NRA status in the world and impact on viability of vaccine production and global vaccine supply

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World Health Organization

Acronyms used

- NRA : National Regulatory Authority
- NCL: National Control Laboratory
- EPI: Expanded Programme on Immunization
- DCVRN: Developing Countries Vaccine Regulatory Network
- GLO: Global Training Opportunities (former GTN)
- GTN: Global Training Network
- PQ: Prequalification
- DCVMN: Developing Countries Vaccine Manufacturers
- CT: Clinical trials
- GMP: Good Manufacturing Practices
- GCP: Good Clinical Practices
- PMS: Post Marketing Surveillance
- AEFI: Adverse Events Following Immunization
- CTD: Common Technical Document promoted by ICH

ICH: International Conference on Harmonization

Outline

1. Stratus of NRA : functionality and performance
2. Impact on viability of vaccine production: Domestic and export market
3. Impact on global vaccine supply:
4. Discussions to the DCVMN

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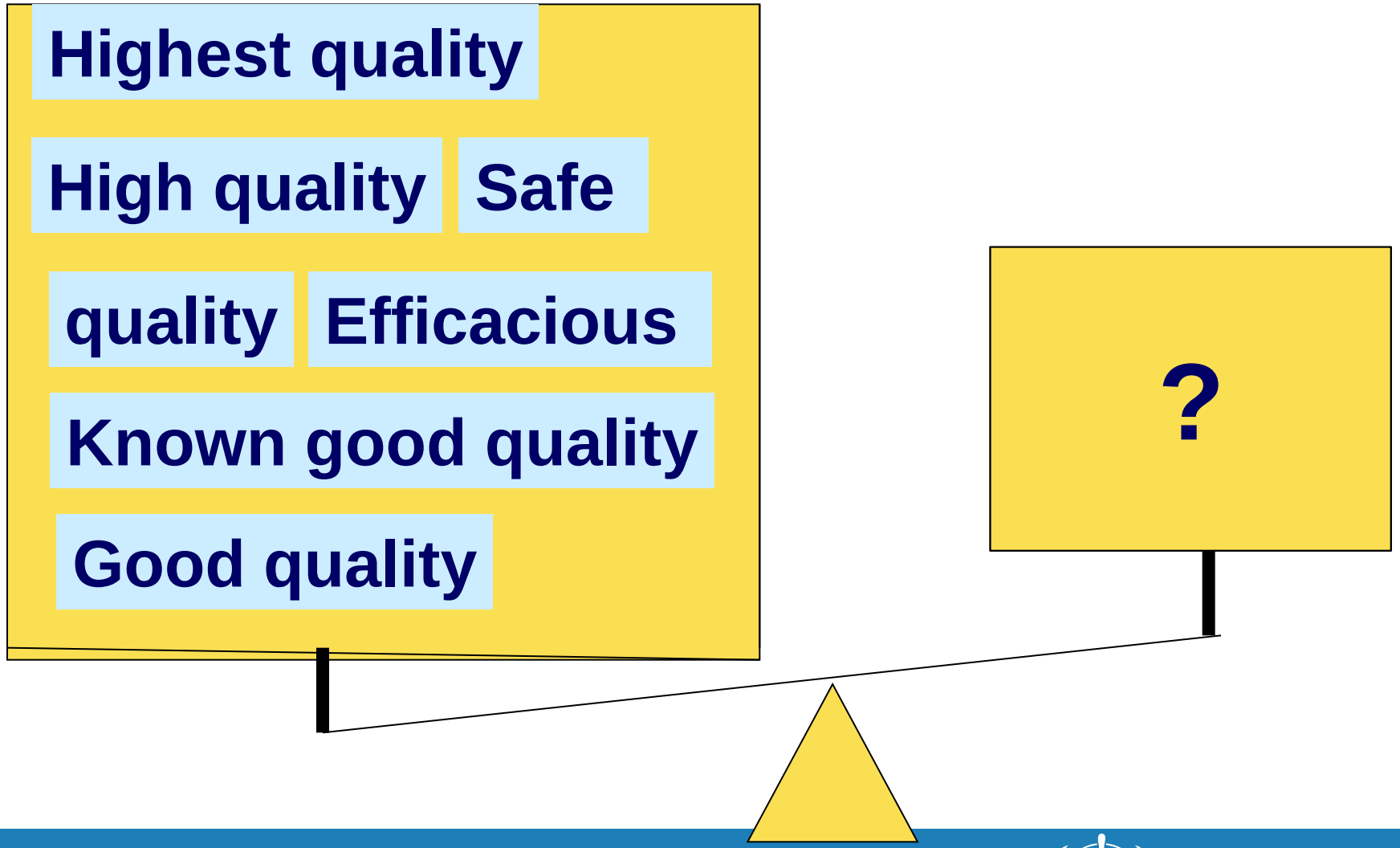
Quality of vaccines: terminology



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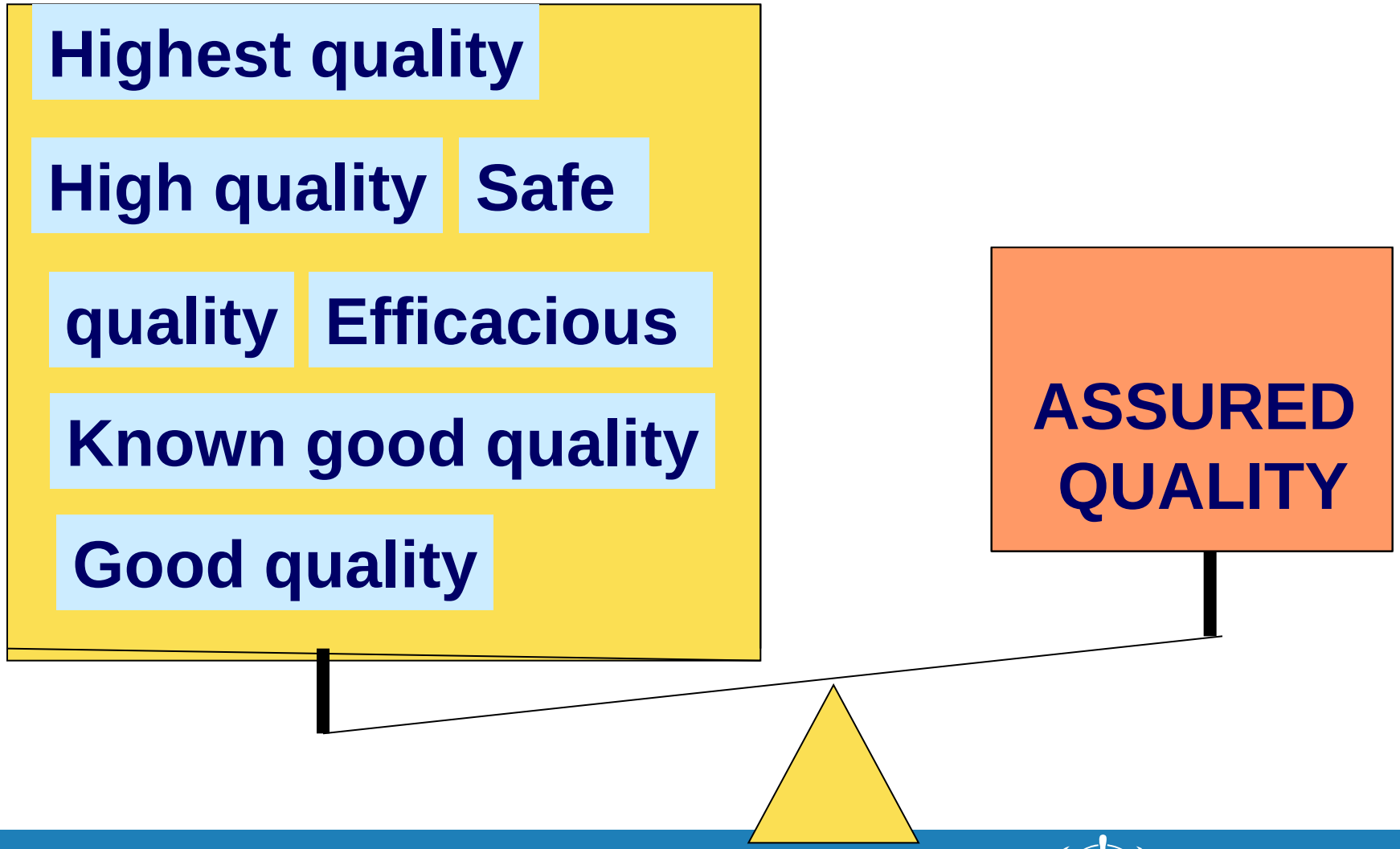
Quality of vaccines: terminology



