Accessible Quality-assured Diagnostics for Public Health Programmes: Global Challenges

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Plan of Presentation

- **Need for affordable, accessible IVDs: a public health perspective**
  - **The power of POC diagnostics in improving access to life saving drugs**
  - **Rapid tests to distinguish malaria from other causes of fever**
  - **Point-of-care diagnostics to save lives and strengthen health systems**
- **Regulatory oversight of IVDs in the developing world**
- **Innovation to meet public health needs: challenges for industry**
- **The way forward**

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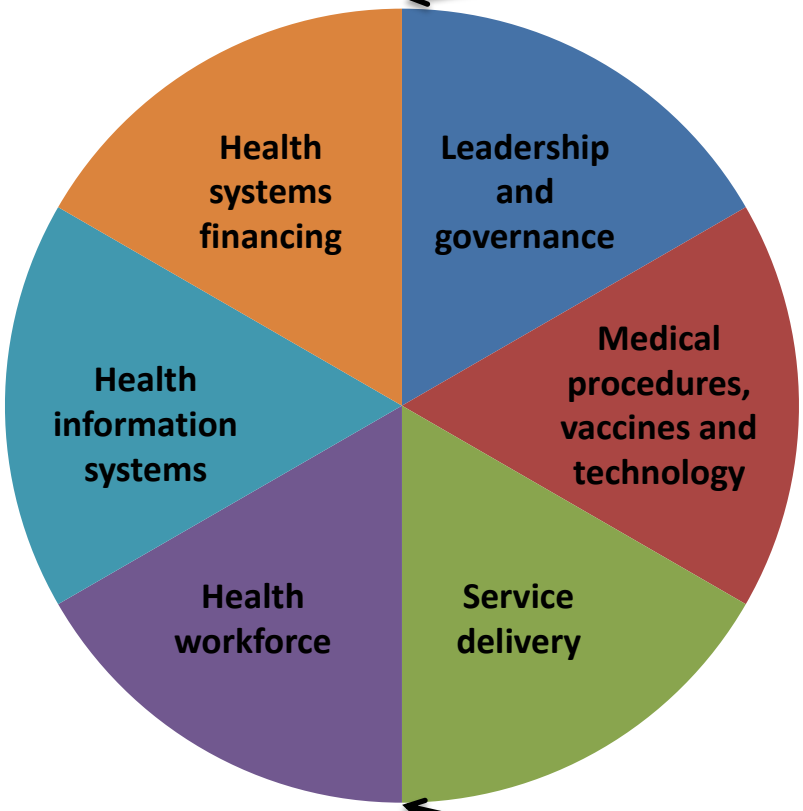
The importance of diagnostics in global health

WHO global health systems components

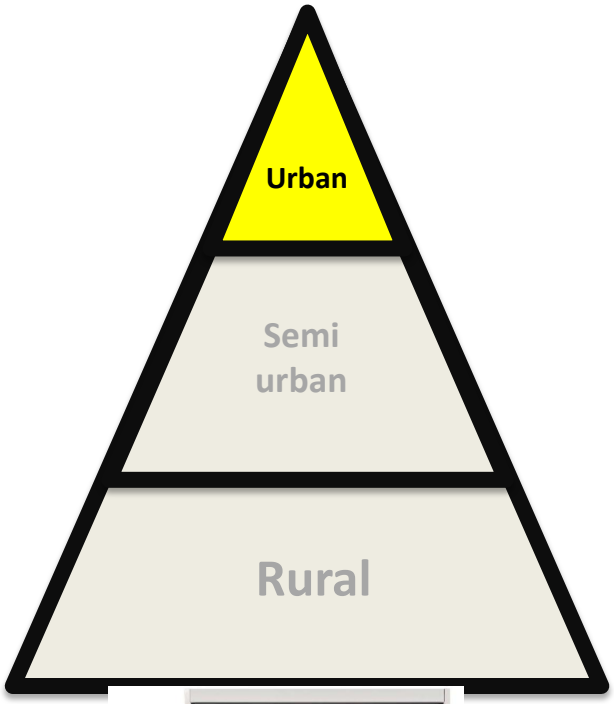


Source:
http://www.who.int/healthsystems/topics/en/

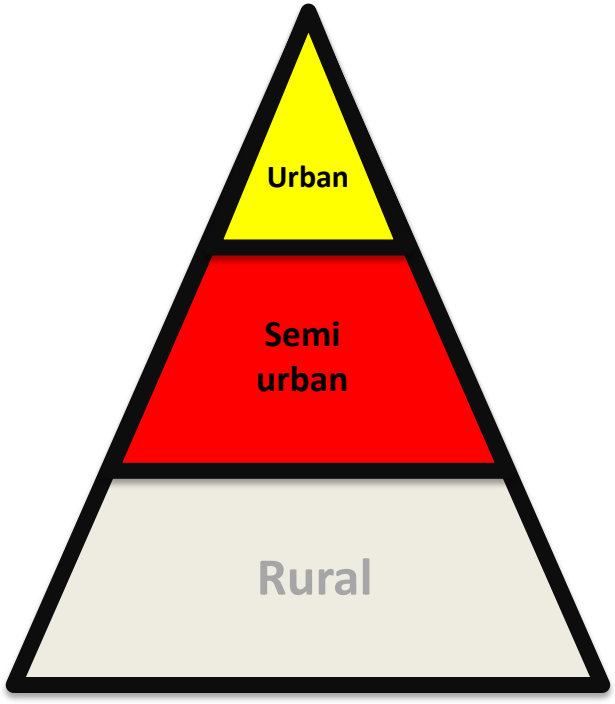
Diagnostics

- represent small proportion of health care spending, e.g. <1% of total global malaria spending vs. 37% each for drug and vaccine development
- influence 60-70% of patient management decisions
- opportunities for innovations to improve public health through genomics/proteomics and rapid detection technology
- Diagnostics have the power to transform health systems and save lives

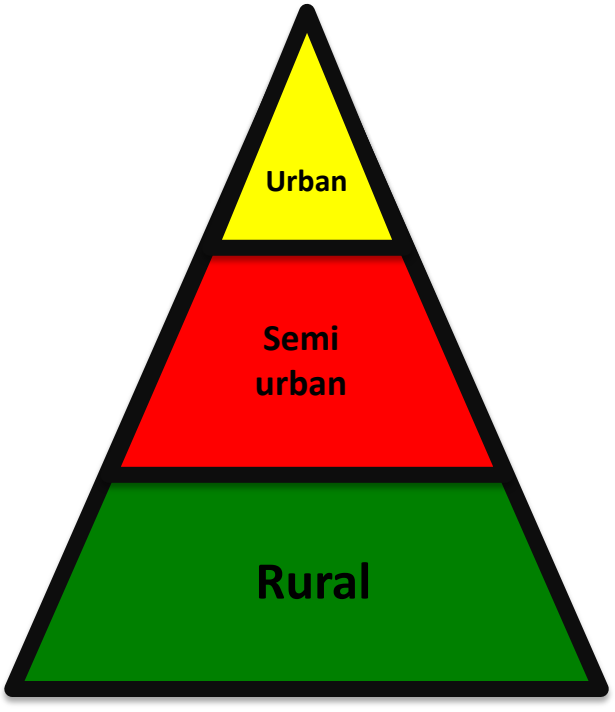
Access to Diagnostics within a Health Care System

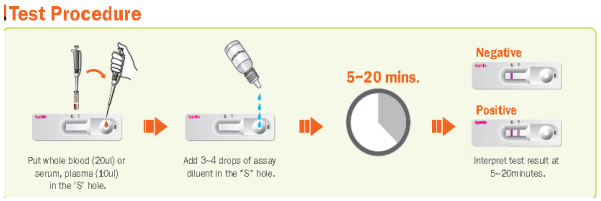


Accurate ✓✓✓
Cheap ×
Fast/simple ×



Accurate ✓✓
Cheap ✓
Fast/simple ✓





Accurate ✓
Cheap ✓✓
Fast/simple ✓✓

ASSURED Tests to Improve Global Health

A = affordable

S = sensitive

S = specific

U = user-friendly

R = rapid and robust

E = equipment-free

D = deliverable

- **Cheap**
- **Accurate**
- **Fast/Simple**

"Pick 2 of 3, you can't have them all."

