

# Dynamics of Pharmaceutical Quality & Effective Sourcing of Quality-Assured Pharmaceuticals

Oct 2, 2014  
Bahir Dar, Ethiopia

**DNDi**

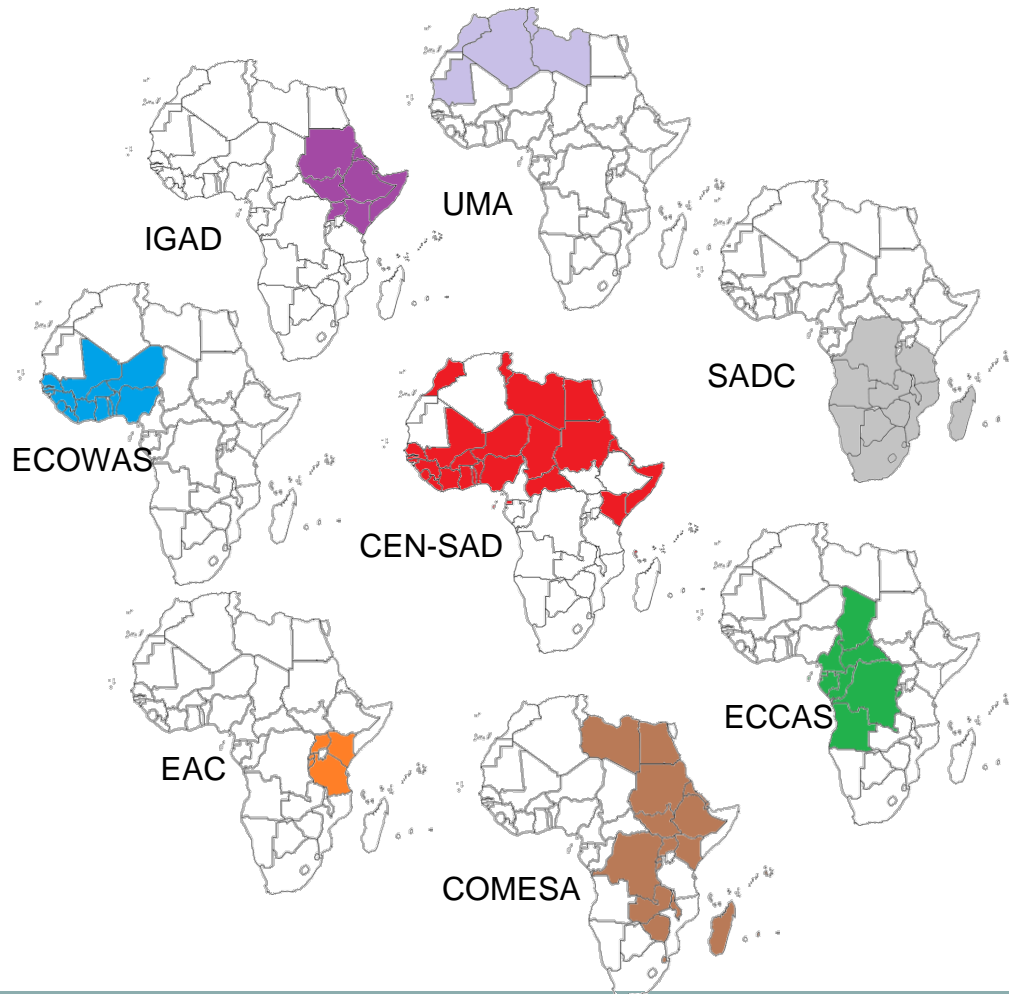
Drugs for Neglected Diseases *initiative*