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Definition of ASSURED QUALITY vaccines

Based on WHO definition published in Vaccine Quality - can a single standard be defined? Vaccine 2956 (2001) 1-4, states that a vaccine of assured quality is a vaccine that is :

1) PRODUCED IN A COUNTRY THAT HAS AN **INDEPENDENT AND FUNCTIONAL** REGULATORY AUTHORITY MEETING ALL WHO RECOMMENDED 6 REGULATORY FUNCTIONS.

and …

2) HAS **NO UNRESOLVED REPORTED PROBLEM** WITH THE VACCINE LOCALLY PRODUCED OR IMPORTED VACCINE

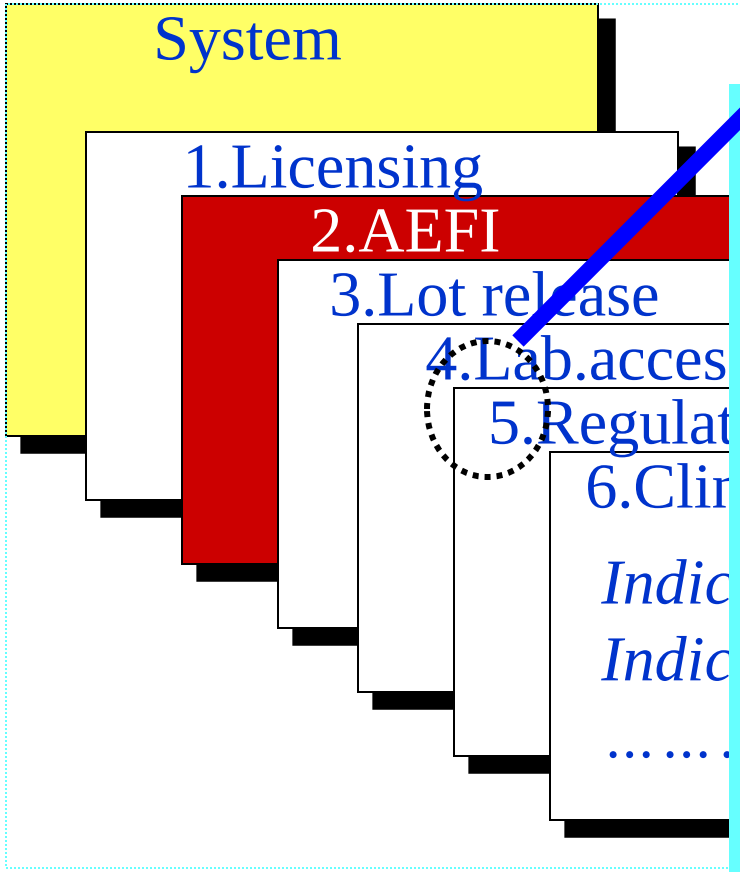
WHO concept: the six NRA functions

National Regulatory System : Governance / Strategic planning

1. **Marketing Authorization (MA) and Licensing Activities**
2. **Post-marketing activities including surveillance of Adverse Events Following Immunization (AEFI)**
3. **NRA Lot Release**
4. **Laboratory access**
5. **Regulatory Inspections**
6. **Authorization/Approval of Clinical Trials**

DEVELOPMENT OF BENCHMARKING SYSTEM : FUNCTIONS & INDICATORS DEVELOPED IN 1997, revised in 1999,2001,2002, 2004 & 2007 through international consultation of experts, next revision planned June 2011 in Geneva.

7 components, 6 functions, indicators and sub-indicators



5.REGULATORY INSPECTIONS	PQ
1. GMP requirements	CRITICAL
2. Mandate to regulate and enforce compliance of GMP	CRITICAL
3. Code of practices and established schemes for conducting inspection at appropriate intervals	CRITICAL
4. Appropriate expertise/qualifications for inspectors	CRITICAL
5. Established procedure to monitor inspection process	
6. Provision for monitoring onward distribution as appropriate	

PQ= Prequalification
NRA =National Regulatory Authority
AEFI= Adverse Events Following Immunization

Country Status: **101(52%) out 193 member states with NRA assessed against WHO published indicators, as of 2010**

NRA assessment conducted & planned

NRA assessment completed

Not yet conducted

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 concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