SUCCESS

Diagnostics Success Story: #1

POC CD4 tests improve access to Life Saving Drugs

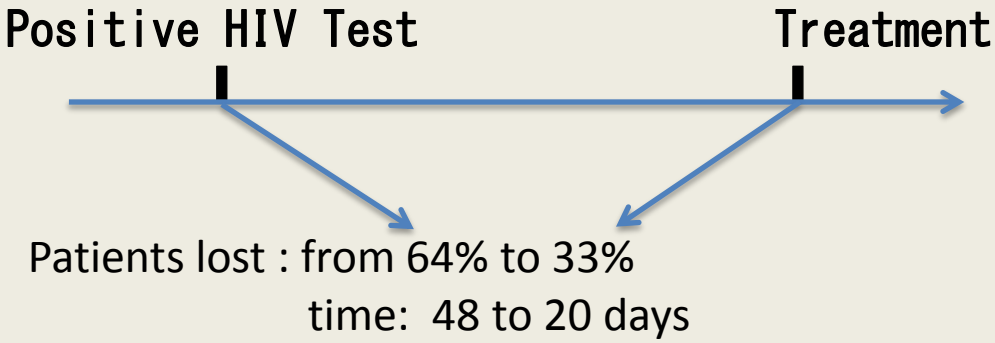
CHALLENGE

- HIV treatment is now more affordable
- CD4 tests needed to determine eligibility for HIV treatment but lab tests for CD4 counts are expensive and inaccessible
- Millions of HIV + patients waiting for a CD4 test to know whether they are eligible for life saving drugs

SUCCESS: New point-of-care (POC) technologies

- reduce % of patients lost between testing HIV + and CD4 testing
- reduced median time to treatment initiation

Mozambique: Jani et al. AIDS 2011; 25:807–12



Diagnostics Success Story: #2

Malaria POC Tests improve fever management and empower workers

CHALLENGE

- Fever = malaria
- Do we have tools for an evidence based management of fever ?

K. Senior Lancet ID 2009

SUCCESS:

- WHO Global Malaria Programme announced the T3 initiative on World Malaria Day 2012: T**est, Treat and Track**
- Rapid malaria tests in Livingstone region, Zambia
  - after the introduction of rapid tests in 2007, reported malaria went from 12,186 cases/quarter to 12.25 cases/quarter in 2009
  - Malaria RDTs enabled health care workers to reduce overuse of antimalarials and focused on non-malarial causes of fever
  - Rapid tests provide accurate disease trend data to inform disease control strategies and policy decisions

The Power of Diagnostics

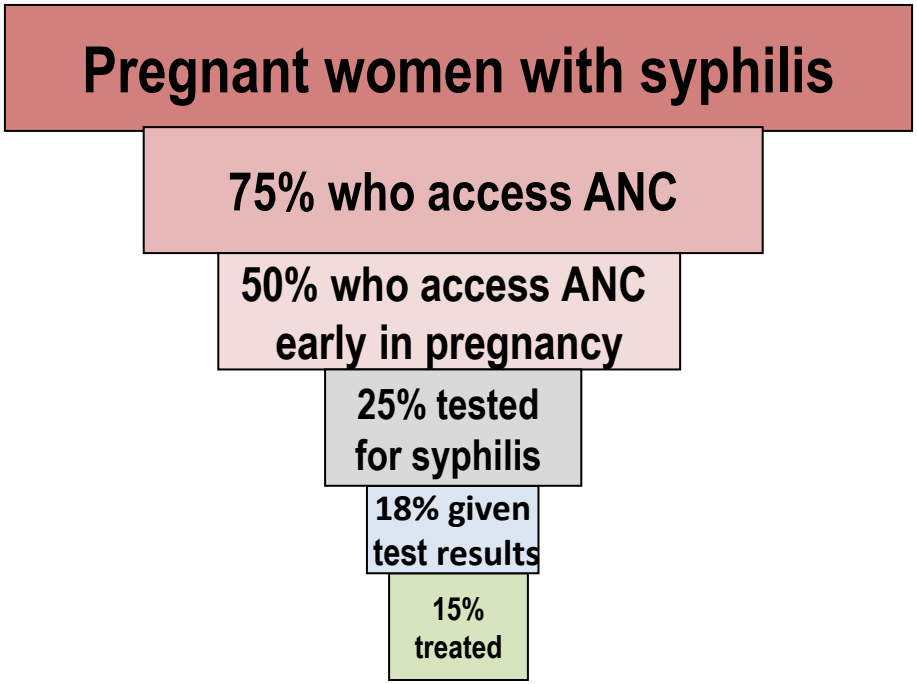
MEETING GLOBAL AND VERTICAL TARGETS

- MDG 4 aims to reduce mortality in children under 5
- Child deaths down from 12 million to < 7 million
- Today, 19,000 children will die: 19,000 too many child deaths
- Neonatal mortality now accounts for 40% of mortality under 5

Syphilis in pregnancy is a major cause of stillbirths and mortality in the first year of life

Success of Diagnostics: #3

POC Syphilis tests save lives and strengthen health systems



CHALLENGE

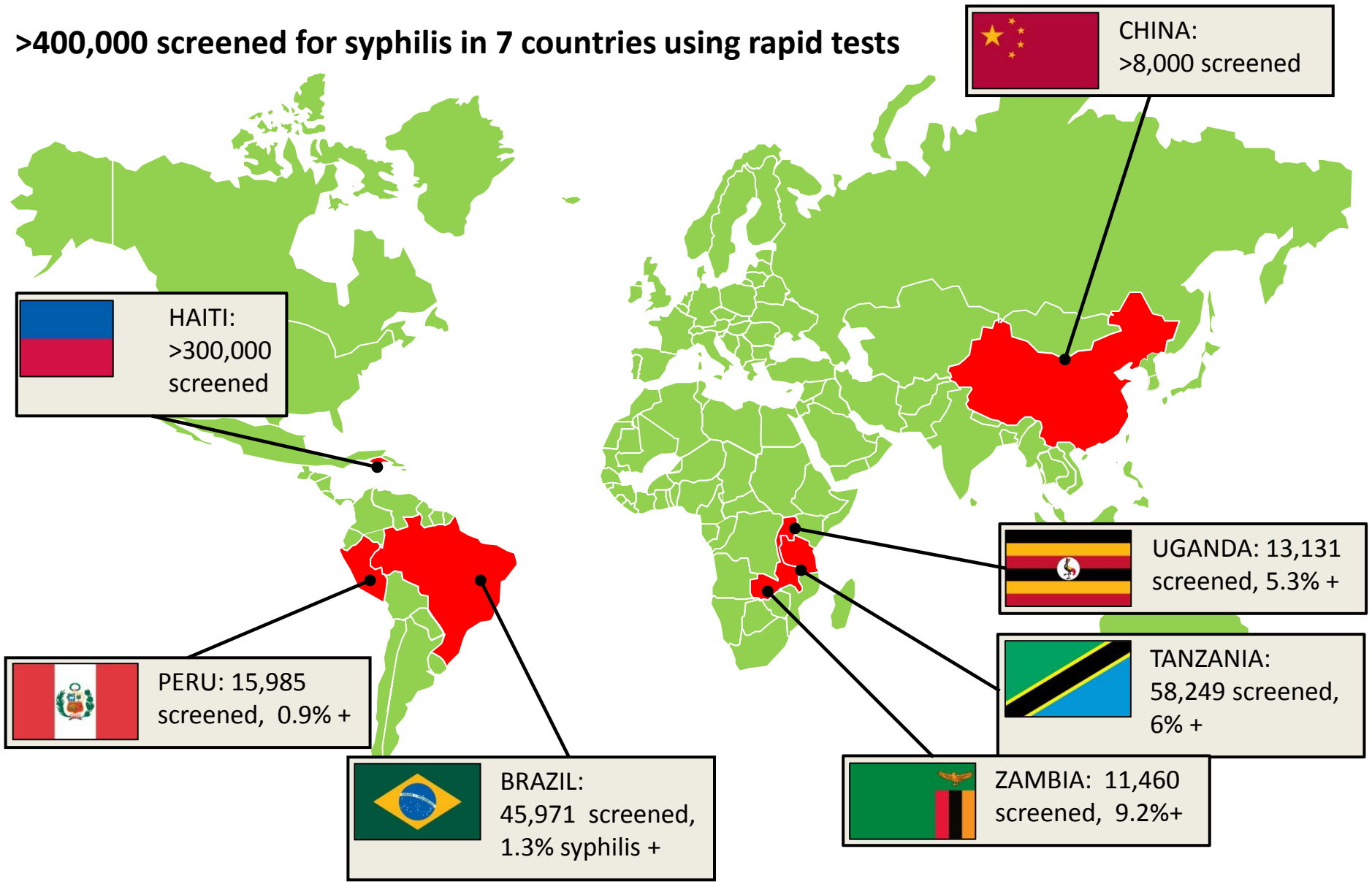
- Syphilis is invisible
- Congenital syphilis causes stillbirth, prematurity, low birth rate and life-long complications
- Access to laboratories offering screening is limited in the developing world

