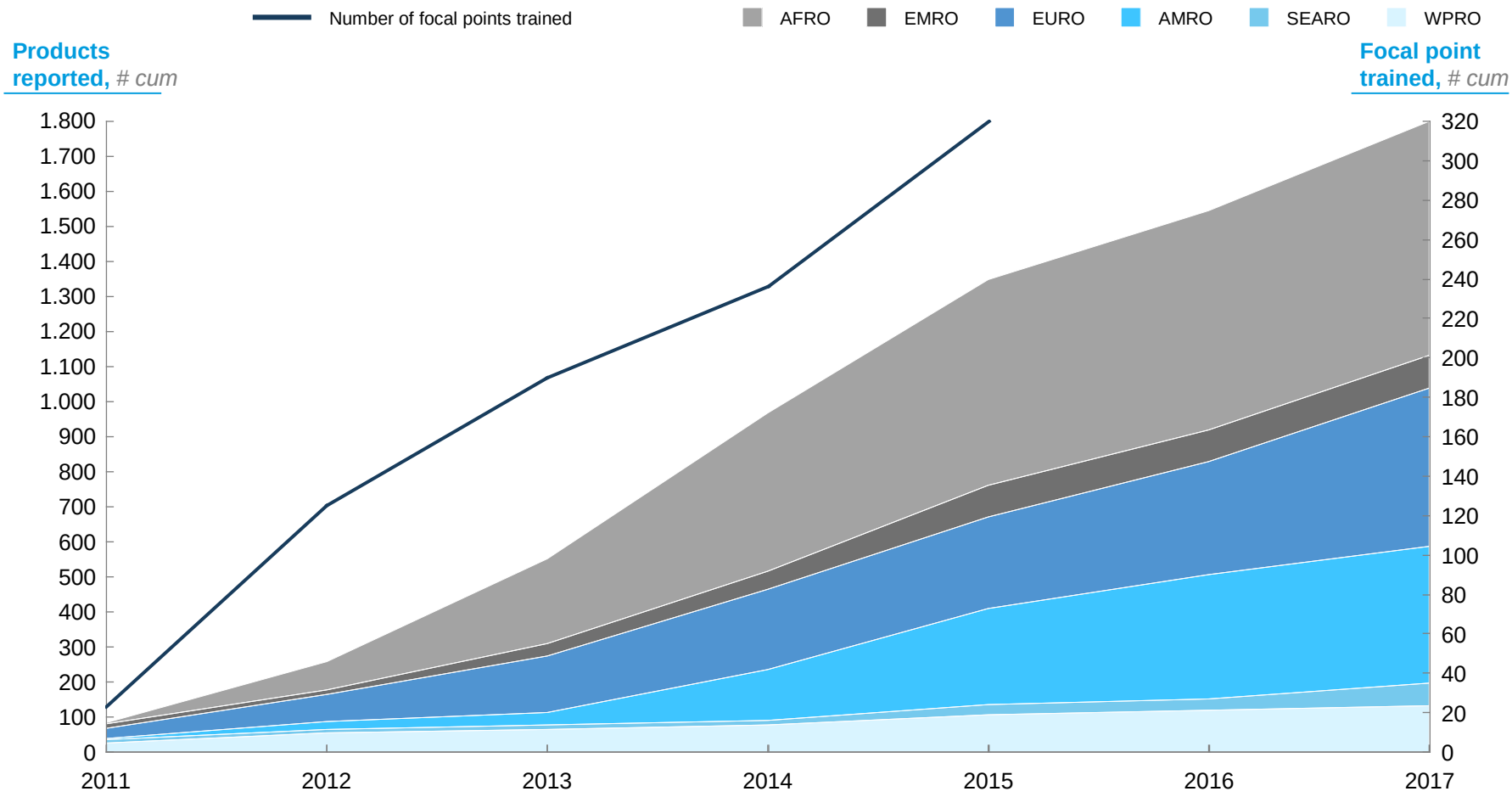
9B Manufacturer, procurer/donor, NRA perception of GBT and activities to strengthen regulatory systems in LMIC



