WHO/UNAIDS ANNUAL MEETING WITH PHARMACEUTICAL COMPANIES AND STAKEHOLDERS

Session V: Regulatory & quality assurance aspects

Update on prequalification of ARVs and regional harmonisation of medicine registration

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D-Building – UNAIDS

Kofi A. Annan Meeting Room

Acknowledgements:

- **Matthias Stahl**
- **Milan Smid**
- **Antony Fake**
- **Jacqueline Sawyer**
- **Iveta Streipa**

Wednesday, 9 March 2016

11:15 – 11:30

World Health Organization

WHO PREQUALIFICATION TEAM

WHO prequalification

Update on prequalification of ARVs

- **WHO-PQT: Goal, strategy & outputs**
- **EOI: List of invited products and APIs**
  - ✓ number prequalified or currently under assessment per product
- **PQT process**
  - ✓ Options of submitting API data for FPP PQ – advantage of using prequalified API.
  - ✓ Simplified procedure for amendment of APIMF
- **Numbers – prequalified FPPs and APIs**
- **Timelines for inspection – numbers for 2015**
  - ✓ Worrying Trends – signs of hope
- **Benefits of PQ for stakeholders**

Goal, strategy & outputs

→ *The mission of WHO prequalification is to ensure timely availability of quality-assured health products for the prevention, diagnosis and treatment of priority diseases in low- and middle-income countries*

Goal

- Make quality priority products available in a consistent and timely manner
- Ensure sustainable supply of quality-assured products
- Create national capacity to evaluate and monitor the ongoing quality of products

Strategy

- Apply and promote unified quality, safety and efficacy/performance standards, for a comprehensive evaluation of health products
- Build the capacity of staff from NRAs, QC labs, manufacturers or CROs

Key outputs

- List of prequalified products and QCLs
- WHO public reports
- Accelerated national registration of prequalified products
- Increased regulatory capacity at national level
- Improved GMP and QMS

Product eligibility

→ *Based on WHO Member States needs, WHO disease programmes set eligibility criteria and determine priorities for prequalification*

- ✓ Medicinal products included on the 13th Invitation
- ✓ http://apps.who.int/prequal/info_applicants/eoi/2015/EOI-HIV-v13.pdf

- ✓ List of all APIs and FPPs invited for prequalification, and number prequalified or currently under assessment per product
- ✓ http://apps.who.int/prequal/info_applicants/eoi/FPPs_APIs_invited.xlsx