Why health services fail:

- **unaffordability**
- **lack of access**

Diagnostics Success Story: #3

>400,000 screened for syphilis in 7 countries using rapid tests

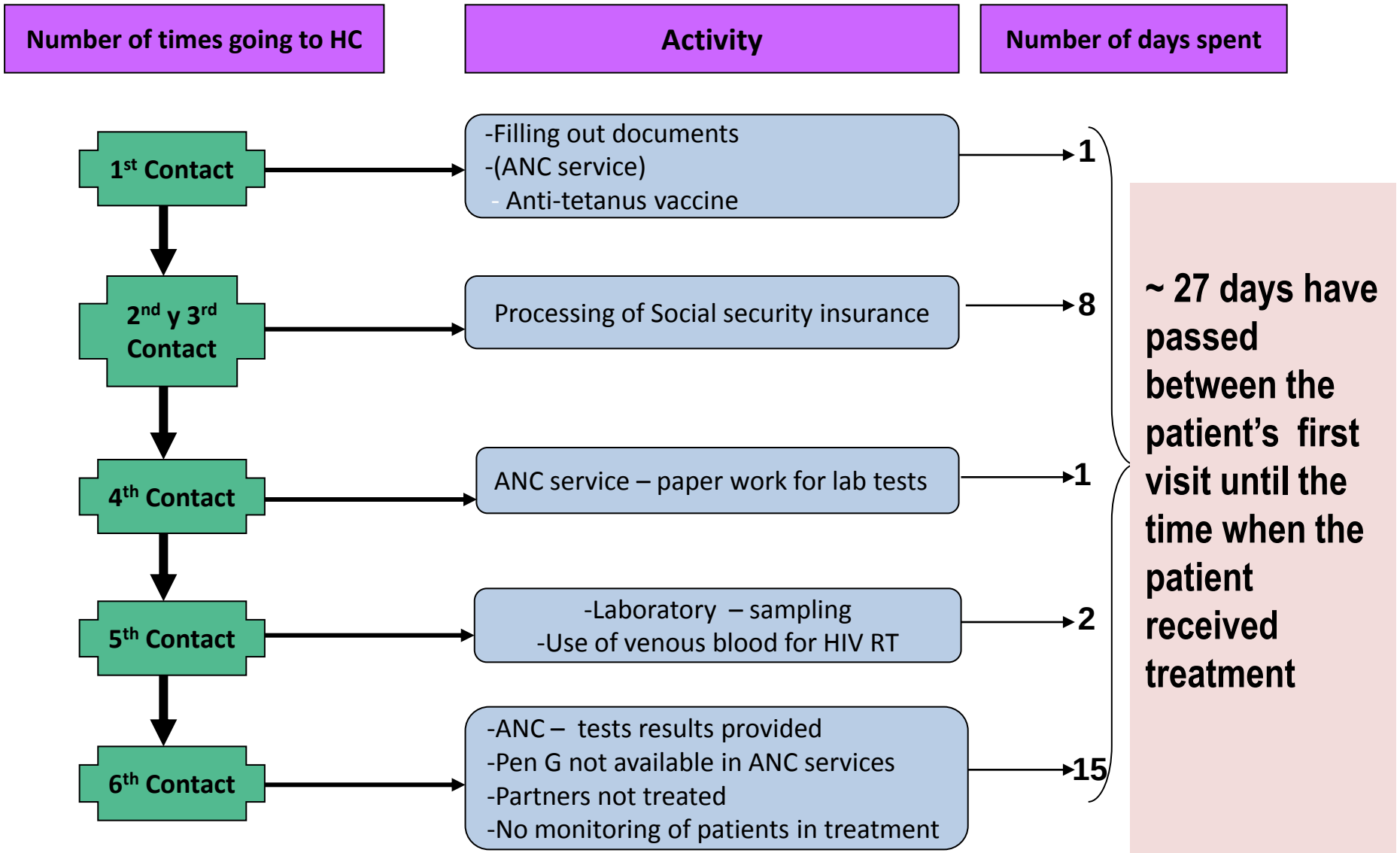


Screening for HIV and Syphilis in Amazonas, Brazil

One Test, Two Lives

(CDC and Global Congenital Syphilis Partnership)

PERU Cisne Project: PATIENT FLOWCHART COMPLEXITY SUMMARY



Point of Care Tests:
Strengthening Health Systems

Health System Indicators	Outcome Measures	Success Criteria
Coverage (increase in access to screening)	# women pregnant screened pre- and post-POCT introduction	90% coverage post-POCT introduction
Improved health outcome	# infected women treated	90% of women who tested positive treated (# stillbirth & congenital syphilis averted)
Acceptability by clients and health workers	Job satisfaction; client satisfaction with service	Increased job satisfaction and client satisfaction with services
Quality assurance	# workers who passed proficiency test	90% of CHWs passed the proficiency test
Service integration	Effect on ANC and prevention of mother-to-child transmission (PMTCT) programmes for HIV	Synergy with existing programmes
Sustainability	# countries which change policy	Policy change, development of national guidelines for use, and plans for scale up