PAUL LALVANI  
DEAN AND DIRECTOR  
EMPOWER SCHOOL OF HEALTH  
NEW DELHI, INDIA

# Africa and Regional Economic Communities (RECs)

2





# RECs Overview

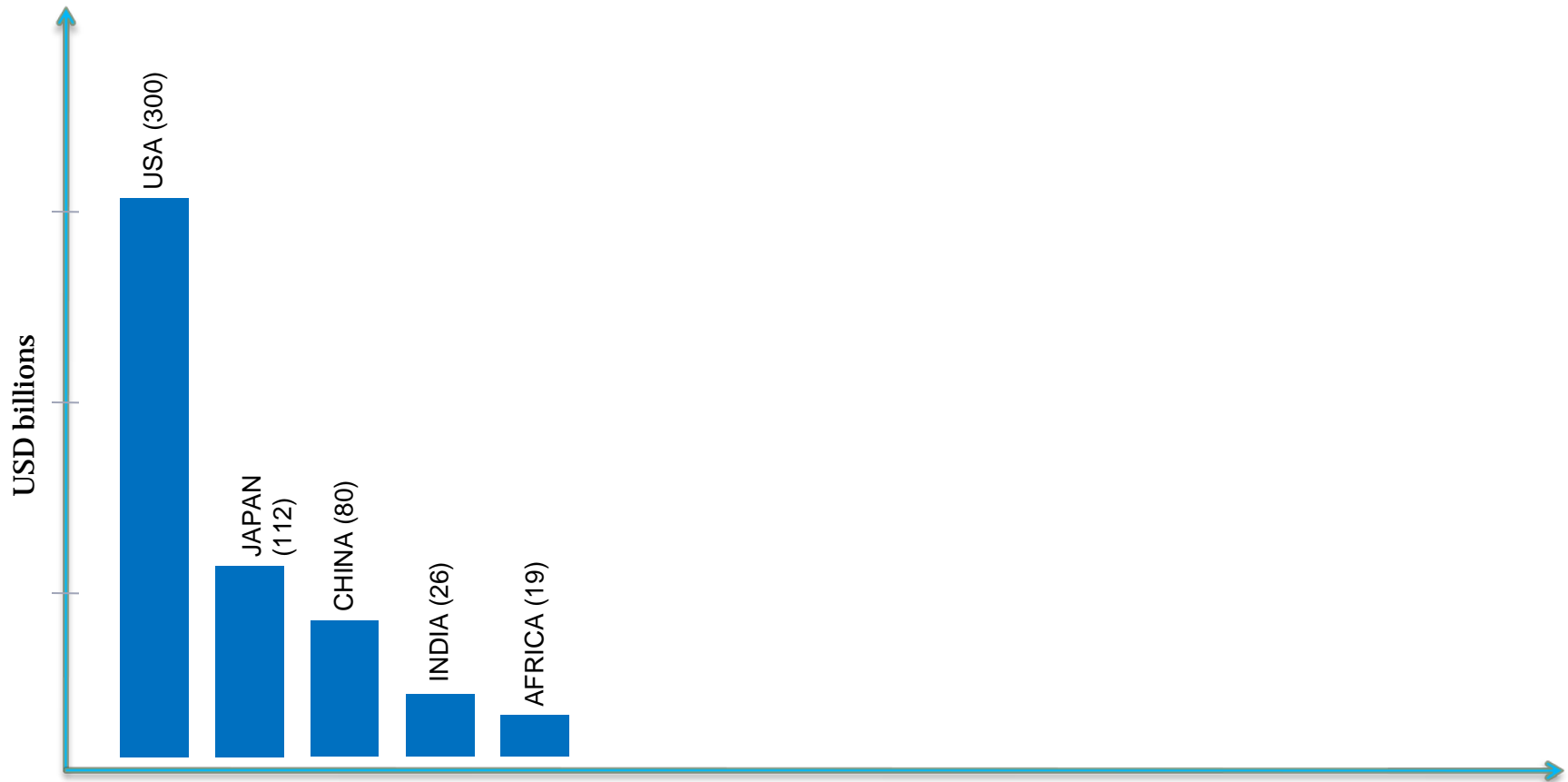
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RECs	Number of member countries	GDP (US\$ billion)	Growth (%)	Population (Million)	Pharmaceutical market (US\$ billion)
EAC (The East African Community)	5	134.6	5.9%	70	1.1
COMESA (Common Market for Eastern and Southern Africa)	14	440.8	5.3%	446	2.7
ECOWAS (Economic Community of West African States)	15	295.3	6.7%	310	2.9
SADC (The Southern African Development Community)	15	269.6	5.23%	472	5.6
UMA (Arab Maghreb Union)	5	391.8	3.6%	87	5.2
IGAD (The Intergovernmental Authority on Development)	7	129.9	6.1%	207	1.7
CEN-SAD (The Community of Sahel-Saharan States)	27	790.2	5.2%	543	4.0
ECCAS (The Economic Community of Central African States)	10	133.9	3.8%	175	1.0