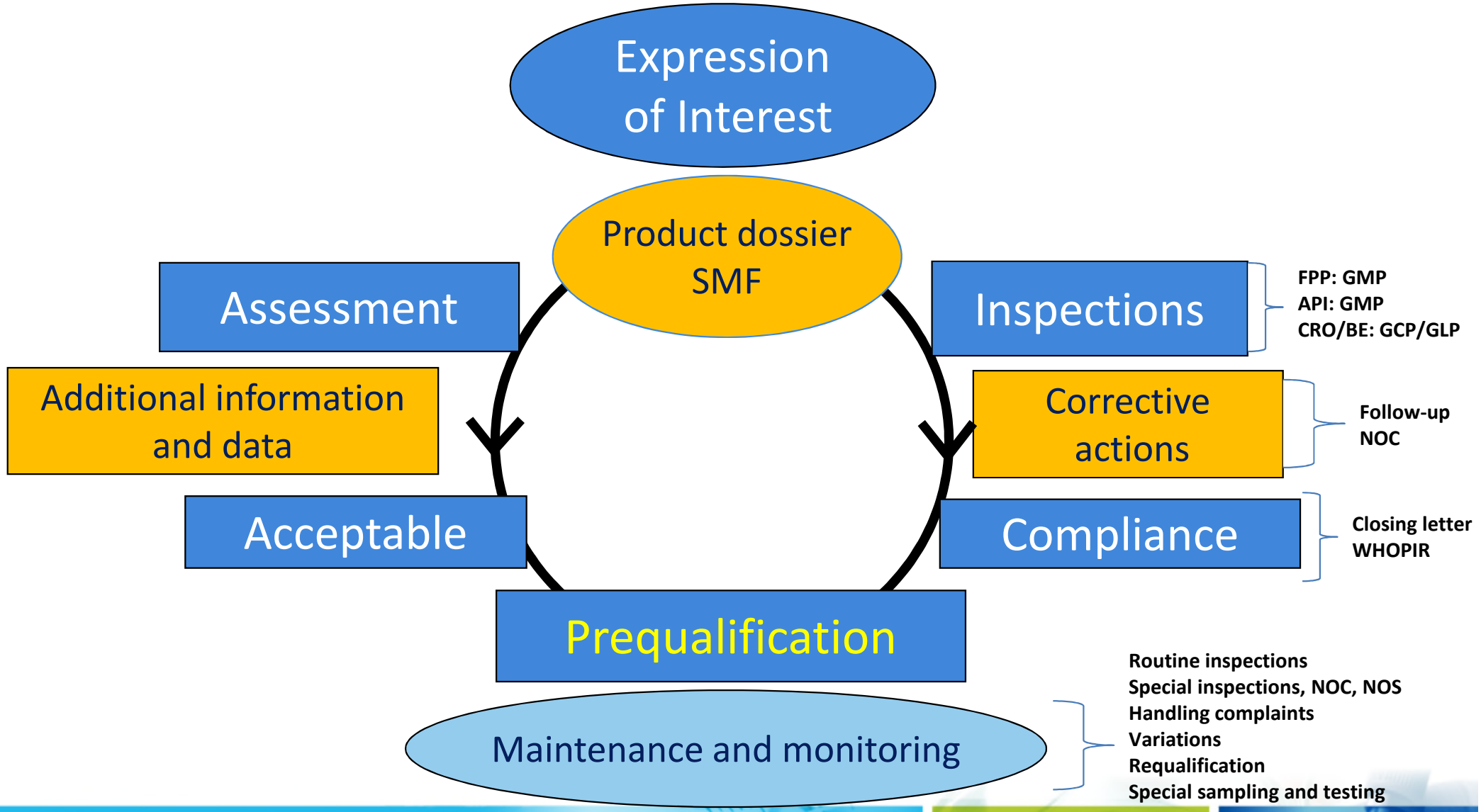
APIs included in the 9th Invitation

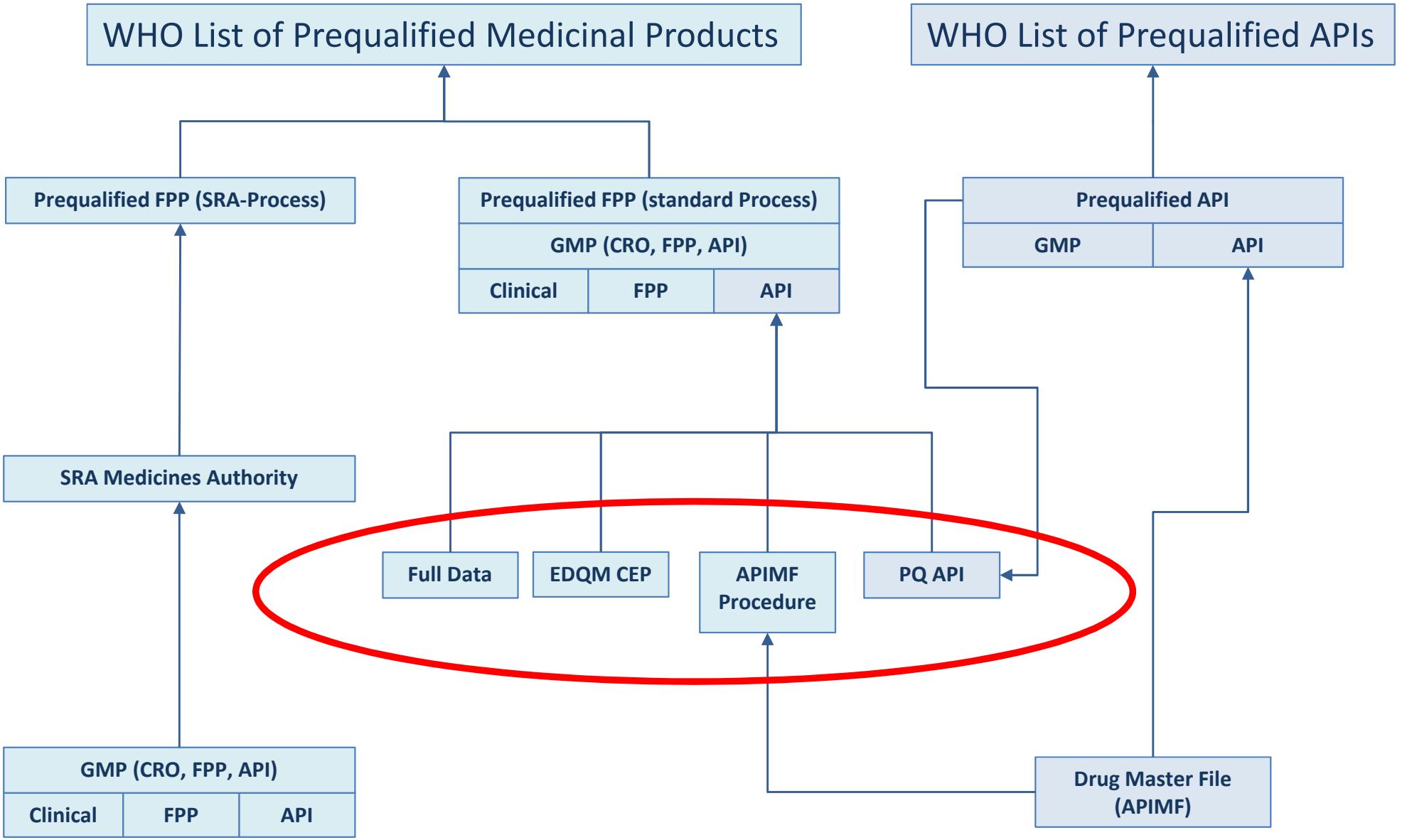
APIs for HIV, Hepatitis B, C and related diseases medicinal products

http://apps.who.int/prequal/info_applicants/eoi/2016/API-EOI_V9-2.pdf

- ✓ Abacavir
- ✓ Atazanavir
- ✓ Ceftriaxone
- ✓ Daclatasvir
- ✓ Darunavir
- ✓ Dasabuvir
- ✓ Dolutegravir
- ✓ Efavirenz
- ✓ Emtricitabine
- ✓ Entecavir
- ✓ Etravirine
- ✓ Lamivudine
- ✓ Ledipasvir
- ✓ Lopinavir
- ✓ Nevirapine
- ✓ Ombitasvir
- ✓ Paritaprevir
- ✓ Raltegravir
- ✓ Ribavirin
- ✓ Ritonavir
- ✓ Simeprevir
- ✓ Sofosbuvir
- ✓ Tenofovir
- ✓ Valgancyclovir
- ✓ Zidovudine

WHO-PQm process




WHO List of Prequalified Medicinal Products
WHO List of Prequalified APIs
Prequalified FPP (SRA-Process)
Prequalified FPP (standard Process)
GMP (CRO, FPP, API)
Clinical
FPP
API
Prequalified API
GMP
API
SRA Medicines Authority
Full Data
EDQM CEP
APIMF Procedure
PQ API
GMP (CRO, FPP, API)
Clinical
FPP
API
Drug Master File (APIMF)

Option 1: Use of a prequalified API

Advantages:

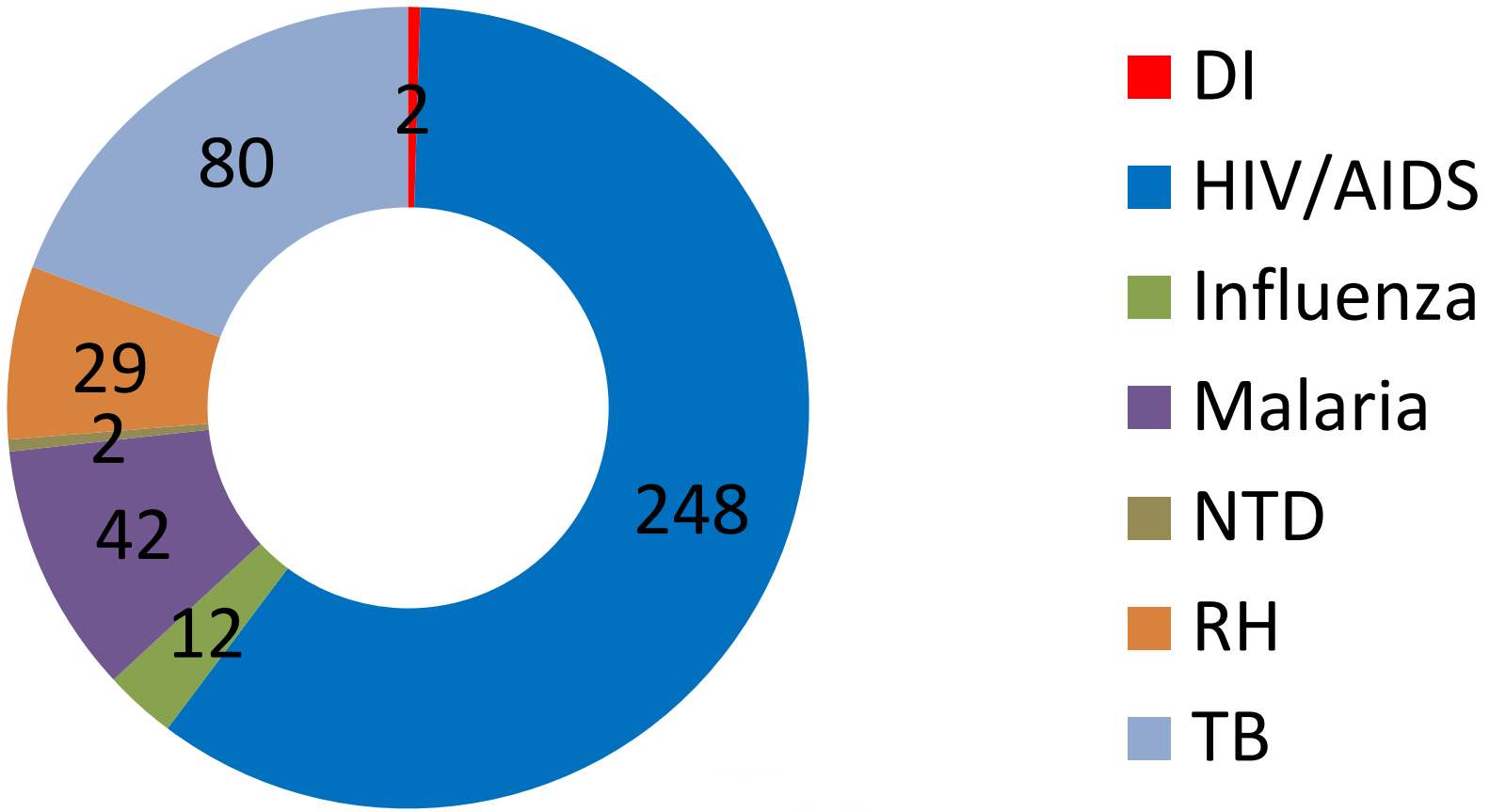
- **Both the APIMF and GMP have already been assessed and found to be acceptable.**
- **There will be no delay to the FPP assessment due to API issues.**

API Changes (Amendments)

- **Ensuring the on-going quality of accepted APIs is as important as the initial approval.**
- **Changes to API details are handled through the APIMF Amendment Guidance.**
- **The API Amendment guidance was revised in June 2014 to:**
  - Increase the number of changes manufacturers may implement without prior consent
  - Improve the efficiency of the overall process in the face of increasing numbers of amendment applications.
- **The success of these revisions is beginning to be seen in the amendment assessment times.**