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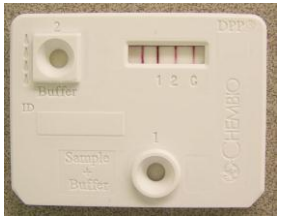
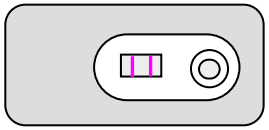
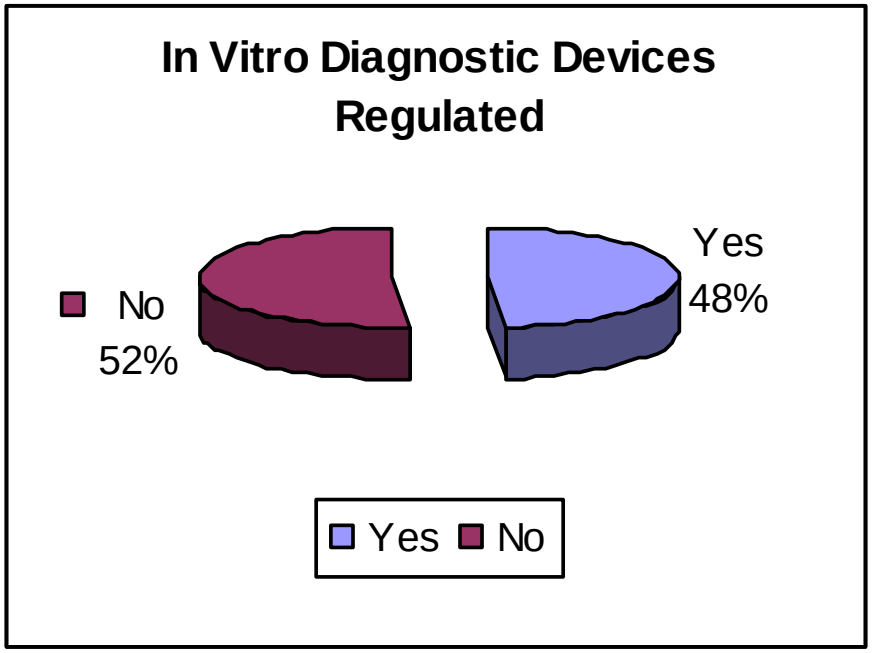
Why Regulate Diagnostics?

- **Ensure safety, quality and effectiveness**
- **Risk – benefit analysis: probable benefit of the test results should outweigh any impact from misdiagnosis**

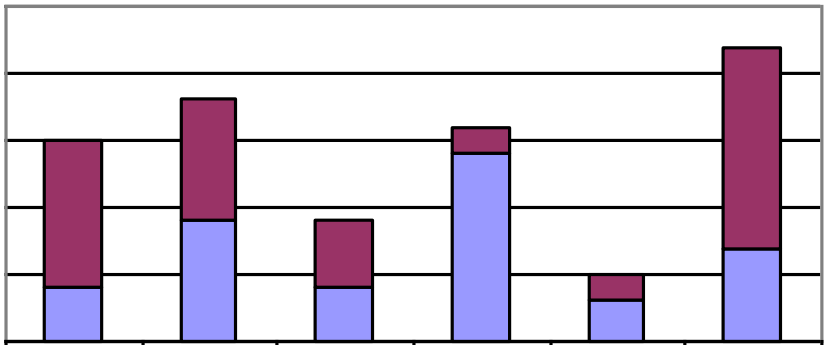




Lack of Regulatory Oversight for Diagnostics in the Developing World



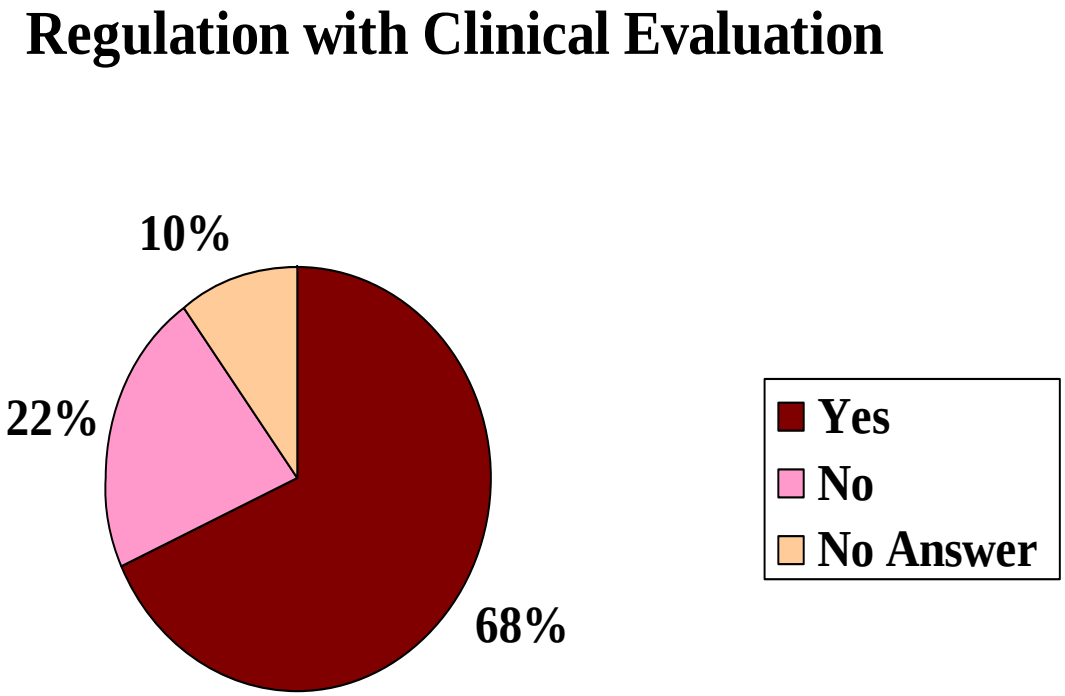
In Vitro Diagnostic Devices Regulation By Region, N = 85



	AFRO	AMRO	EMRO	EURO	SEARO	WPRO
No	11	9	5	2	2	15
Yes	4	9	4	14	3	7

TDR survey 2002

Quality Standards in Diagnostic Evaluations?



HIV:	83%
Hepatitis:	92%
STIs:	42%
TB:	13%
Malaria:	13%

Cost of clinical evaluations range from $2,000 to $2,000,000

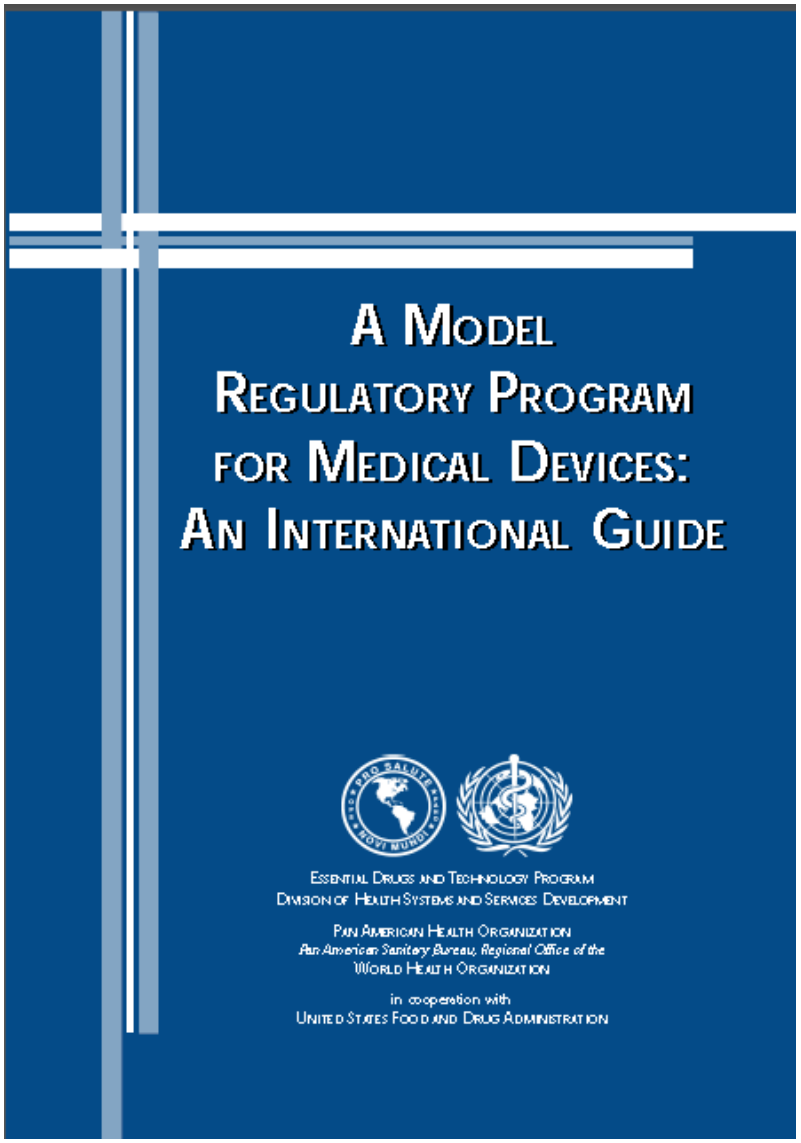
Regulation of *In-vitro* Diagnostics: Top 10 Challenges