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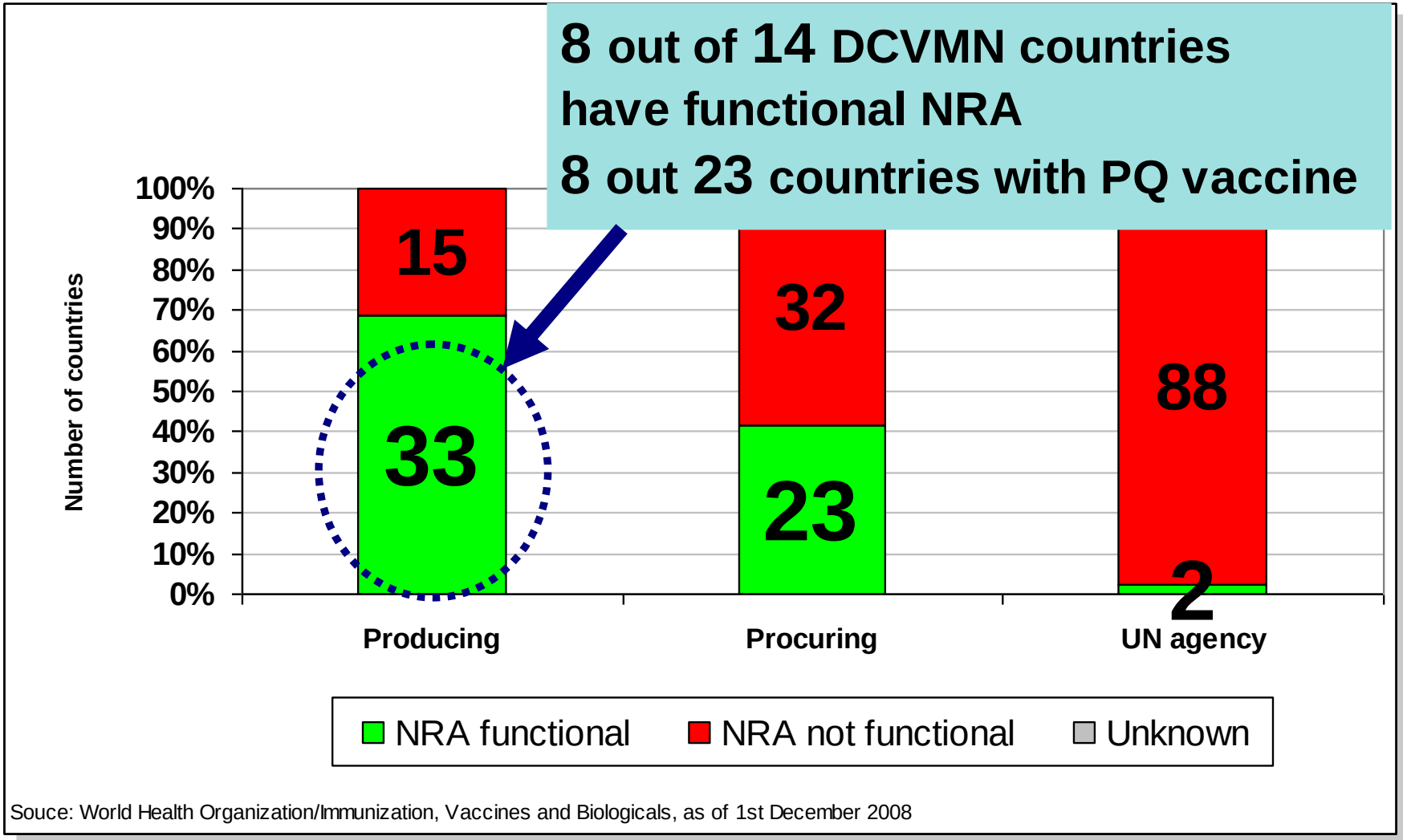
PRIORITY FOR IMPLEMENTING REGULATORY FUNCTIONS

Regulatory functions	Source of vaccines: UN agency	Procure	Produce
Regulatory system	✓	✓	✓
Marketing Autorization & Licensing activities	✓	✓	✓
Postmarketing: AEFI	✓	✓	✓
Lot release	Functions undertaken in producing Countries that	✓	✓
Laboratory access		✓	✓
Regulatory inspections		are functional	✓
Authorization & monitoring of CTs	✓ in countries that conduct clinical trials	✓	✓

STRENGTHENING NATIONAL REGULATORY AUTHORITIES (NRA)
STATUS OF NRA, 2008



Souce: World Health Organization/Immunization, Vaccines and Biologicals, as of 1st December 2008

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Vaccines prequalified by WHO: Status 2010 (* DCVMN countries)

15
industrialized country mfrs

- ✓ Australia
- ✓ Belgium
- ✓ Canada
- ✓ Denmark
- ✓ France
- ✓ The Netherlands
- ✓ Germany
- ✓ Hungary
- ✓ Italy
- ✓ Japan
- ✓ Rep. of Korea*
- ✓ Switzerland
- ✓ Sweden
- ✓ United Kingdom
- ✓ USA

8
emerging economy country mfrs

- ✓ Brazil *
- ✓ Bulgaria
- ✓ Cuba *
- ✓ India *
- ✓ Indonesia *
- ✓ Russia
- ✓ Senegal *
- ✓ Thailand *