ACTIVE PHARMACEUTICAL INGREDIENTS (APIs) - Total numbers of APIMFs (API Prequalified or seeking API Prequalification)		
APIs FOR MEDICINAL PRODUCTS FOR HIV AND RELATED DISEASES	Accepted APIMFs (API Prequalified)	Under assessment (seeking API Prequalification)
Abacavir	4 (2)	
Acyclovir		1 (0)
Atazanavir	1 (1)	5 (2)
Ceftriaxone		
Daclatasvir		
Darunavir		3 (1)
Dasabuvir		
Dolutegravir		2 (1)
didanosine		2(0)
Efavirenz	5 (3)	2 (1)
Emtricitabine	7 (3)	1 (1)
Entecavir		
Etravirine		1 (1)
Lamivudine	8 (4)	1 (1)
Ledipasvir		
Lopinavir	2 (1)	1
Nevirapine	9 (3)	
Ombitasvir		
Paritaprevir		
Raltegravir		
Ribavirin		
Ritonavir	7 (3)	
Simeprevir		
Sofosbuvir		3 (1)
stavudine	2 (0)	1 (0)
Tenofovir	9 (5)	4 (4)
Valgancyclovir		1 (0)
Zidovudine	7 (4)	2 (0)

Products in the PQ list as of March 4, 2016



WHO-PQT-Rx: Target Inspection Timelines

- ✓ **First inspection:** 6 months from dossier acceptance for assessment or from site confirms it is ready.
- ✓ **Surveillance/Routine monitoring inspection:**
  - ✓ **due date:** risk-based, 1 – 3 years from date of previous inspection
  - ✓ **Actual date:** ± 3 months from due date.
- ✓ **Notification:**
  - ✓ Announced: 1 – 2 months before inspection.
  - ✓ Unannounced/shot announced: 0 – 7 days before inspection
- ✓ **Onsite days:** 3 – 5 days.
- ✓ **Report:** 30 days from last date of inspection.
- ✓ **CAPAs:** 30 days from receipt of report (max 2 rounds, comprehensive, on CDs and not hard copies)
- ✓ **Closing of inspection:** 6 months from inspection.
- ✓ **Follow-up inspection:** 6 months from inspection

NUMBER OF INSPECTIONS			
	2013	2014	2015
1. MEDICINES			
FPP SITES	34	39	25
API SITES	22	32	34
CRO SITES	11	11	8
QCL SITES	16	12	12
TOTAL	83	94	79
2. DIAGNOSTICS		24	14
3. VACCINES		10	15

- **High number of inspections - good oversight of manufacturing and testing facilities.**
- **Reduced number in 2015 due to many special inspections for investigations and verification of data integrity**

Worrying Trends – signs of hope

Media is awash with NOCs, warning letters, import alerts, statements of non-compliance, complaints, recalls, etc.

- Data integrity and falsification
  - **The honest way is always the "right way"**
  - **unbalanced focus on QC (quality built in – not tested in).**
  - **New very good guidelines - WHO and MHRA**
- « Show-case » and « shadow » industries.
- « Knee-jerk » responses to inspection observations.
- Many « Awaits CAPAs » on routine inspection:
  - poor maintenance of quality systems
  - work hard to pass first inspection and then go on holiday

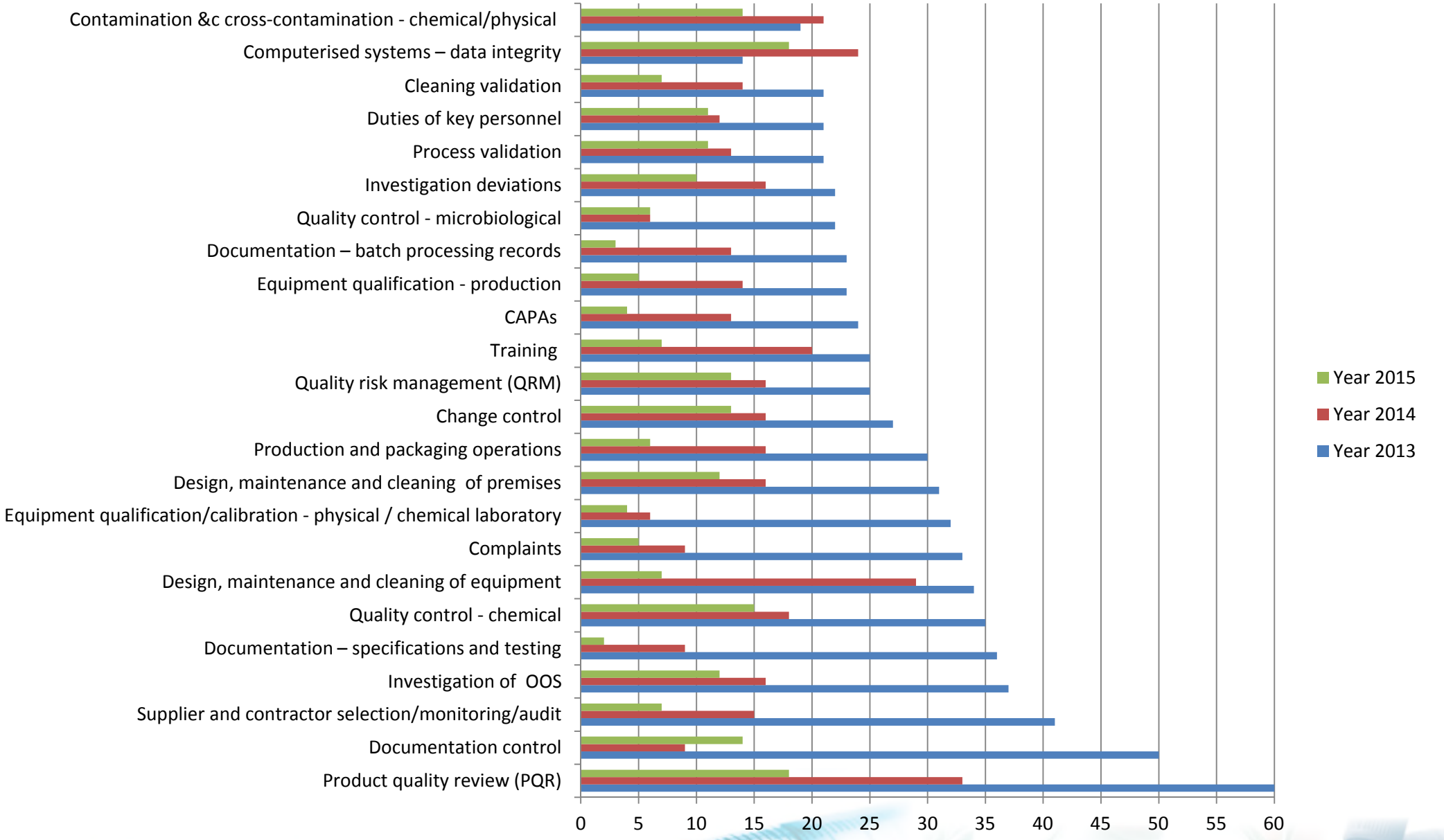
RESPONSES TO INSPECTION OBSERVATIONS (1)

- An inspection is a sampling exercise and by consequence not all aspects of the manufacturing process may be inspected.
  - The manufacturer is encouraged to take the information provided in the inspection report as examples and to consider **vertical and horizontal analysis** of the issues.
  - nonconformities described in the report that are designated to be of lesser degree of severity, may **increase in severity if not satisfactorily addressed in a timely manner**.