1. Regulatory landscape highly **variable**
2. Path to approval is **not transparent**
3. Approval process often **costly** and **lengthy**, especially for imported tests
4. Clinical trials often not required or **lack rigour**
5. **Regulatory frameworks have been slow to respond to advances in science and technology.**
6. **Tests are sold and used in the developing world without evidence of effectiveness**
7. **Companies with quality tests unable or unwilling to compete in market flooded with low quality tests**
8. **Companies have difficulties securing funding for clinical trials**
9. **Cost of regulatory approval passed onto end-users**
10. **Companies often do not bother registering in small countries or countries with small markets because of lack of return for investment**

Global Harmonization Task Force (GHTF)

- **conceived in 1992 in response to the growing need for international harmonization in the regulation of medical devices to ensure the safety, quality, and effectiveness of medical devices**
- **a voluntary group of representatives from national medical device regulatory authorities and industry**
- **In 2006, GHTF included three Liaison Body members: the Asian Harmonization Working Party (AHWP), International Organization for Standardization (ISO), and International Electro-technical Commission (IEC)**
- **GHTF publishes and disseminates harmonized documents on basic regulatory practices and serves as an information exchange forum. GHTF documents are developed by 5 Study Groups (SG):**
  - SG1 - Premarket Evaluation
  - SG 2 - Post-Market Surveillance/Vigilance
  - SG 3 - Quality Systems
  - SG 4 - Auditing
  - SG 5 - Clinical Safety/Performance
- **In 2013, GHTF will transition to a purely regulatory body called the International Medical Devices Regulatory Federation (IMDRF) which will continue to promote the principles of harmonization.**

Guiding Principles for Regulation of Medical Devices



1. The primary goal is to protect public health and safety
2. A regulatory system should ensure that valuable new technologies are made available to the clinical community and to patients and consumers expeditiously while preventing unsafe or ineffective devices from reaching the market
3. Regulatory decisions must be based on strong and clear science, free of external influences and consistent with the directives of law
4. As the guarantor of public health, enforcement of the law must be vigorously, fairly and uniformly carried out and appropriate regulatory and legal actions taken against violators
5. Government-prescribed rules and procedures must be clearly articulated for those who must comply with them
6. Assuring medical device safety entails more than the functioning of the device itself; it requires oversight of the use of medical devices
7. Information on product risks must be openly communicated with health professionals and consumers
8. Countries instituting medical device programs should be cognizant of ongoing international harmonization efforts so as to preclude regulatory controls that conflict with actual harmonized rules and guidelines or with the spirit and goals of international harmonization

Current Pathway for Approval of Medical Devices

1. Premarket Controls	China	India*	Brazil	Zambia	Nigeria*	South Africa*
a. Legal Framework	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**Yes**
b. Medical device definition	**Yes**	Yes	**Yes**	**No**	**Yes**	**Yes**
c. Risk Based classification	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**Yes**
d. Premarket evaluation	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**Yes**
e. Manufacturing controls	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**Yes**
2. Marketing Controls						
a. Advertising control	**Yes**	Yes	**Yes**	**No**	**No**	**No**
b. Market entry controls	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**Yes**
3. Post-marketing Controls						
a. Post approval studies	**No**	**No**	**No**	**No**	**No**	**No**
b. Device tracking	**Yes**	**Yes**	**yes**	**No**	**Yes**	**Yes**
c. Device reporting	**Yes**	**Yes**	**yes**	**No**	**Yes**	**Yes**
d. Corrections/Recall	**Yes**	**Yes**	**yes**	**No**	**Yes**	Yes

* Countries with medical devices legislation but currently developing an IVD Directive

TB IVD classification

US FDA:

Class I Reg. No. 886.3370; Product Codes GRT, NDZ, NJO
Class I Reg No.886.2660; Product Code JSY
Class III Product Code OJN (Enzyme-linked immunospot), MWA (NAAT), NCD (Immunity Test)

EU:

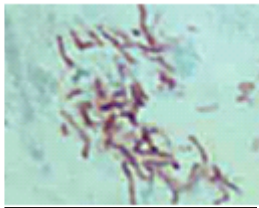
IVDD Annex II, Non-List A, Non-List B

Australia/Canada:

Class C; GHTF IVD Classification Rule No.3 (SG1-N45:2008)
Class D; GHTF IVD Classification Rule No.1 (SG1-N45:2008)
Class B; GHTF IVD Classification Rule No.6 (SG1-N45:2008)

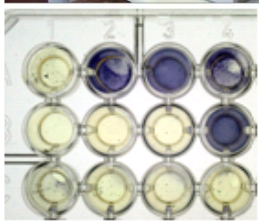
Japan:

Class III









Regulatory Approval of IVDs: Issues

- **Ministries of health often not consulted on effectiveness**
- **Lack of clarity on what changes to an IVD require a new submission --**

  a disincentive to improve products in response to customer feedback
- **Lack of standardization in:**
  - nomenclature
  - definition of a lot and lot size for POC tests
- **Duplications in**
  - Facility inspections and quality audits
  - Clinical trials to demonstrate effectiveness
- **Small and medium size companies have limited in-house expertise in regulatory affairs:**
  - Limited information on regulatory requirements in countries where they intend to market
  - limited access to trial sites in developing countries
  - Difficulties raising funds to support large number of trials
  - Little influence on country policy development and adoption of their product
-

Influence of other approvals on Regulatory Approval in 17 countries in South America

	Assists	Pre-requisite/Expedites	Not considered/Unknown
US FDA	6	5	6
EU CE Mark	5	5	7
WHO/PQ & Bulk Procurement	4	4	9
USAID waiver list	1	1	15
CDC Evaluation	6	3	8