24 manufacturers

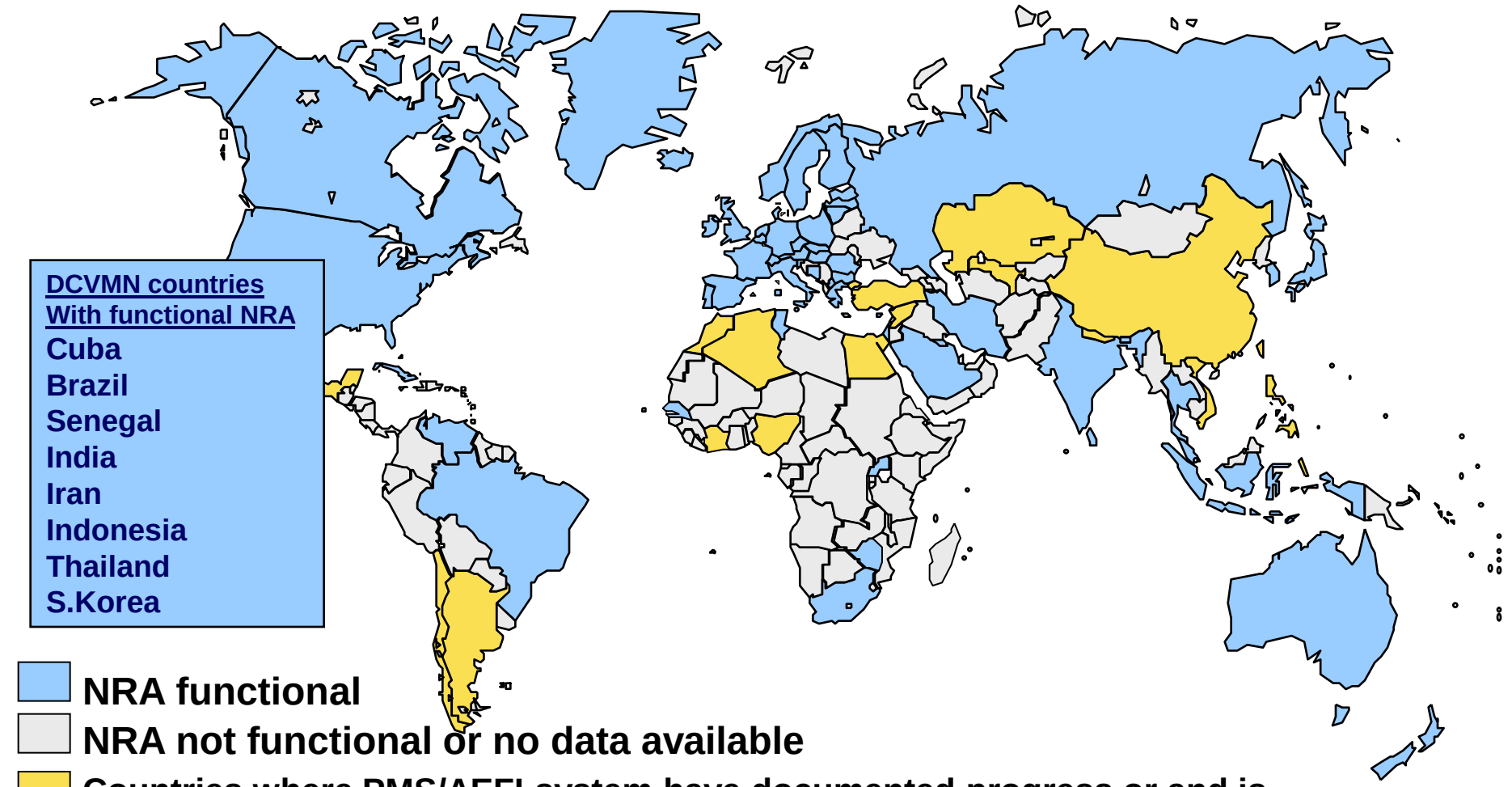
36 Sites

108 pre-qualified vaccines

used in **124** countries

64% global population

59 (31%) OUT OF 193 MEMBER STATES HAVE A FUNCTIONAL NRA TO REGULATE VACCINES



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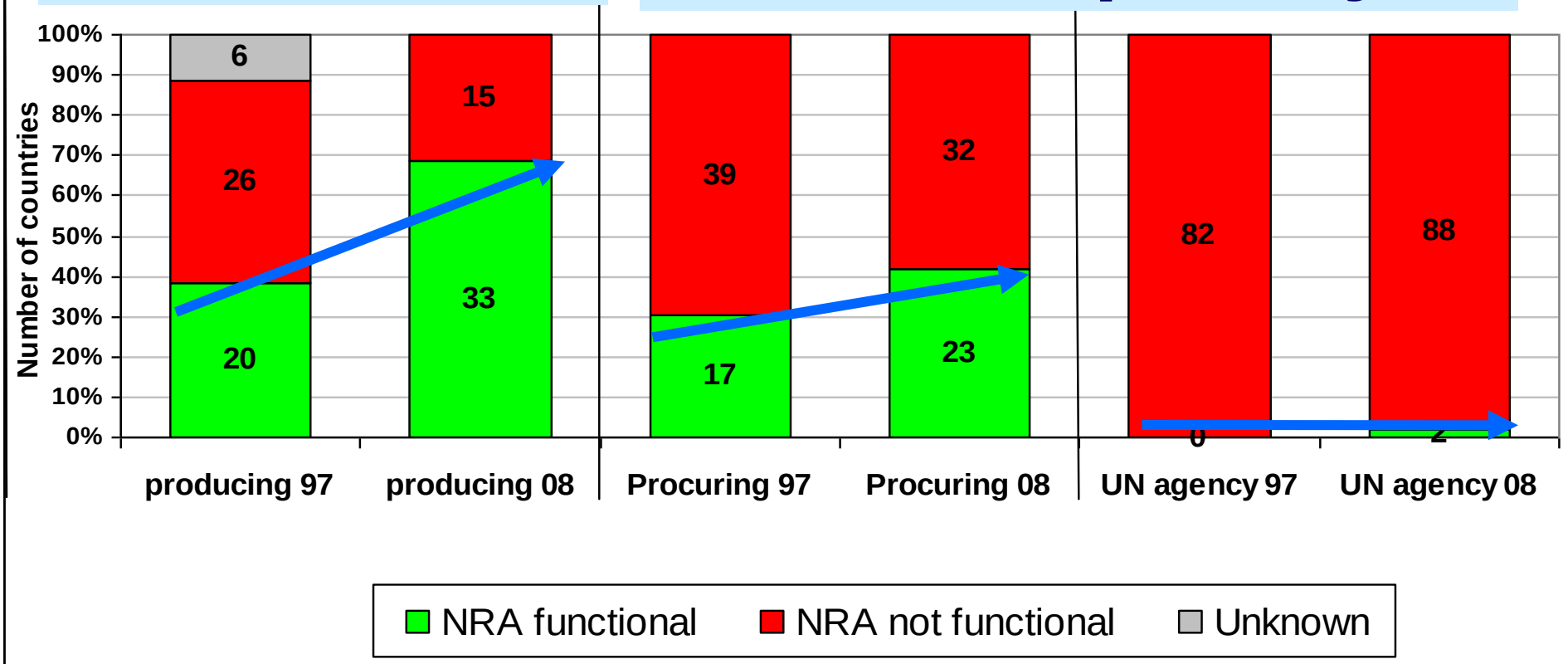
STRENGTHENING NATIONAL REGULATORY AUTHORITIES (NRA)
STATUS OF NRA, 1997 & 2008

High priority

Medium priority



Souce: World Health Organization/Immunization, Vaccines and Biologicals, as of 1st January 2009