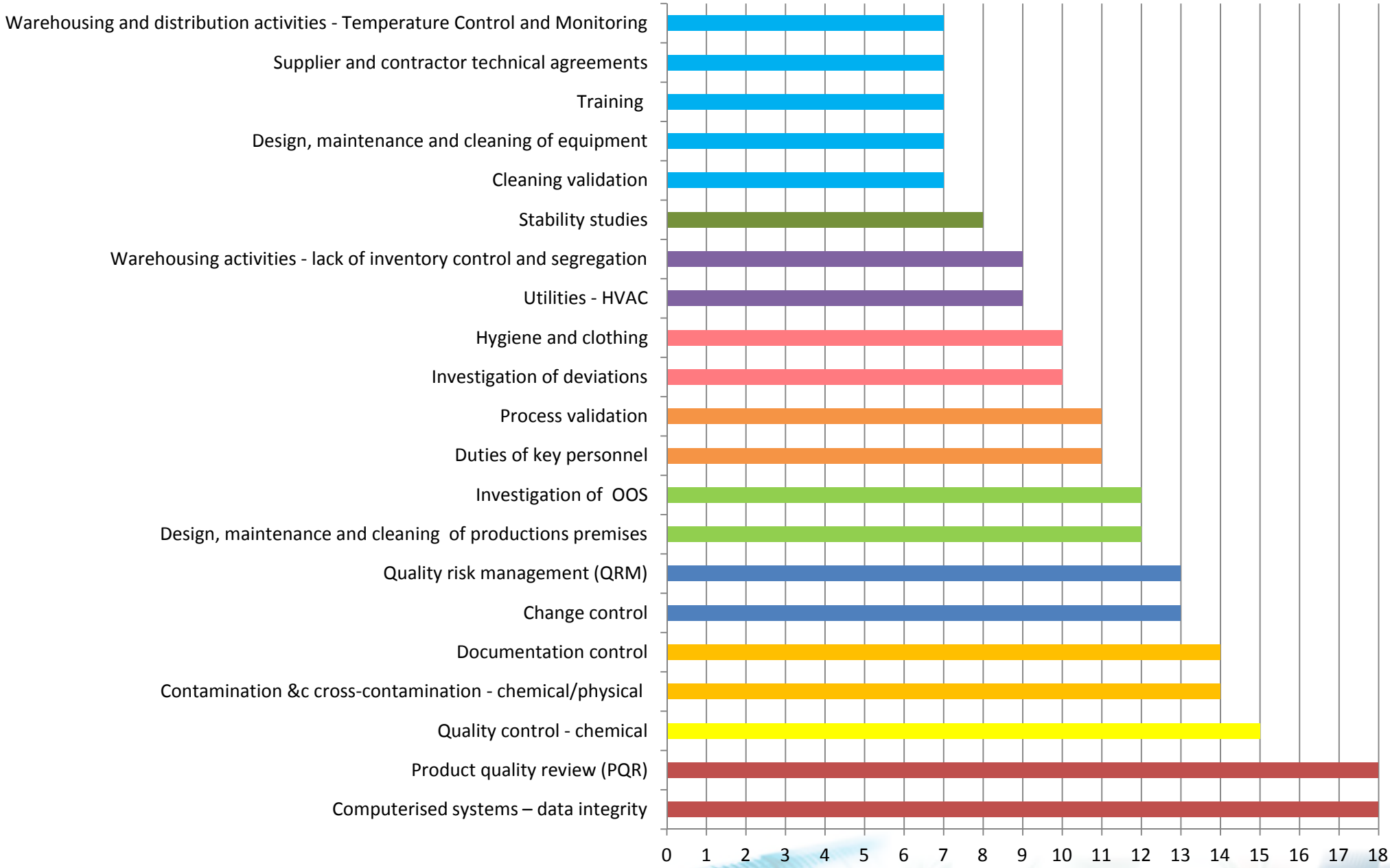
RESPONSES TO INSPECTION OBSERVATIONS (2)

- The manufacturer is required to submit an action plan in response to the observations and all nonconformities noted in the final inspection report within **30 days after receipt of the report.**
- **It is suggested that the action plan incorporates:**
  - root cause analysis (how/why did this happen),
  - analysis regarding related areas (is this same issue impacting/occurring elsewhere),
  - correction (fix now) with completion dates,
  - corrective action (to prevent recurrence) with completion dates and,
  - The plan for demonstration of effectiveness of the actions taken.

FPP: Top common deficiencies comparison 2013 (29 sites) - 2014 (32 sites) - 2015 (21 sites)



TOP 20 Major FPPs 14 re-inspected sites deficiencies 2015



Impact of Root-cause analysis:

- **The need for and the number of follow up inspections has reduced**

- **Number of site complying after first CAPAs has increased**

Benefits for 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*

Patients

- ✓ Access to quality-assured products, adapted to their specific needs
- ✓ Accurate prevention, diagnosis, and treatment

WHO Member States & NRAs

- ✓ Reduced burden for regulatory approval
- ✓ Increased regulatory capacity & harmonization of regulatory practices in WHO MS
- ✓ Implementation of specifically developed and road-tested international guidelines
- ✓ Access to quality-assured products

Donors, procurers and UN agencies

- ✓ List of prequalified products
- ✓ Increased availability of quality-assured products
- ✓ Monitoring quality of prequalified products
- ✓ Healthy market: diversity and affordability of products

Benefits for 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*

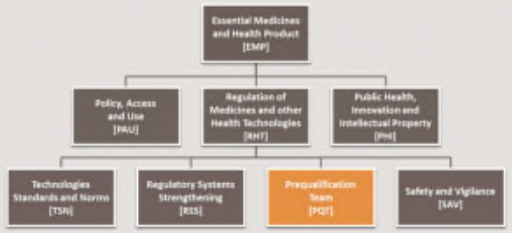
Manufacturers

- ✓ Access to donor-sponsored tenders
- ✓ Faster regulatory approval
- ✓ Timely assessment of variations and changes
- ✓ International quality-assured product status (improved image)
- ✓ Recognition of GMP status, beyond prequalified products
- ✓ Increased capacity in quality management systems
- ✓ Target Product Profiles
- ✓ Harmonization of regulatory practices within WHO Member States
- ✓ Reduced operating and manufacturing costs

QC labs

- ✓ International recognition of prequalified QCLs
- ✓ Technical assistance and scientific advice

Contacts



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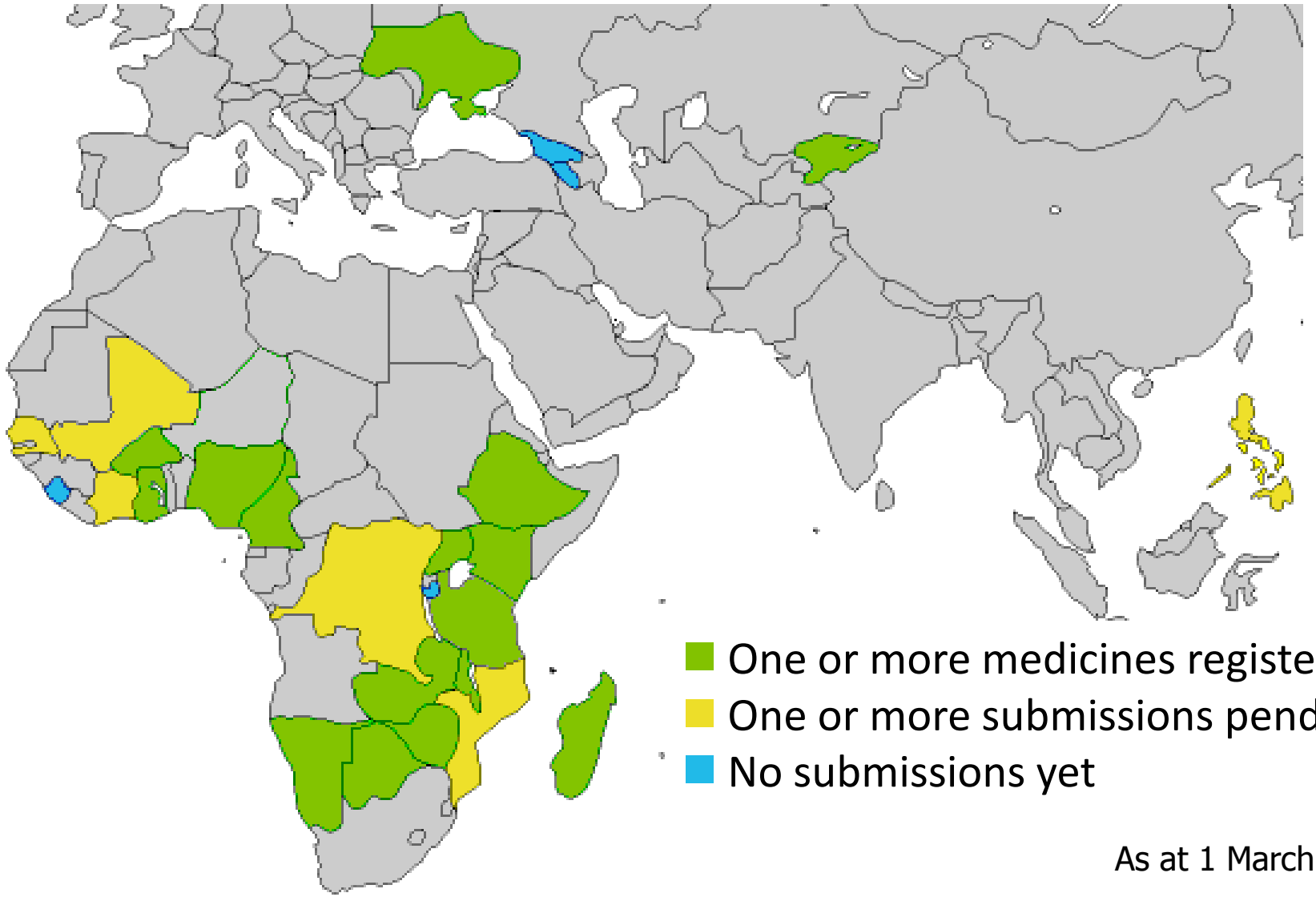
PQTm – support to manufacturers