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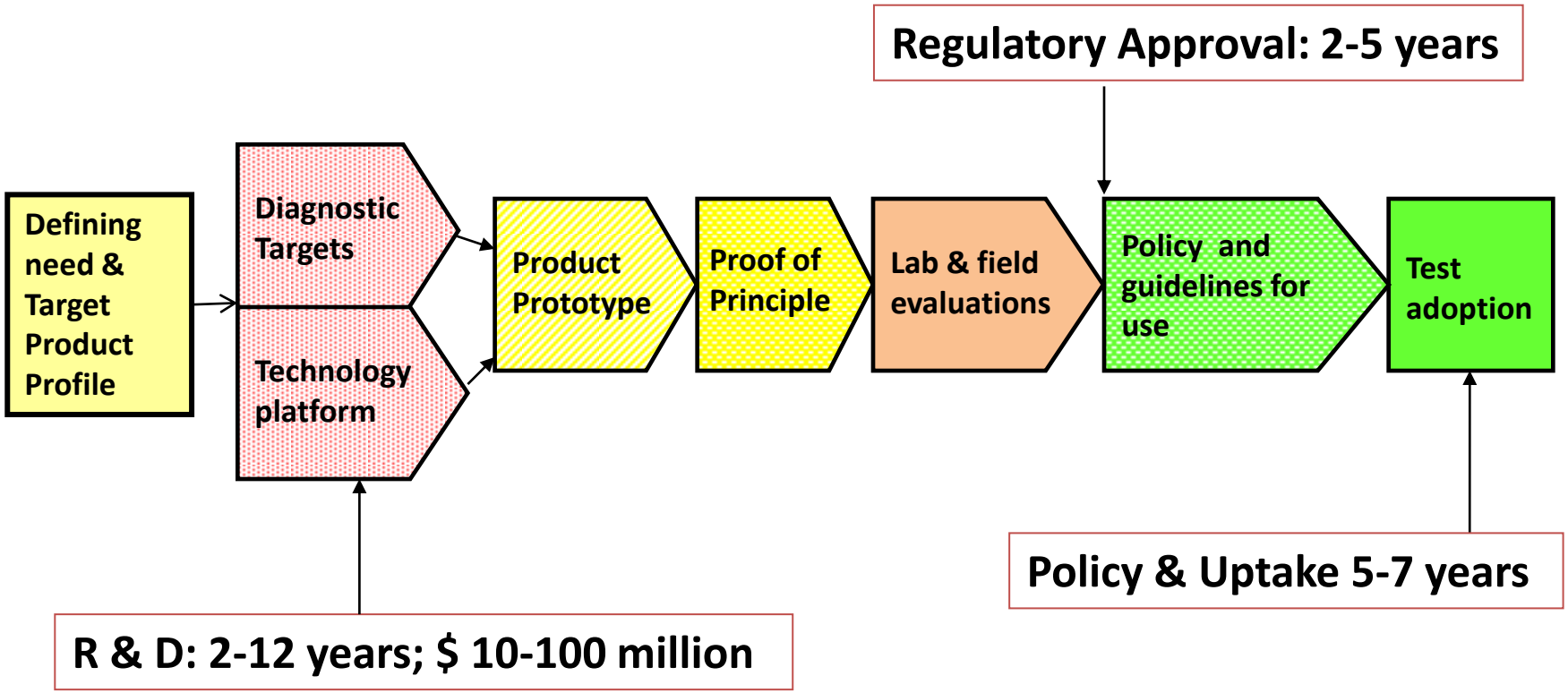
Bench to Bedside: Fragmented Landscape, Lack of Coordination, Delayed Access, and Disincentive to Innovation



Post adoption: ongoing problems with quality and supply chain management

Point-of-Care CD4 Technologies in the Pipeline*

PointCare

PIMA

BD

Zyomyx

Partec Mini

Daktari

mBio

Burnet

2009 2010 2011 2012 2013

Instruments

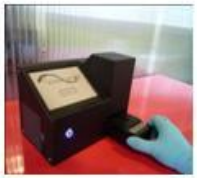
Disposable

*Estimated; timeline and sequence may change.

Point-of-Care Viral Load and EID Technologies in the Pipeline*

Liat

SAMBA VL



WAVE 80
EOSCAPE

Micronics

ALL

Alere

NWGHF EID

NWGHF VL

SAMBA EID

GeneXpert

Biohelix

2012 2013 2014 2015

*Estimated; timeline and sequence may change.

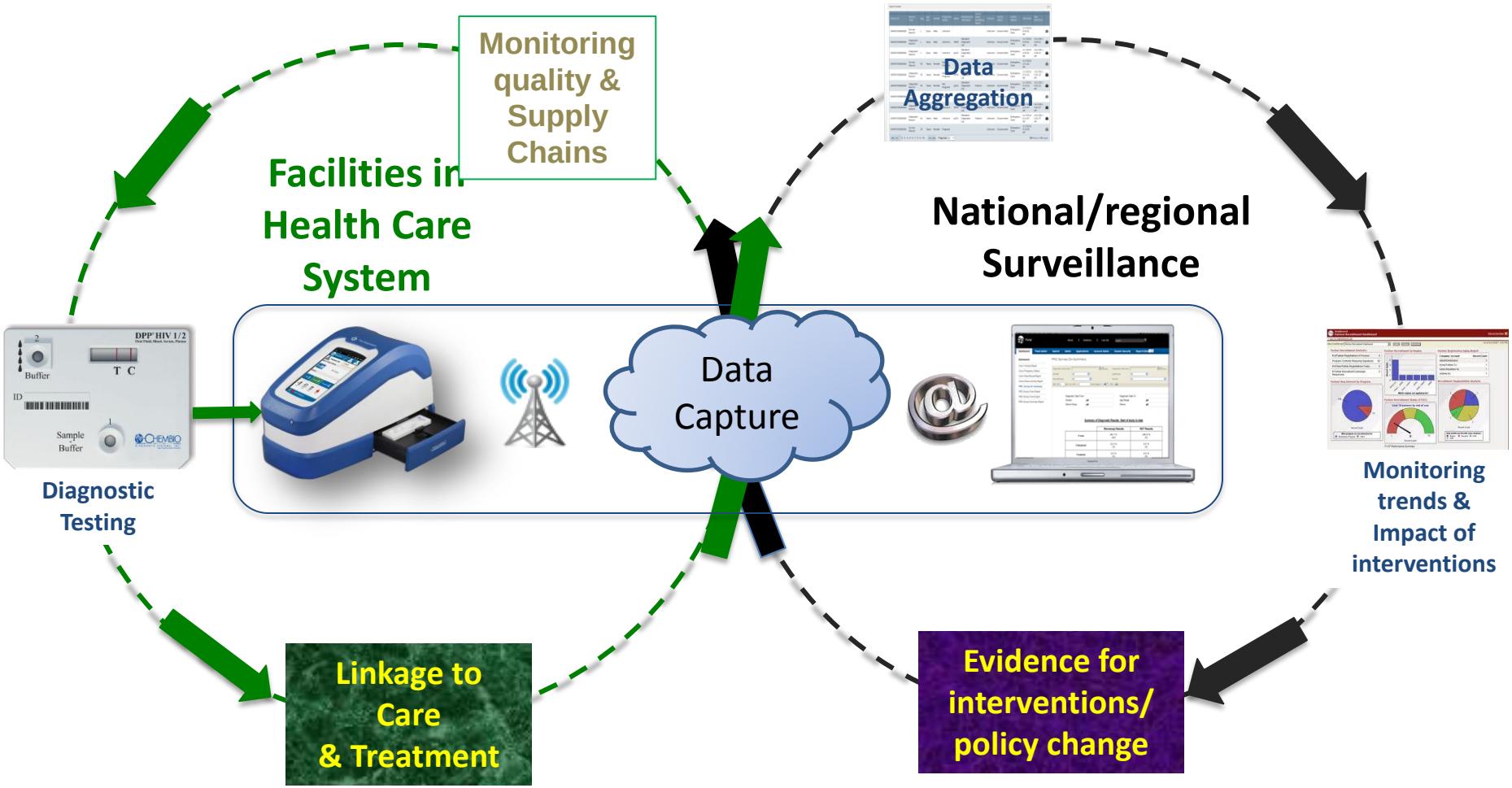
Duplication of Pre-market Evaluation

- Alere, the first company to market a POC CD4 assay, the PIMA. The product was launched in mid-2010. To date, it has conducted > 49 trials worldwide and is still continuing to do them.