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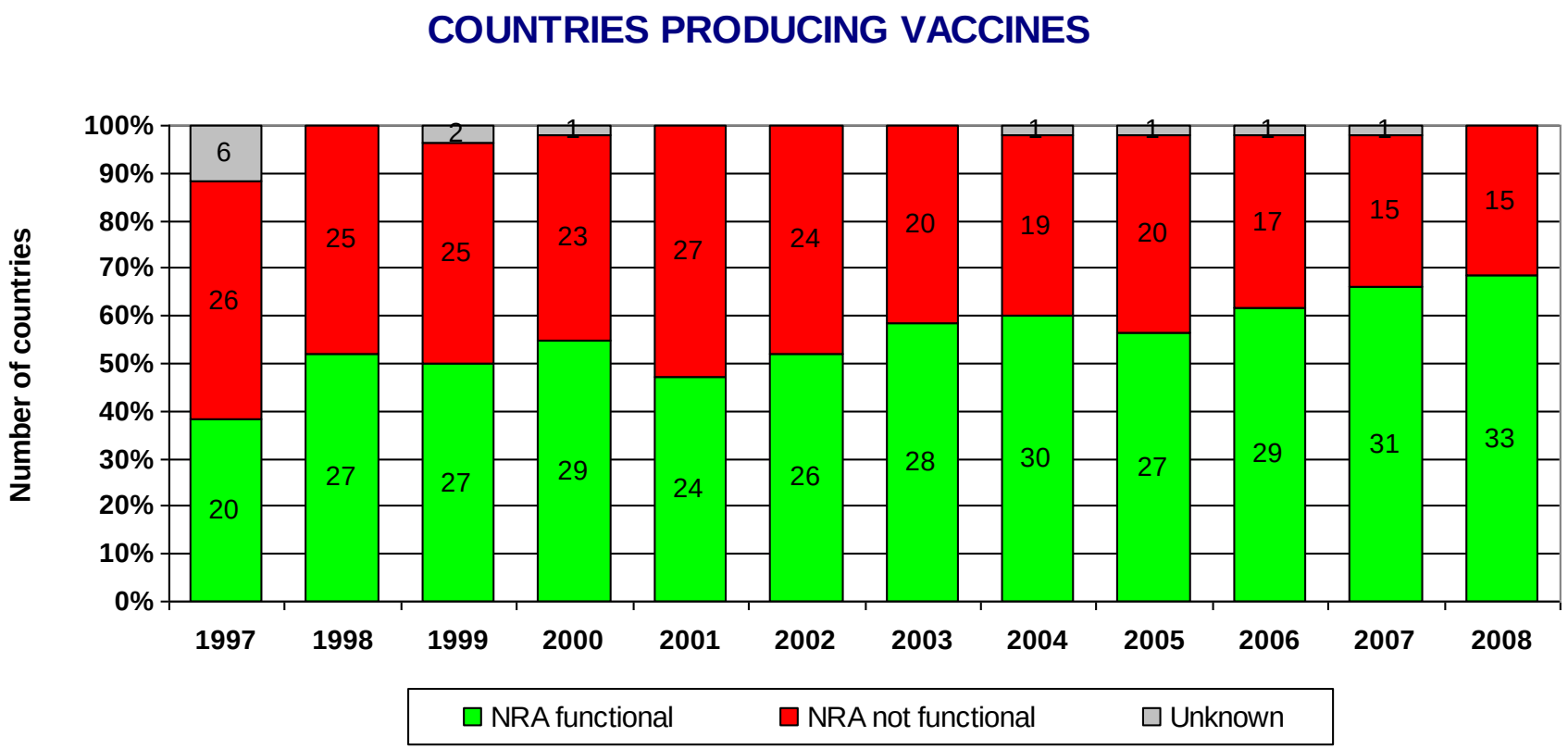
STRENGTHENING NATIONAL REGULATORY AUTHORITIES (NRA)
STATUS OF NRA, 1997 - 2008



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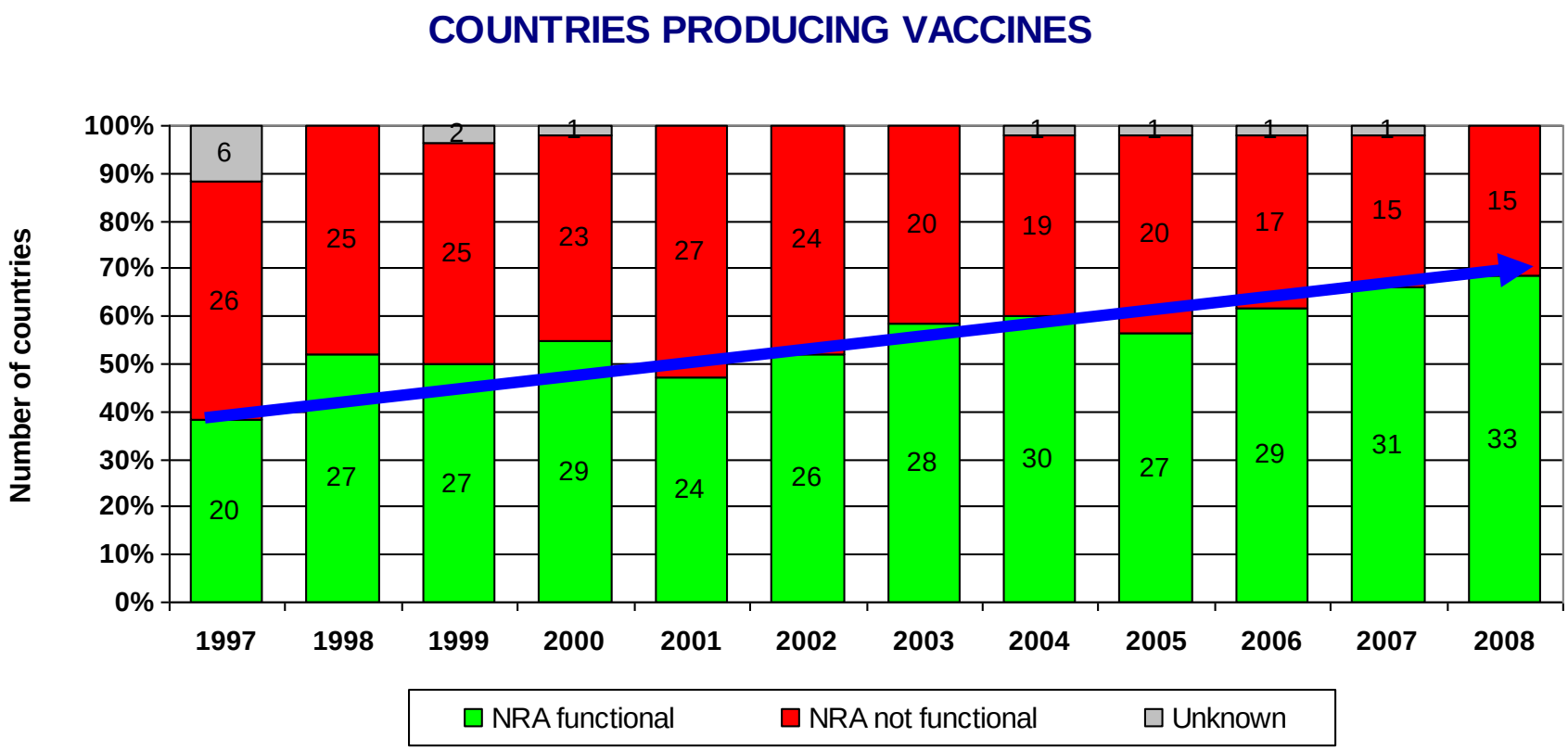
STRENGTHENING NATIONAL REGULATORY AUTHORITIES (NRA)
STATUS OF NRA, 1997 - 2008