- **Provision of information**
  - Website (guidelines, templates, statistics, reports)
  - Meetings, workshops, trainings
  - Face to face advice and consultations
- **Technical assistance (pre-inspections)**
- **Facilitation of national registrations**

http://who.int/prequal

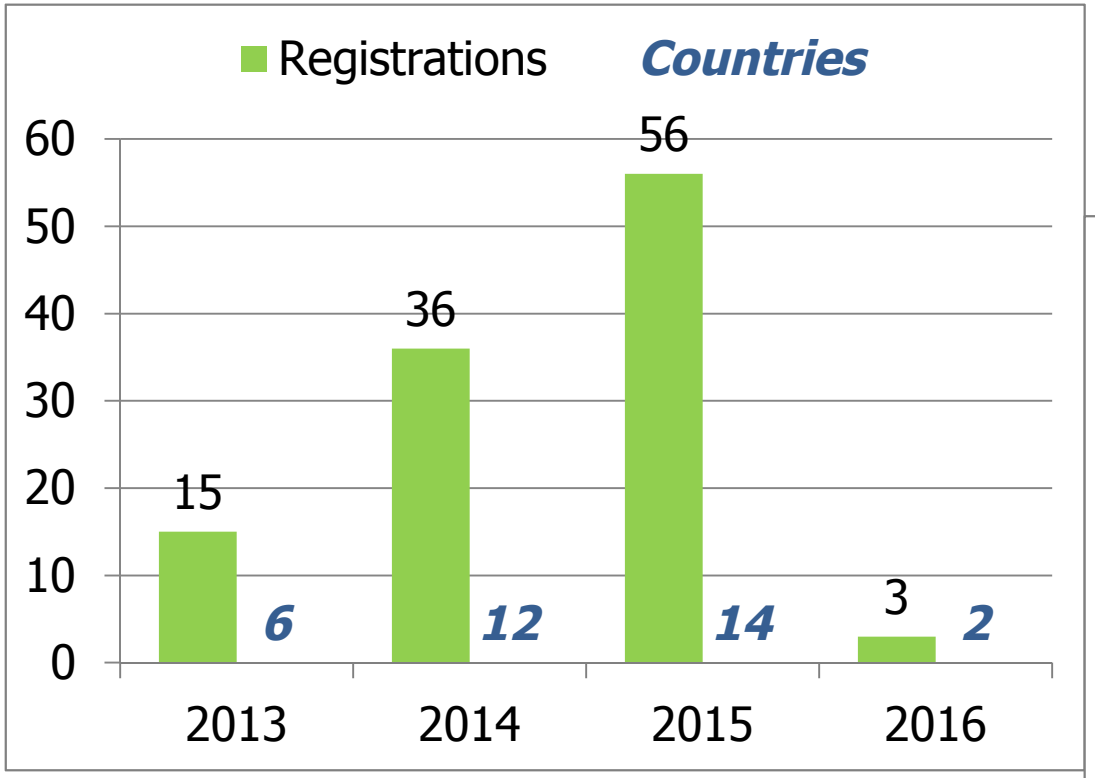
Participating NMRAs

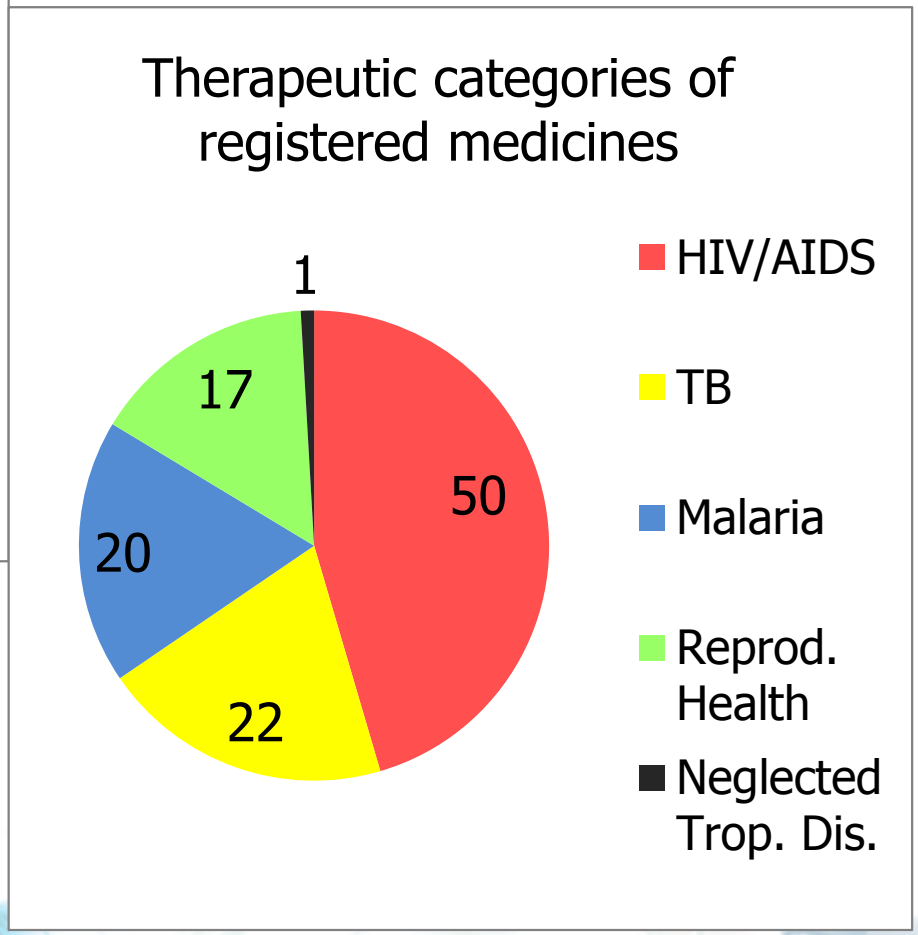


As at 1 March 2016

	PQ number	Notes	Product	Prequalification holder	Country	Registration date	Registration number
6	HA275		Lamivudine + Nevirapine + Zidovudine Tablets 150mg + 200mg + 300mg	Hetero Labs Limited	Namibia	6/Jun/13	13/20.2.8/0144
7	HA399		Efavirenz Tablets 600mg	Hetero Labs Limited	Ghana	7/Jul/14	FDB/SD.143-6055
8	HA436		Abacavir (as sulfate) + Lamivudine + Zidovudine Tablets 60mg + 30mg + 60mg	Mylan Laboratories Ltd	Zimbabwe	6/Feb/13	2013/7.13/4762
9	HA448		Lamivudine + Tenofovir disoproxil fumarate Tablets 300mg + 300mg	Hetero Labs Limited	Ghana	1/Oct/13	FDB/GD.133-9038
10	HA459		Lamivudine + Zidovudine Tablets 150mg + 300mg	Macleods Pharmaceuticals Ltd	Ukraine	29/Dec/14	UA/14139/01/01
11	HA473		Didanosine Delayed release capsules 250mg	Mylan Laboratories Ltd	Zimbabwe	6/Feb/13	2013/7.13/4763
12	HA492		Lopinavir + Ritonavir Tablets 200mg + 50mg	Hetero Labs Limited	Namibia	6/Jun/13	13/20.2.8/0145
13	HA492		Lopinavir + Ritonavir Tablets 200mg + 50mg	Hetero Labs Limited	Nigeria	19/Sep/13	B4-0455
14	HA492		Lopinavir + Ritonavir Tablets 200mg + 50mg	Hetero Labs Limited	Ghana	1/Oct/13	FDB/GD.133-9034
15	HA492		Lopinavir + Ritonavir Tablets 200mg + 50mg	Hetero Labs Limited	Zimbabwe	11/Mar/14	2014/7.13/4864
16	HA498		Emtricitabine + Tenofovir disoproxil fumarate Tablets 200mg + 300mg	Hetero Labs Limited	Ghana	1/Oct/13	FDB/GD.133-9035
17	HA498		Emtricitabine + Tenofovir disoproxil fumarate Tablets 200mg + 300mg	Hetero Labs Limited	Namibia	3/Oct/13	13/20.2.8/0201