1 Only stakeholders that provided scores listed.

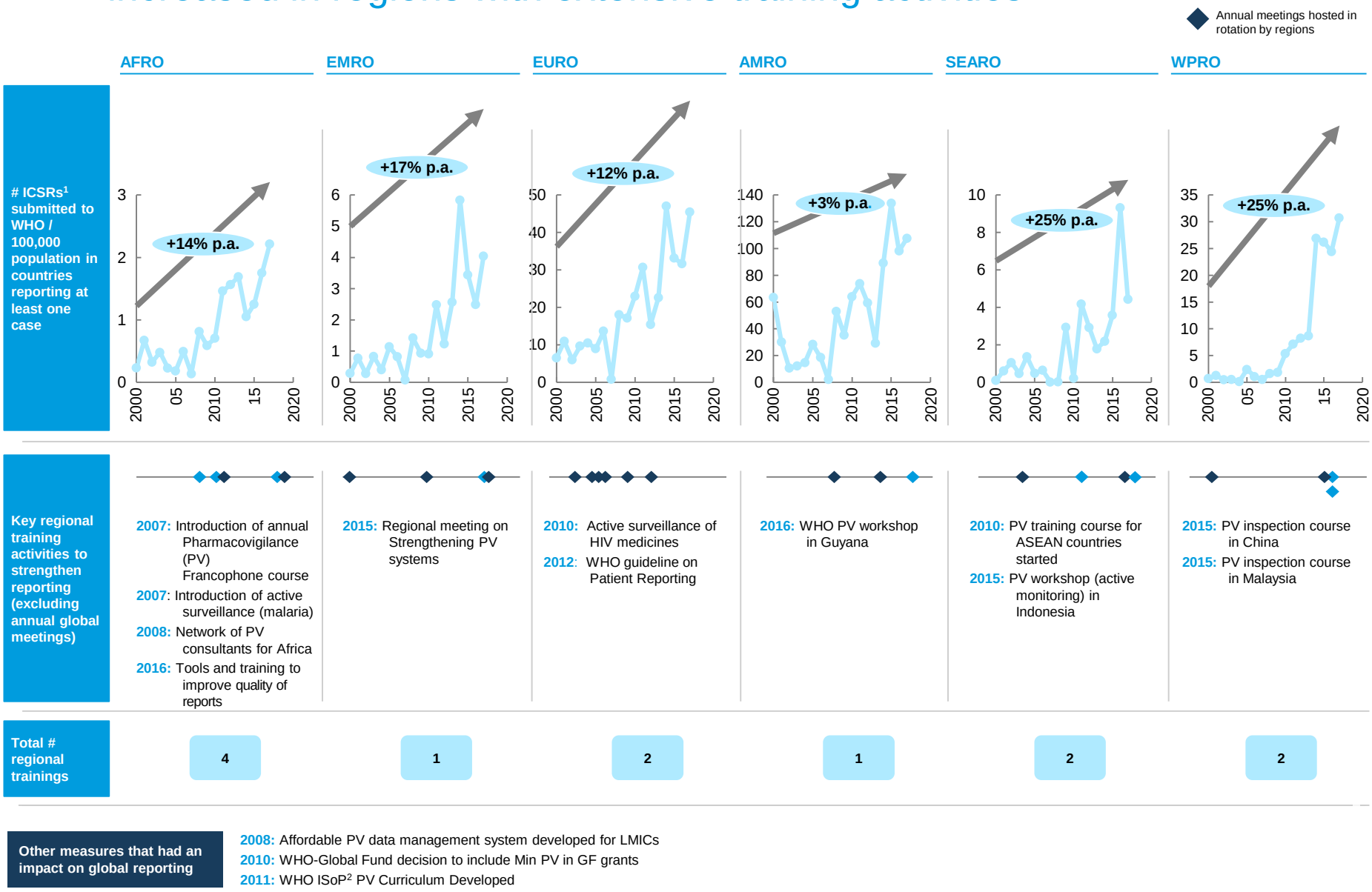
10A A positive correlation is observed between the number of substandard and falsified medical products reported and the number of trained focal points

Cumulative number of focal points trained and of SF products reported[1] to the WHO Global Surveillance and Monitoring System between 2011 and 2017



SOURCE: WHO Global Surveillance and Monitoring System (GSMS) 1 Not necessarily leading to adverse drug reaction

10A Number of reports on adverse events in medicines has increased in regions with extensive training activities