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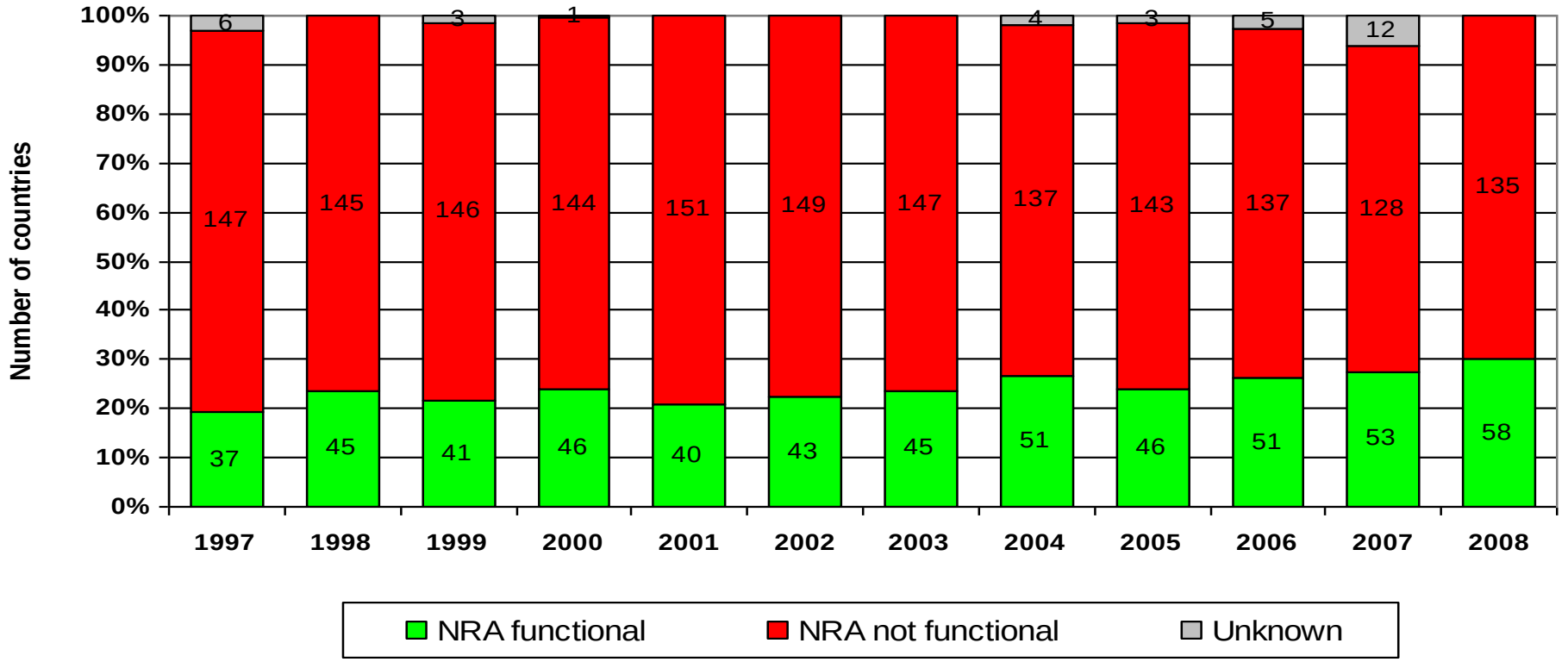
STRENGTHENING NATIONAL REGULATORY AUTHORITIES (NRA)
STATUS OF NRA, 1997 - 2008



Souce: World Health Organization/Immunization, Vaccines and Biologicals, as of 1st december 2008

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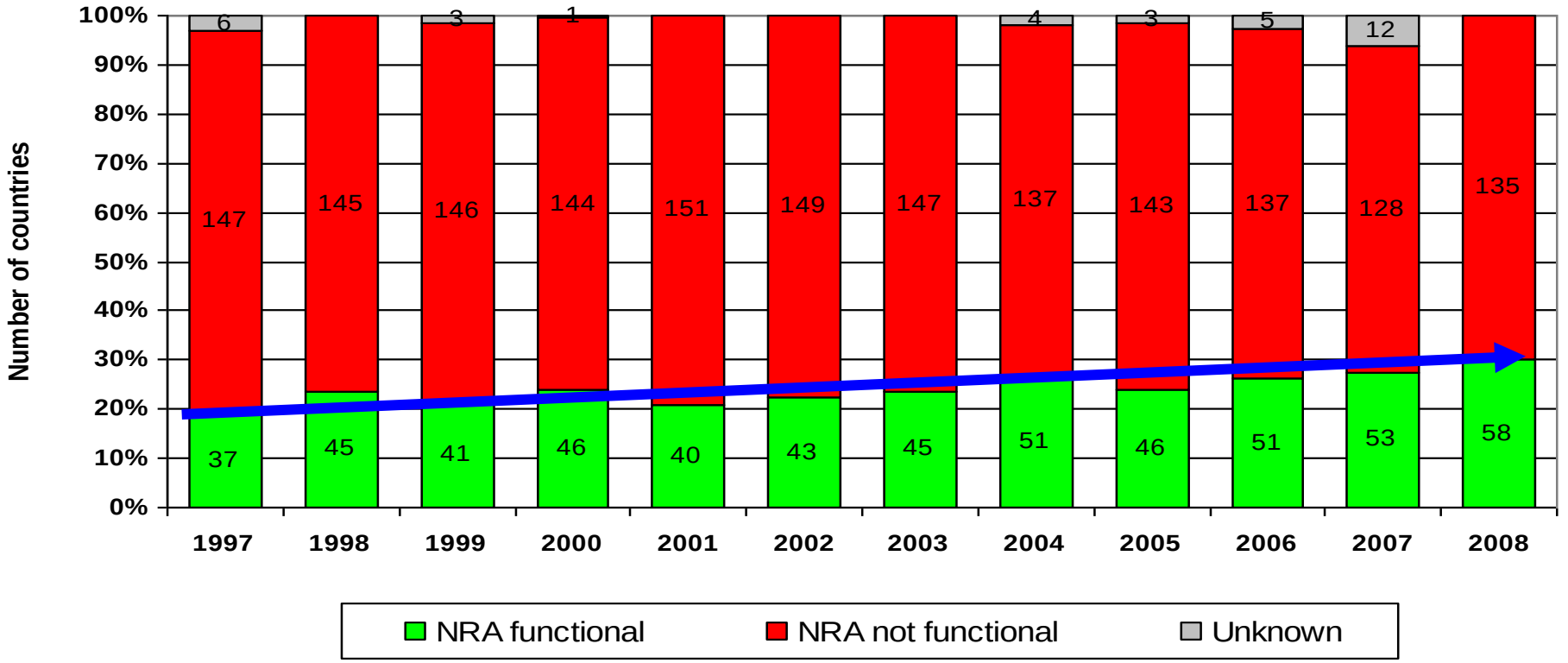
STATUS OF NRA, 1997 - 2008



Souce: World Health Organization/Immunization, Vaccines and Biologicals, as of 1st december 2008