18	HA498		Emtricitabine + Tenofovir disoproxil fumarate Tablets 200mg + 300mg	Hetero Labs Limited	Tanzania	19/Sep/14	TZ14H0188
19	HA500		Efavirenz + Emtricitabine + Tenofovir disoproxil fumarate Tablets 600mg + 200mg + 300mg	Cipla Ltd	Ukraine	31/Mar/14	UA/13533/01/01
20	HA508		Tenofovir disoproxil fumarate Tablets 300mg	Hetero Labs Limited	Ghana	1/Oct/13	FDB/GD.133-9037
21	HA512		[Tenofovir disoproxil fumarate + Lamivudine] + Atazanavir (as sulfate) + Ritonavir Tablets + Capsules + Tablets [300mg + 300mg] + 300mg + 100mg	Mylan Laboratories Ltd	Zimbabwe	6/Feb/13	2013/7.13/4764
22	HA521		Lamivudine + Zidovudine Tablets 150mg + 300mg	Hetero Labs Limited	Ghana	1/Oct/13	FDB/GD.133-9036
23	HA521		Lamivudine + Zidovudine Tablets 150mg + 300mg	Hetero Labs Limited	Zimbabwe	31/Dec/13	2013/7.13/4818
24	HA538		Efavirenz + Emtricitabine + Tenofovir disoproxil fumarate Tablets 600mg + 200mg + 300mg	Hetero Labs Limited	Tanzania	5/May/14	TZ14H0111
25	HA538		Efavirenz + Emtricitabine + Tenofovir disoproxil fumarate Tablets 600mg + 200mg + 300mg	Hetero Labs Limited	Namibia	3/Jul/14	14/20.2.8/0045
26	HA538		Efavirenz + Emtricitabine + Tenofovir disoproxil fumarate Tablets 600mg + 200mg + 300mg	Hetero Labs Limited	Ghana	27/Nov/14	FDB/GD.143-11098
27	MA078		Artesunate + Mefloquine (as hydrochloride) Tablets 25mg + 50mg	DNDi, Switzerland (Cipla Ltd is the supplier and is responsible for the product)	Tanzania	7/Jan/14	TZ14H057
28	MA079		Artesunate + Mefloquine (as hydrochloride) Tablets 100mg + 200mg	DNDi, Switzerland (Cipla Ltd is the supplier and is responsible for the product)	Tanzania	7/Jan/14	TZ14H058
29	MA091		Artemether + Lumefantrine Tablets 20mg + 120mg	Macleods Pharmaceuticals Ltd	Namibia	3/Apr/14	14/20.2.6/0011
30	MA091		Artemether + Lumefantrine Tablets 20mg + 120mg	Macleods Pharmaceuticals Ltd	Nigeria	6/Aug/14	B4-2289

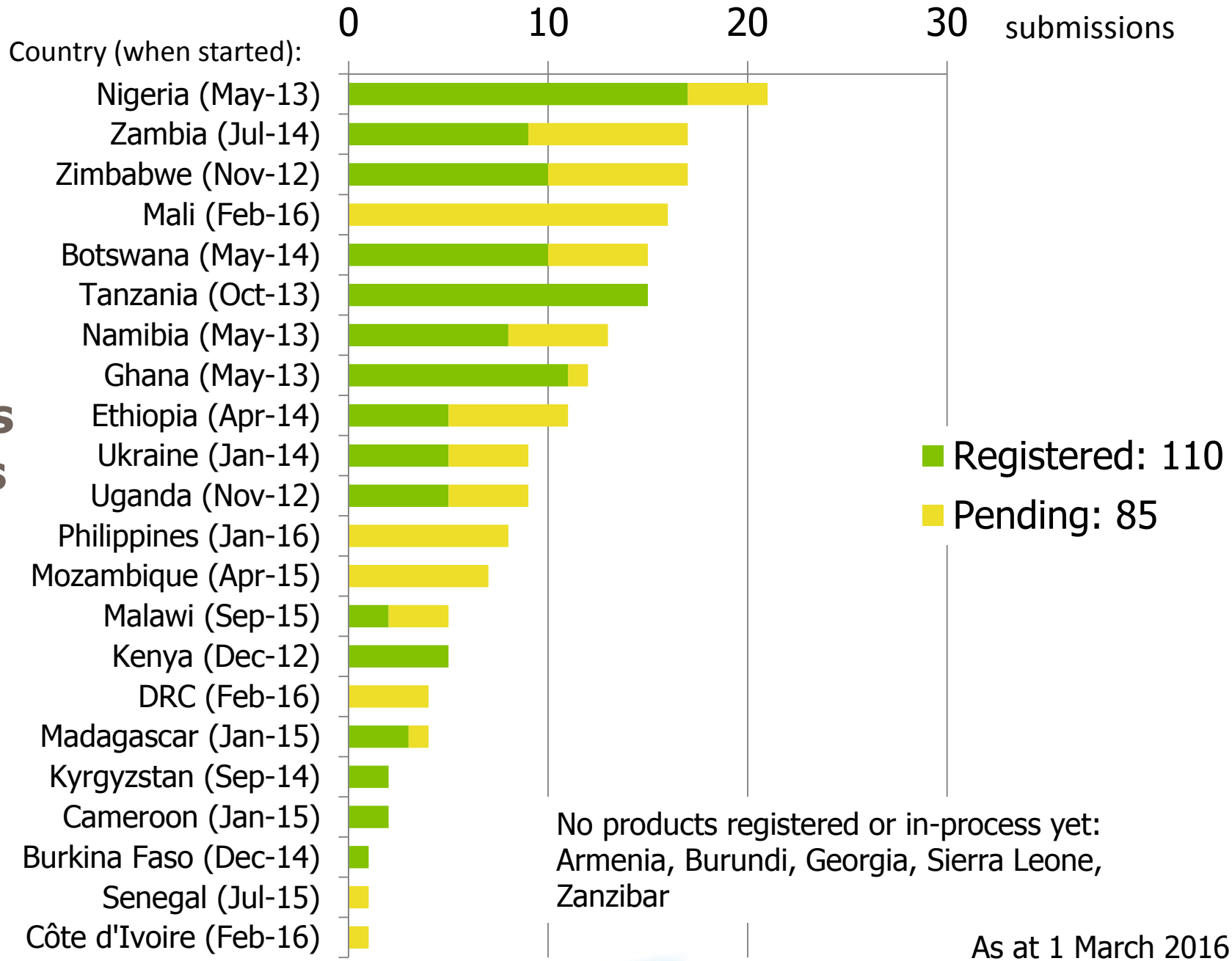
Growing acceptance by manufacturers and NMRAs