Other measures that had an impact on global reporting

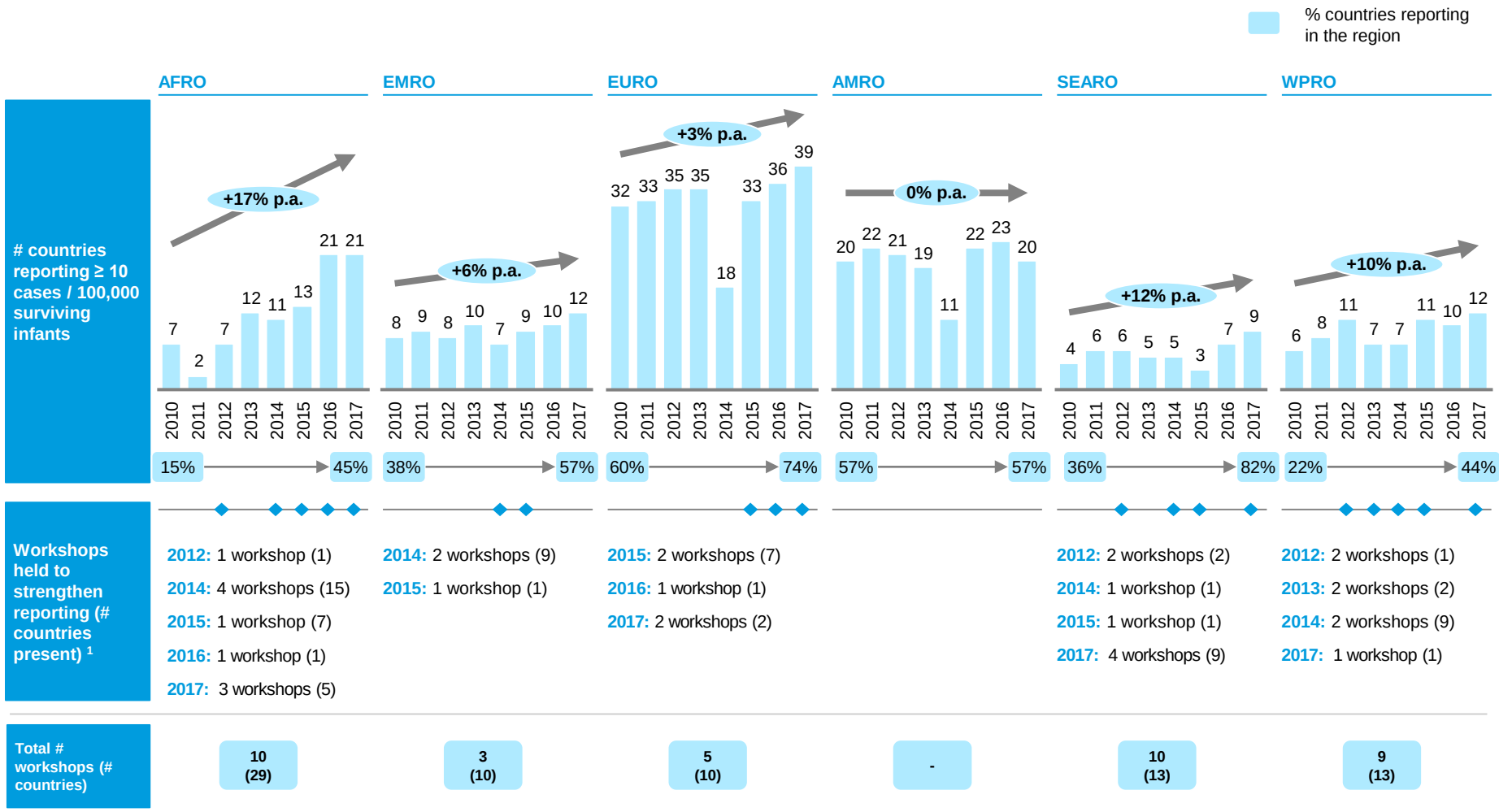
- **2008:** Affordable PV data management system developed for LMICs
- **2010:** WHO-Global Fund decision to include Min PV in GF grants
- **2011:** WHO ISoP[2] PV Curriculum Developed

SOURCE: WHO global database of ICSRs (VigiBase)