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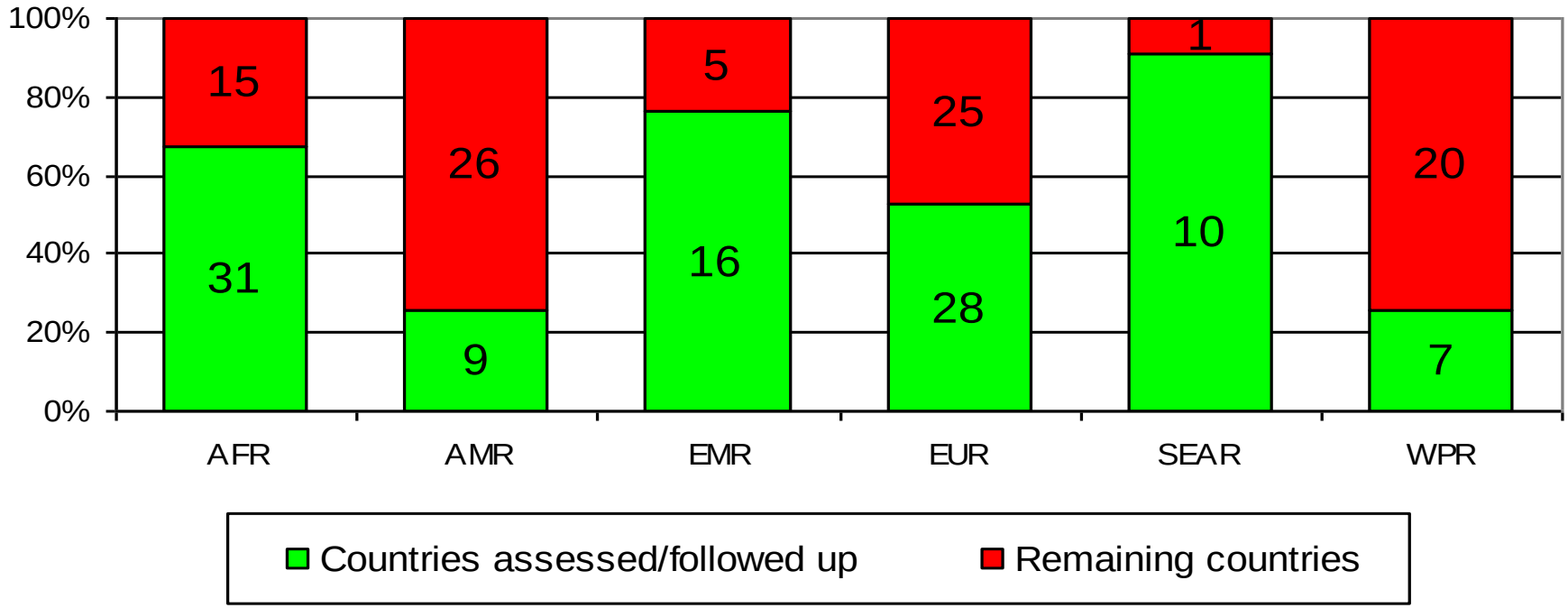
STRENGTHENING NATIONAL REGULATORY AUTHORITIES (NRA)
101 COUNTRIES WHO* NRA ASSESSED AND FOLLOWED UP
1996 - 2008



*World Health Organization
**Immunization Vaccines and Biologicals

Source: WHO*/IVB**, as of November 2008

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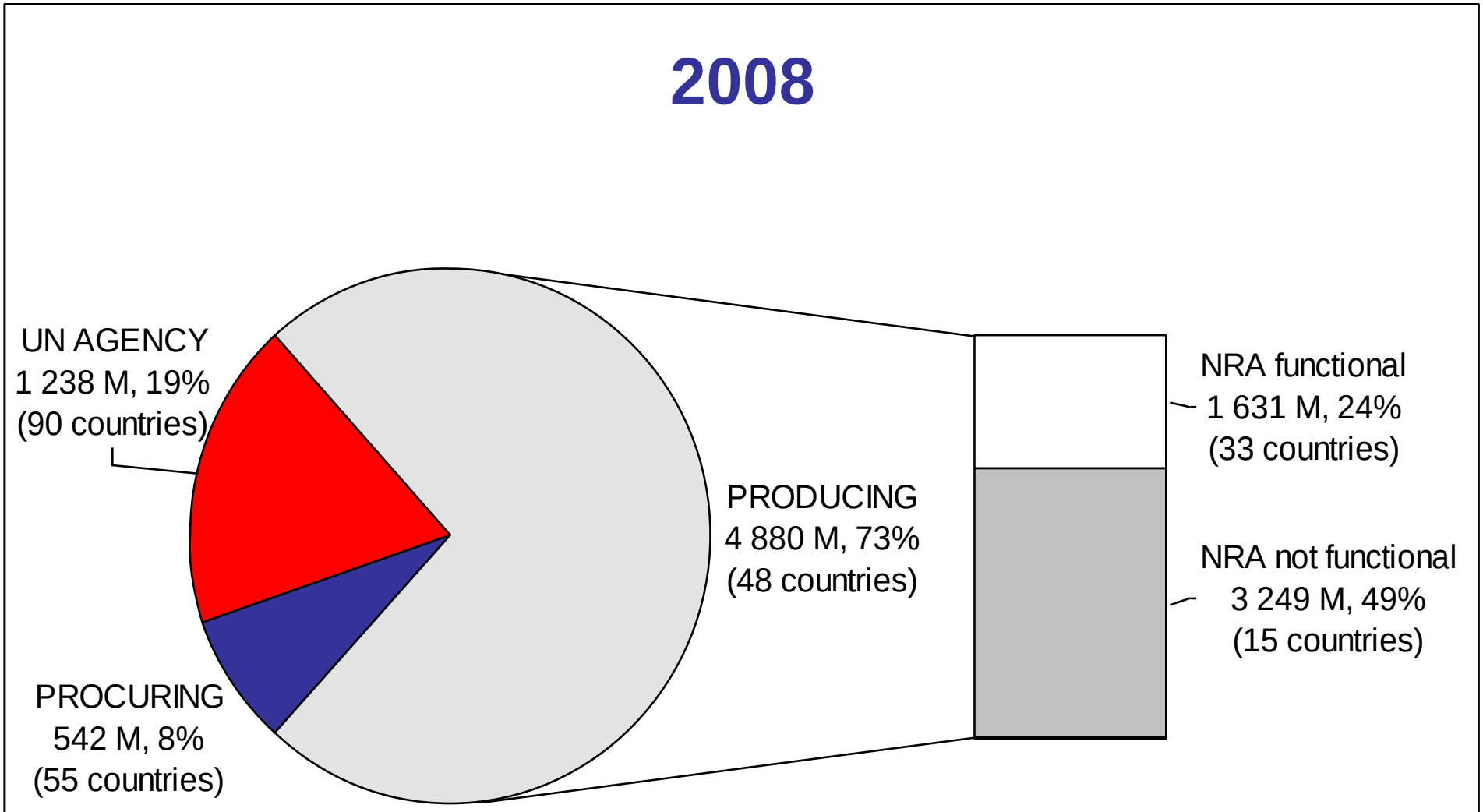
STATUS OF NRA ACCCORDING TO THE MAIN SOURCE OF VACCINES
COUNTRIES AND TOTAL POPULATION STATUS



Population in millions (M)
Souce: World Health Organization/Immunization, Vaccines and Biologicals, as of 1st december 2008