- Many small and medium size companies seek to market globally, but do not have the regulatory expertise in-house to navigate the complex and variable regulatory approval process

- This and other barriers to market entry have now become a major disincentive to innovation

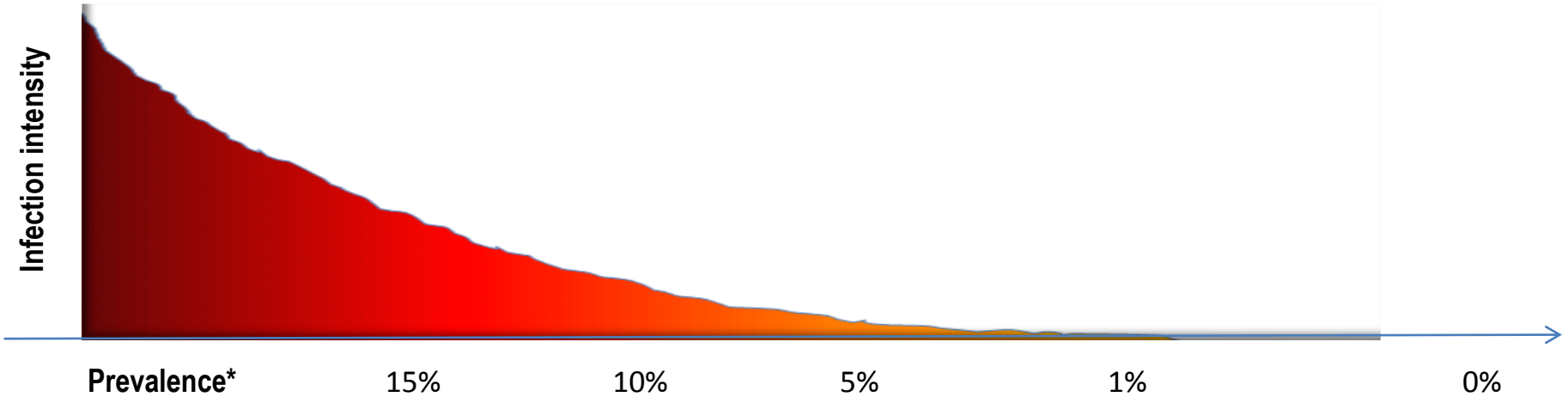
Readers: linking POC Testing Results to Surveillance and Supply Chain Management



Diagnostics for NTDs Targeted for Control/Elimination

Disease	Control strategy	Diagnostic Need	Diagnostic Tests Available
Schistosomiasis	MDA, health education, sanitation, snail control	surveillance	Microscopy (stool or urine), antigen or antibody detection
Onchocerciasis	MDA, (vector control)	surveillance	Skin snip, DEC patch
Lymphatic filariasis	MDA, vector control	surveillance	Antigen or antibody detection,
Trachoma	MDA, water and sanitation, health education	surveillance	Antigen detection, Nucleic acid amplification tests
Soil transmitted helminths	MDA	surveillance	microscopy
Chagas disease	Vector control, blood screening	surveillance	Antibody detection, PCR
African trypanosomiasis	Case finding and treatment, (vector control)	Case detection	Antibody detection, Microscopy (CSF and blood),
Visceral leishmaniasis	Case finding and treatment	Case detection	Antibody detection, microscopy (splenic aspirate or bone marrow)
Leprosy	Case finding and treatment	Case detection	Clinical diagnosis, microscopy (slit skin smears)
Guinea worm	Safe water, health education	Not needed	Clinical diagnosis

Diagnostics to inform policy decisions at different stages of schistosomiasis control



Control threshold	Morbidity control		Infection control	Transmission control	Transmission interruption / Elimination
Treatment strategy	Mass chemotherapy	Selective chemotherapy		Individual treatment	Cessation of treatment
Tools for targeting treatment	Questionnaire	Serological assay (Highly sensitive, high throughput)		Serological assay, followed by stool examination in seropositive individuals	
Tools for surveillance	Stool examination sampling	Serological assay followed by stool examination in seropositive individuals			Serological assay in children as a sentinel population

* Prevalence is calculated as % stool examination positive/number of people screened

Zhou et al. PLoS NTD 2011; 5(12): e1408.

Table 2: Target product profiles for diagnostic tools for selected NTDs, post-elimination surveillance

	LF	Trachoma	Schistosomiasis	Onchocerciasis
Intended use	Post-elimination incidence of infection	Post-elimination incidence of infection	Post-elimination incidence of infection	Post-elimination incidence of infection
Possible target population	Children born after the elimination date	Children born after the elimination date	Children born after the elimination date	Children born after the elimination date
Possible sample types	Blood spot	Blood spot	Blood spot or urine (avoid stool if possible)	Blood spot
Ideal diagnostic marker	Antibody	Antibody to a conserved species-specific epitope of MOMP	Antibody	Ov16 antibody
Availability of ideal diagnostic marker	Not available	Libraries available	In development	Available, but additional validation needed
Ideal test format	High throughput laboratory assay	High throughput laboratory assay	High throughput laboratory assay	High throughput laboratory assay
Population infection thresholds (for stopping MDA)	1%	Not defined	10% of school-aged children	1/3000
Probable sampling strategy	PBPS	PBPS	PBPS or school surveys (or sentinel occupations)	PBPS

ICT=immunochromatographic card test, LF=lymphatic filariasis, MOMP=major outer membrane protein of *C. trachomatis*, NTDs=neglected tropical diseases, PBPS=population-based prevalence survey.

Solomon et al. PLoS NTD 2011; 6(7): e1746

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Regulatory Approval of IVDs:

Better, Safer, Faster, Cheaper

Pacific Health Summit, London June 2012

Strengthening Regulatory Frameworks to Fuel Health Technology Innovation

Pacific Health Summit London June 2012 http://www.nbr.org

Understanding the Bigger Picture

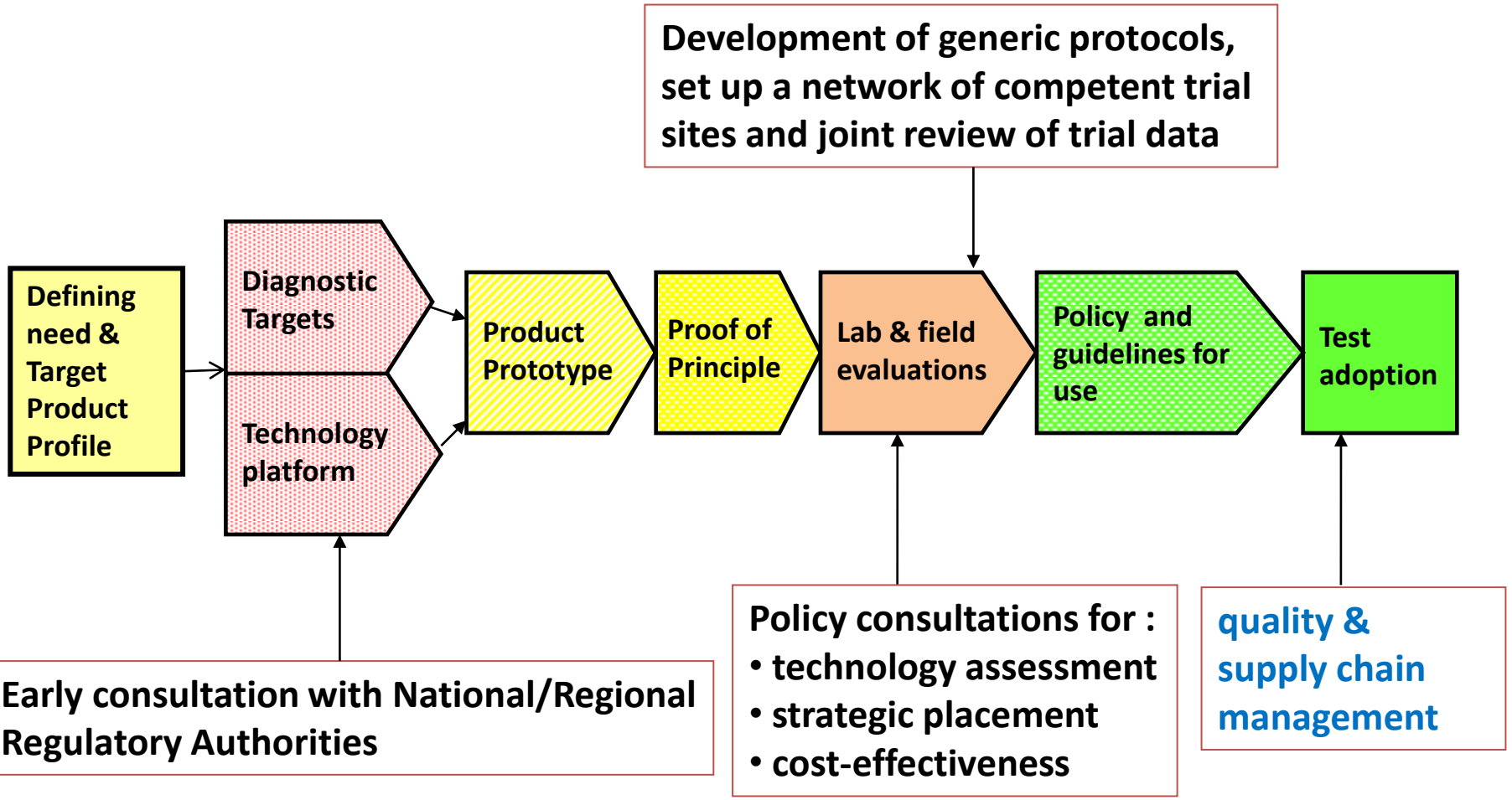
- **The regulation of health technologies is often viewed in isolation. I suggest that it should be seen as an opportunity for "joined-up" policy-making.**