As at 1 March 2016

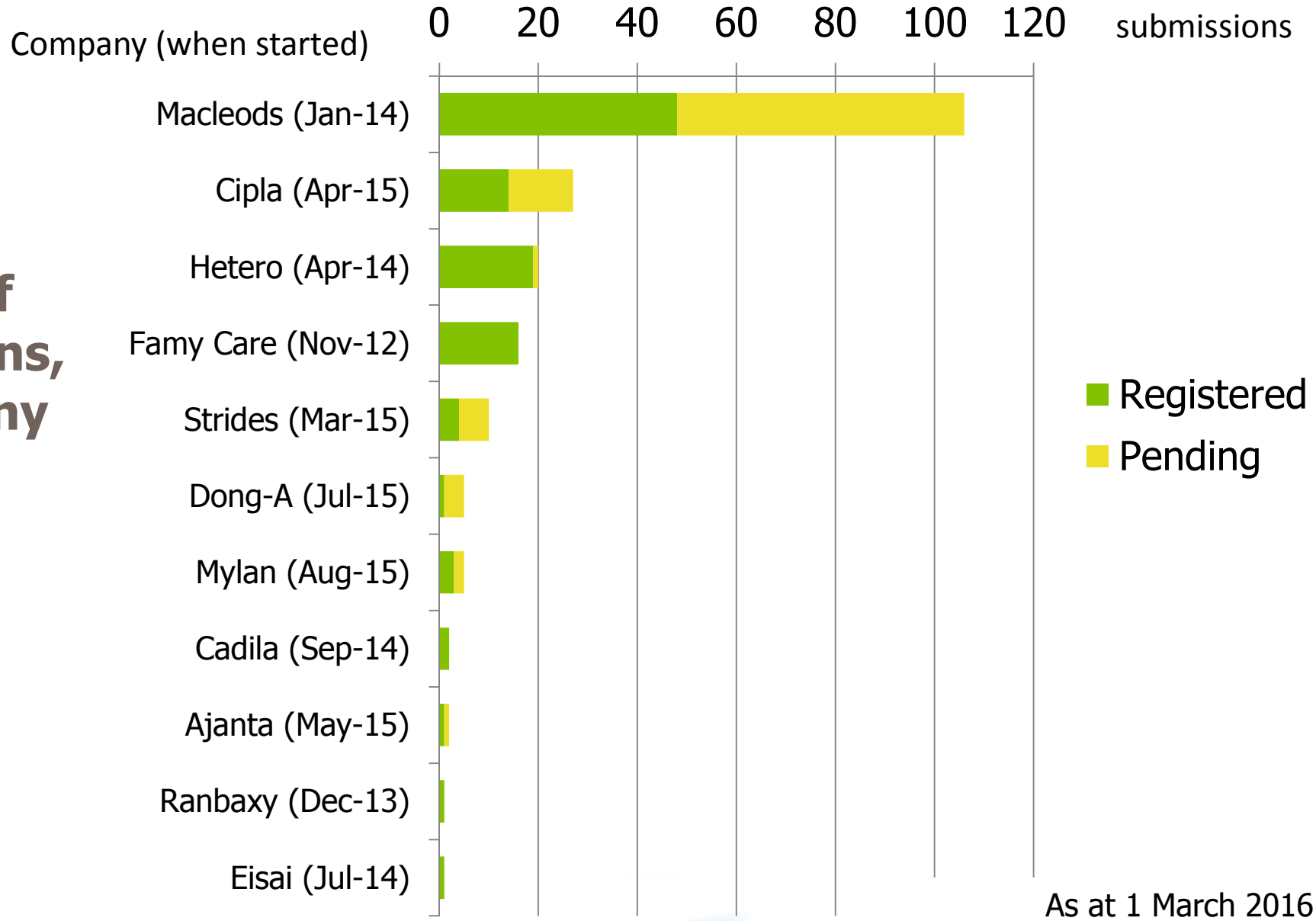
Pipeline of applications in countries



No products registered or in-process yet: Armenia, Burundi, Georgia, Sierra Leone, Zanzibar