1 ICSR: Individual Case Safety Report

2 WHO International Society of Pharmacovigilance

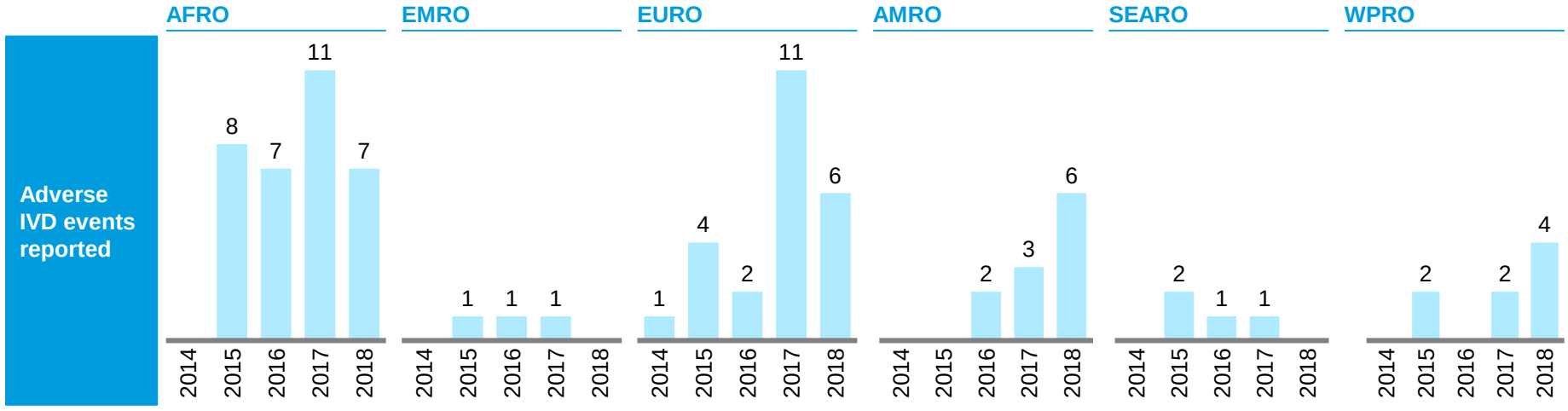
10A Number of countries with basic vaccine safety monitoring system has increased with workshops held in the regions[1]



1 Only workshops conducted by WHO HQ shown

SOURCE: WHO UNICEF JRF reports; WHO PQ team

10A While still at a low level, number of adverse events reported for diagnostics is concentrated in regions with trainings conducted



Trainings conducted

2016: Training for 9 Anglophone African countries[1]

2016: PMS session with at least 20 regulators

2017: Training for 11 Francophone African countries[2]

2018: Training for 11 Russo-phone European countries[3]

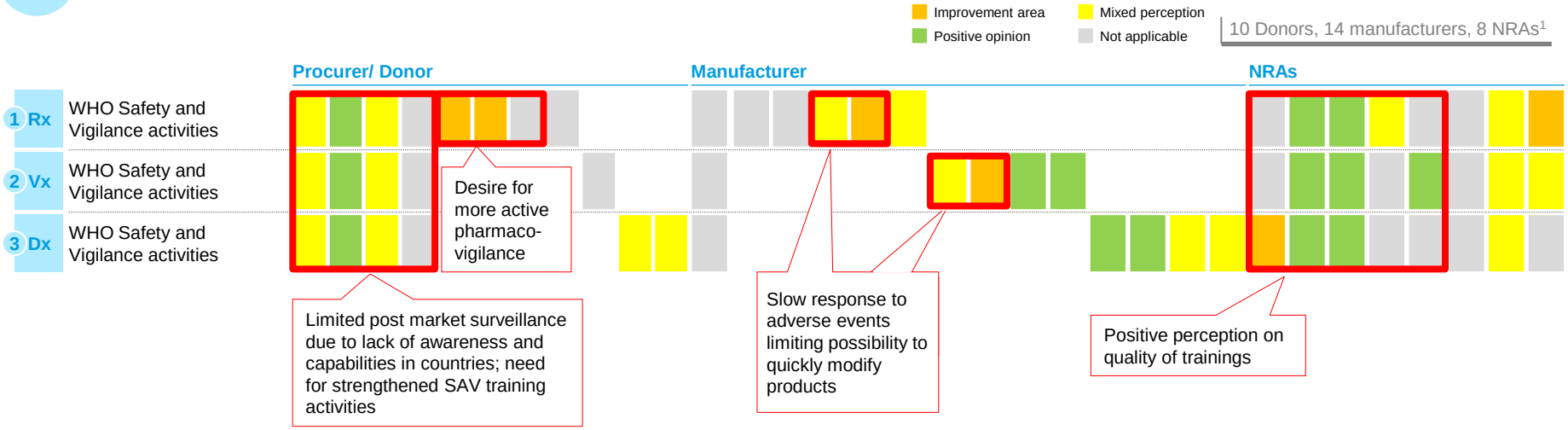
WHO's post market surveillance for Dx was **launched in 2015**, contributing to a limited number of trainings conducted so far

Total # trainings (# countries)	AFRO	EMRO	EURO	AMRO	SEARO	WPRO
	3 (20)	-	1 (11)	-	-	-

1 Burundi, Ethiopia, Kenya, Nigeria, Rwanda, Tanzania, Uganda, Zambia, Zimbabwe; 2 Benin, Burundi, Burkina Faso, Cameroon, Chad, Gabon, Guinea, Mali, Rwanda, Senegal, Togo; 3 Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Russia, Tajikistan, Turkmenistan, Ukraine

SOURCE: In-vitro Diagnostics complaint database

10B Manufacturer, procurer, NRA perception of utility of SAV activities



1 Only stakeholders that provided scores listed.

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