- **Protection and promotion of public health can coexist with encouragement of private and public investment in R&D, facilitation of trade, education policy, health care delivery policies, and economic development.**

- **We should recognize the important contribution health technologies make – not only to individual health but to economic and social development as well.**

Michael Gropp, Medtronics

Affordable Access to IVDs: A Coordinated and Streamlined Approach – we can all do our part



Standardization and Harmonization: Faster and Cheaper

Item	Status quo	Proposed Harmonisation model	Impact
Dossier for registration	Forms unique to each country	Common standard submission form	Save companies time and costs
Facility Inspections	-ISO 13485 -Unique visits by NRAs; delay in approval due to long queues and high costs to companies	-adoption of common standard -Mutual recognition of audits -recognition of third party audits by an “accredited” body	Shorten time to approval and reduce costs
Clinical Trials	Large number of trials conducted for each product	-Common trial protocol -Network of competent sites -Joint review of trial data but final approval country specific	Approval in more countries with fewer trials; clear path for approval = in process and expectation reduced costs
Post-marketing surveillance	Limited capacity for identifying low quality products and product failures	-Network of evaluation sites act as sites for post-marketing surveillance	Ensure quality of tests post approval
Capacity building	Many countries do not regulate IVD; NRAs increasingly risk adverse	Easier approval process for quality products and keeping low quality products from entering the market	Better balance between risk vs benefit

Regulatory Harmonization: Vaccines

- Formation of The Developing Countries' Vaccine Regulators Network to accelerate the launch and introduction of vaccines
- Recommendation that consideration be given to agreements for:
  - joint reviews of clinical trial applications by similarly affected NRAs
  - review of applications for licensure

Progress Towards IVD Regulatory Harmonization

Asia Harmonization Working Party (23 countries). IVD sub group:

Latin America Diagnostic Association (ALADDIV)

East African Community

\+ Ethiopia, Nigeria, South Africa

Asia Harmonization Working Party (AHWP)

- **A non-profit organization by experts from medical device regulatory authorities and the medical device industry**
- **Goals: to study and recommend ways to harmonize medical device regulations in the region in coordination with the Global Harmonization Task Force, APEC and other related international organizations**

Member Economies: (N=23)

- Brunei, Cambodia, China, Hong Kong, India, Indonesia, Korea, Laos, Malaysia, Myanmar, Pakistan, Philippines, Singapore, Taiwan, Thailand, Vietnam
- Abu Dhabi, Chile, Jordan, Kuwait, Saudi Arabia, South Africa, Yemen

- **The biggest challenge that AHWP currently faces is the need to help member economies lacking in regulatory systems establish IVD regulation. AHWP considers training and capacity building to be critical in developing more stringent regulatory authorities (SRAs)**

Asia Harmonization Working Party (AHWP)

- **Six working groups**:
  - Work Group 1 (WG1) - Pre-Market Submission and CSDT
  - Work Group 1a (WG1a) - IVDD
  - Work Group 2 (WG2) - Post-Market Surveillance and Vigilance
  - Work Group 3 (WG3) - Quality Management System
  - Work Group 4 (WG4) - Quality System Audit
  - Work Group 5 (WG5) - Clinical Safety/Performance
  - Work Group 6 (WG6) - Capacity Building and Regulatory Training
  - Special Task Group (STG - Nomenclature) - Medical Device Nomenclature

- **Committed to our Affordable Access to IVDs project**
  - STED Standard Technical Document
  - Design a pilot study to determine critical elements of the regulatory approval process that can be harmonized for a point-of-care IVD

Creation of Latin America IVD Association: April 2012

➢**80 participants from regulatory authorities, MOH, research institutes and laboratories from:**

Argentina, Bolivia, Brazil, Colombia
Cuba, Guatemala, Paraguay, Peru,
Uruguay, Venezuela, Mexico, Panama

Industry representation from 13 companies:

Abbott, Alere, BioEasy, BioMerieux, BioRad, Diasorin, LabTest, Novociclo, OrangeLife, Roche, Sysmex, Thermofisher, WAMA diagnostics And diagnostic associations

Commitment for convergence of standards and pooling regulatory expertise – next meeting Nov 19-20 2012 in Brasilea

WORKSHOP

“Testes de Diagnóstico in Vitro Acessíveis e com Qualidade Assegurada para Programas de Saúde Pública”

17 e 18 de Abril de 2012 - Brasília/ Brasil

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

cbdl DIAGNÓSTICO PARA A VIDA

FONDATION MÉRIEUX

East African Community (EAC)

- A regional intergovernmental organisation:


Kenya


Uganda


Tanzania


Rwanda


Burundi

- EAC was established in 1999, with a treaty ratified by the original 3 Partner States – Kenya, Uganda and Tanzania. Rwanda and Burundi became full Members in 2007. Its headquarters: Arusha, Tanzania
- **Vision:** a prosperous, competitive, secure, stable and politically united East Africa
- **Mission**: to widen and deepen Economic, Political, Social and Culture integration in order to improve the quality of life of the people of East Africa through increased competitiveness, value added production, trade and investments
- Launched **the EAC Medicines Registration Harmonization Project** on 30 March 2012, Arusha, Tanzania with support from New Partnerships for African Development (NEPAD), WHO, Wold Bank, BMGF, Clinton Health Access Initiative, DFID, GIZ and others.
- EAC Secretariat co-hosted a meeting with LSHTM in Nairobi July 30-31 2012 with representation from all EAC member states and from Ethiopia, Nigeria and South Africa - a Technical Working Group will be created to work towards the creation of a **PAN-Africa Harmonization Working Party as a counterpart to AHWP**.
- Next meeting and training course – Dec 1-3 2012 in Cape Town, in collaboration with African Society for Laboratory Medicine

About the project

Currently the regulation of in vitro diagnostic tests is not optimal. In some countries tests are being sold and used without checks on their quality or effectiveness. Where regulation of tests does take place access to the new products can often be delayed for years due to complex and costly requirements for regulatory approval.

The London School of Hygiene & Tropical Medicine, with the Support of Grand Challenges Canada is working with regulatory authorities, ministries of health and the diagnostics community to improve regulatory oversight for *in vitro* diagnostic tests in the developing world.

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Improving health worldwide

For more information on the Affordable Access Project contact

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AFFORDABLE ACCESS FOR *IN-VITRO* DIAGNOSTIC TESTS


Thank You!