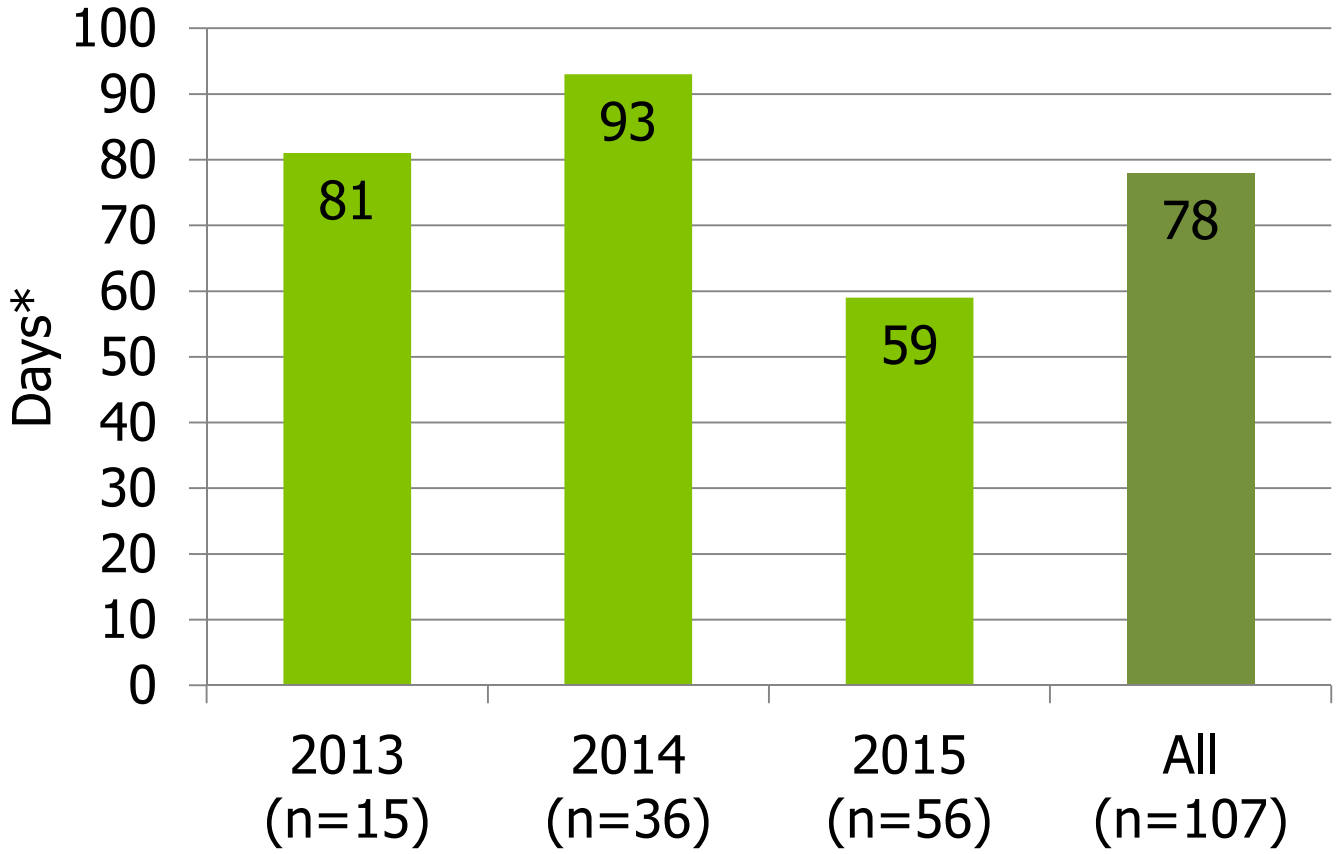
As at 1 March 2016

Pipeline of applications, by company



As at 1 March 2016

Median time to registration



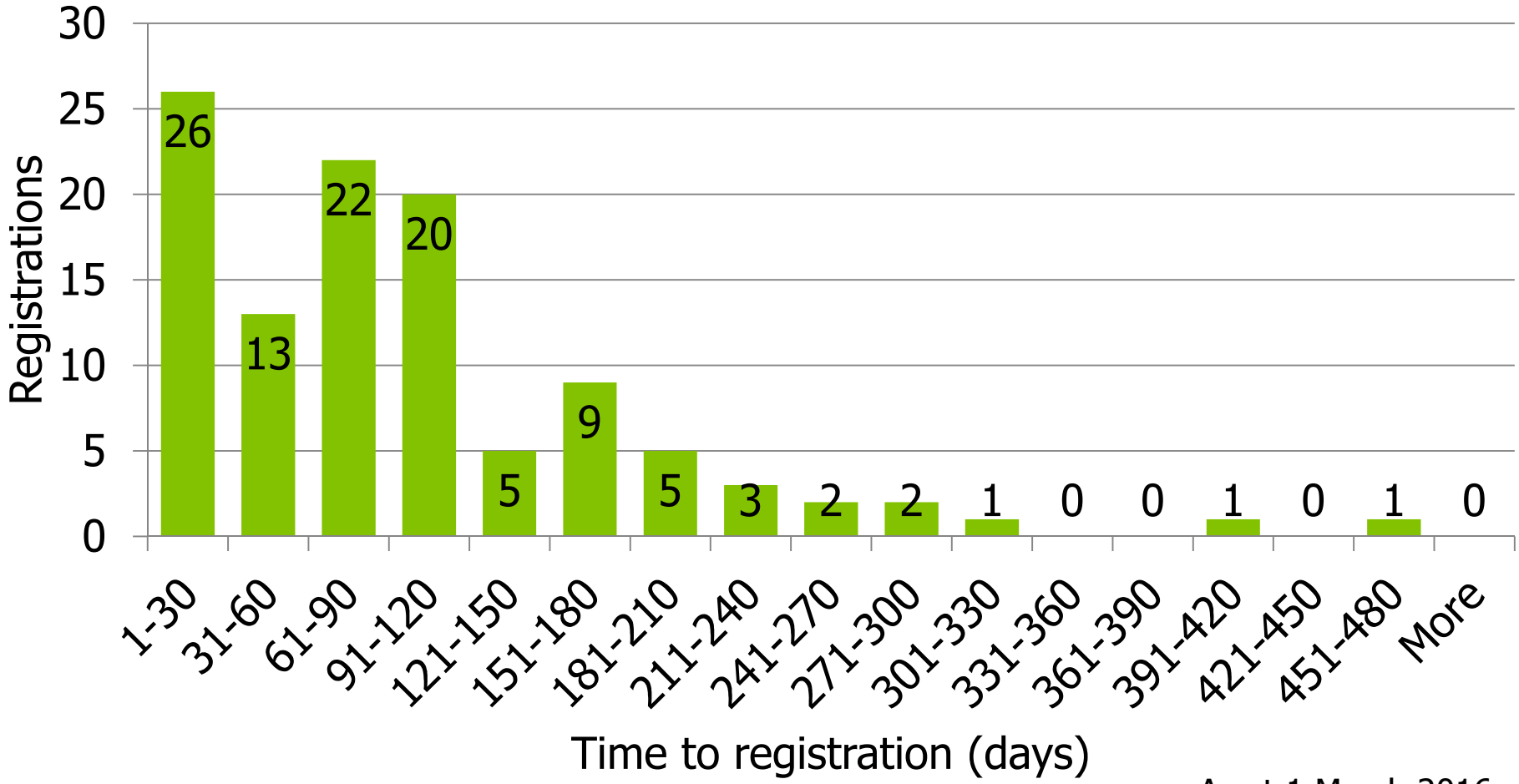
*Including regulatory time and applicant time

As at 1 March 2016

Time to registration

(2013-2015, n=107)

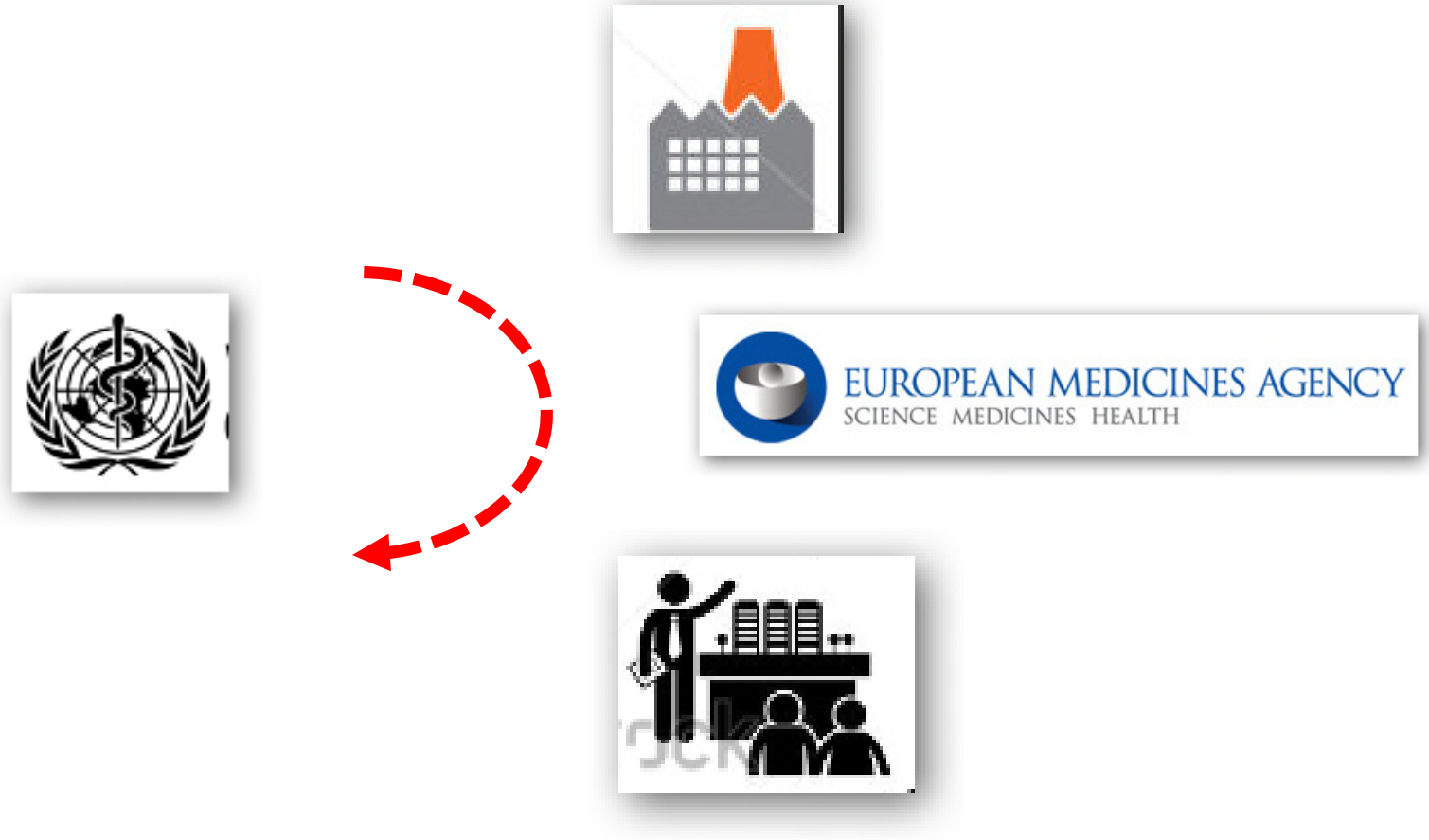
Including regulatory time and applicant time



As at 1 March 2016

Collaborative registration of ‘SRA’ approved medicines

Piloted scheme – involved parties



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