	Countries	Number Manufacturers	WHO prequalified products	NRA functional	Meet WHO GMP	Ongoing production	Plan to expand capacity	Export	Potential for new PQ products
1	India	12	several	Yes	90% private, 20% public	Yes	Yes	Yes, several	VERY HIGH
3	Indonesia	1	several	Yes	100% public	Yes	Yes	Yes, several	VERY HIGH
6	Cuba	2	several	Yes	100% public	Yes	Yes	Yes, several	VERY HIGH
7	Brazil	3	several	Yes	100% public and private	Yes	Yes	Yes, several	VERY HIGH
8	Iran	2	0	Yes	20% public	Yes	Yes	No	HIGH
9	Senegal	1	1	Yes	Production stopped but 100% public	No, but will start again in early 2011	Yes	Yes, YF only	LOW
1	Korea	3	several	Yes	100% private	Yes	Yes	Yes, several	HIGH
1	Thailand	3	1	Yes	60% private/public	Yes	Yes	Yes, Measles	VERY HIGH

DCVMN countries	NRA functional	POTENTIAL FOR NEW PQ	CONSTRAINTS MET
India	YES	VERY HIGH	PUBLIC UNITS
Egypt	NO	LOW	GMP
Indonesia	YES	VERY HIGH	RESSOURCES
Mexico	NO	LOW	STOP
China	NO	VERY HIGH	QMS AND GMP
Cuba	YES	VERY HIGH	RESSOURCES
Brazil	YES	VERY HIGH	QMS AND GMP
Iran	YES	MEDIUM	QMS AND GMP
Senegal	YES	LOW	RESSOURCES
Yugoslavia	NO DATA	NO DATA	NO DATA
Korea	YES	VERY HIGH	NONE
South Africa	NO DATA	NO DATA	NO PRODUCTION
Viet Nam	NO	VERY HIGH	QMS, GMP AND RESSOURCES
Thailand	NO	VERY HIGH	QMS AND GMP

	Countries	Number Manufacturers	WHO prequalified products	NRA functional	Meet WHO GMP	Ongoing production	Plan to expand capacity	Export	Potential for new PQ products
1	India								VERY HIGH
3	Indonesia								VERY HIGH
6	Cuba								VERY HIGH
7	Brazil								VERY HIGH
8	Iran								HIGH
9	Senegal								LOW
1	Korea								HIGH
1	Thailand	3	1	Yes	private/public	Yes	Yes	Yes, Measles	VERY HIGH

This group of countries will Have better environment opportunities to:

- -Expand vaccine production
- -Scale up existing production
- -Meet demand of export market
- -Adapt to more stringent quality standards
- -Supply additional PQ products

NRA are developing new business model to regulate biologicals

- Expanding and enhancing their Quality Management System and risk benefit/management approach/concept
- Identifying better their customers and defining new services to customers (Public, manufacturers, delivery programme, etc..)
- Increasing internal expertise and developing network of national experts
- Expanding their role in postmarketing surveillance *(provision for PMS IV , GMP inspection using risk management approach, NCL lot release data, trend analyis data),*
- Collaborative networks through international network, *twinning or during parallel product evaluation (India/Canada, Thailand/Australia/US), DCVRN, AVAREF, etc.*

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Impact on viability of vaccine production: Domestic and export market constraints

- Implementation of CTD for marketing authorisation/licensing
  - Requirements increased through thorough documentation
  - Assessment of product involving expert committees and increase leadership from internal expertise
  - Onsite evaluation linked to Marketing authorisation process
  - Development skills and expertise in evaluation and supervision of clinical trials

- Enforcement of a more stringent GMP
  - Risk approach concept applied to regulatory inspections
  - Environmental monitoring
  - Validation
  - Quality management system consistent with ISO principles
  - Monitoring and tracking of variations
  - Foreign inspections providing opportunities to raise skills

Impact on viability of vaccine production: Domestic and export market

- Expansion of NRA lot release activities
  - Risk approached testing
  - Procuring countries are now implementing also lot release
  - Use of trend analysis data and active monitoring of manufacturer QC deviations

- PMS and AEFI surveillance
  - Increase capacity for AEFI surveillance : India, China, Viet Nam, Senegal will increase oversight of marketed products
  - Better coordination among regulators, manufacturers and immunization surveillance programme improve causality assessment.

Possible impact and challenges

- **<u>Increasing of registration fees is likely to happen:</u>** NRA needs to adjudt to increasing workload and be more responsive:
  - registration fees varies between 50 usd to max 1.500 USD in developing countries.
  - May be tier pricing fees can be promoted to reduce barriers for DCVMN.
- Introduction of CTD is likely to increase manufacturer workload and guide manufacturers to strenghten their regulatory affairs teams:
  - CTD had been introduced and adapted in Egypt, India , Iran and Thailand in 2009, will be introduced in Viet Nam, All ASEAN countries, Senegal,by end of 2011.

Areas of emphasis in SEAR regional vaccine policy (2011-2015)

Regional Vaccine Policy (2011-2015)
1. Guiding principles and lessons learned
2. Specific policy objectives
3. Policy framework
3.1 Vaccine research and development, technology transfer and public private approaches
3.2 Vaccine selection, introduction, financing based on burden of disease and national prioritization, and NCIP/NITAG recommendations
3.3 Vaccine quality and regulation
3.4 Regional vaccine security
3.5 Human resources development
3.6 Knowledge centre; information clearing house; centres of excellence with focus on diseases with global eradication/elimination goals
3.7 National vaccine policy

Special thanks to major contributors

- BMGF for supporting vaccine producing countries and Global/regional coordination
- USAID for supporting INDIAN NRA
- AUSAID for supporting Asean countries
- JICA and MOFWA for supporting Viet Nam
- DFID for supporting training in several countries
- EDCTP for supporting African countries
- EU for supporting NRA assessments in developing countries
- World Bank for supporting training and assessment
- Islamic development Bank for supporting producing countries
- GAVI for supporting Global and regional coordination as well as GAVI countries
- Govt. of Italy for supporting NRA assessments

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information sources

- WHO Web site: http://sharepoint.who.int/sites/ATT/default.aspx
- WHO Web site: :http://www.who.int/vaccines-access/
- Reference document: ***Strengthening National Regulatory Authorities***
  - Aide-memoire - strengthening national regulatory authorities
  - GPV Policy Statement - vaccine donations, WHO/VSQ/97.05
  - Informal consultation of experts on national regulation of vaccines, WHO/V&B/99.08
  - Policy Statement of the partners of the Global Alliance for Vaccines and Immunization, WHO/V&B/00.25
  - Regulation of vaccines: building on existing drug regulatory authorities, WHO/V&B/99.10
  - Statement on vaccine quality, WHO/VSQ/GEN/96.02 REV 1
  - Training manual: licensing, lot release, laboratory access WHO/V&B/01.16
  - Training manual on the critical regulatory function for vaccines: evaluation of critical performance through authorized trials ,WHO/V&B/03.12
  - Vaccine Quality - can a single standard be defined? Vaccine 2956 (2001) 1-4

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