# World Pharmaceutical Market

(\$ billions, 2011-12)

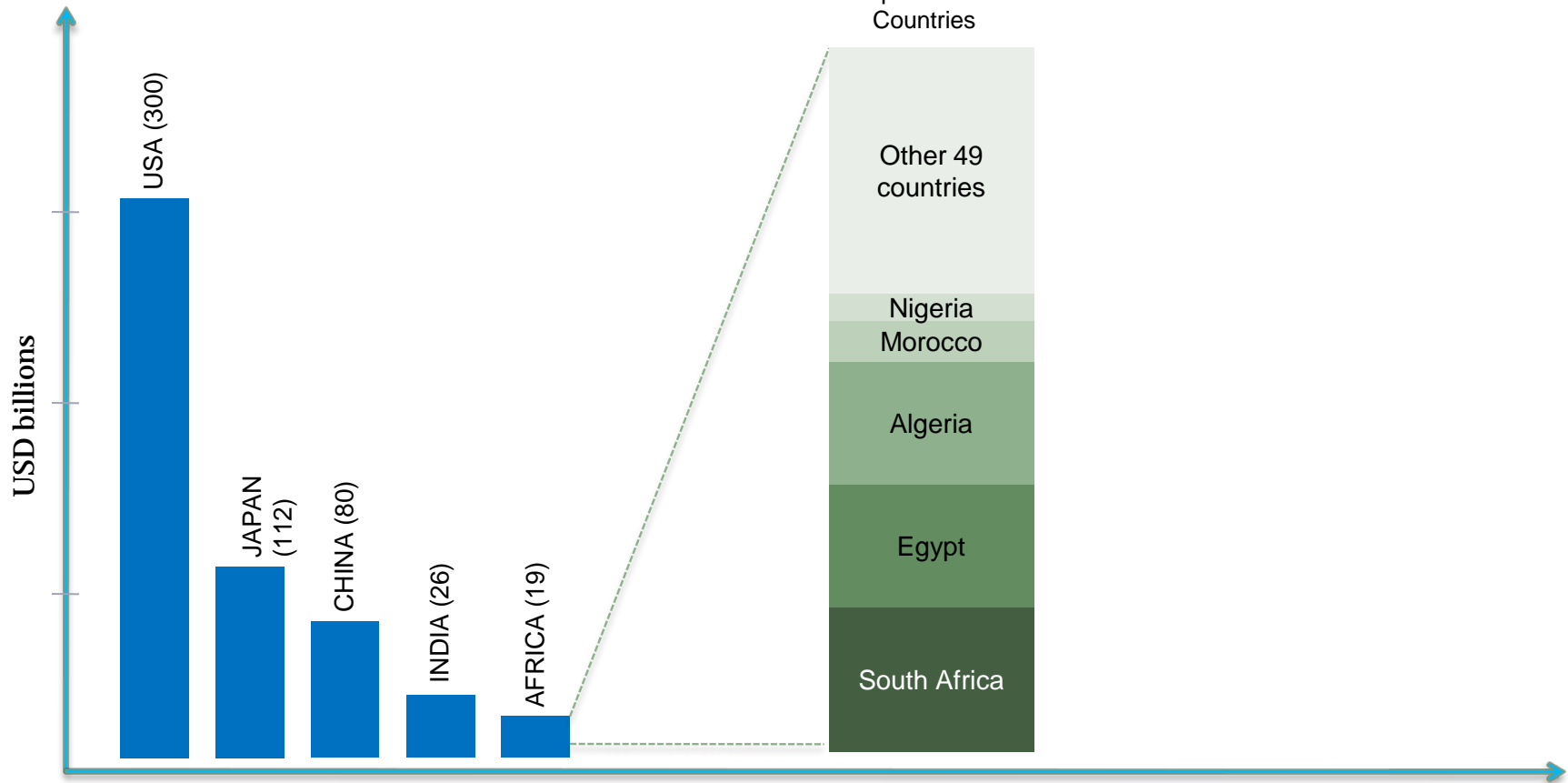
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# World Pharmaceutical Market

(\$ billions, 2011-12)

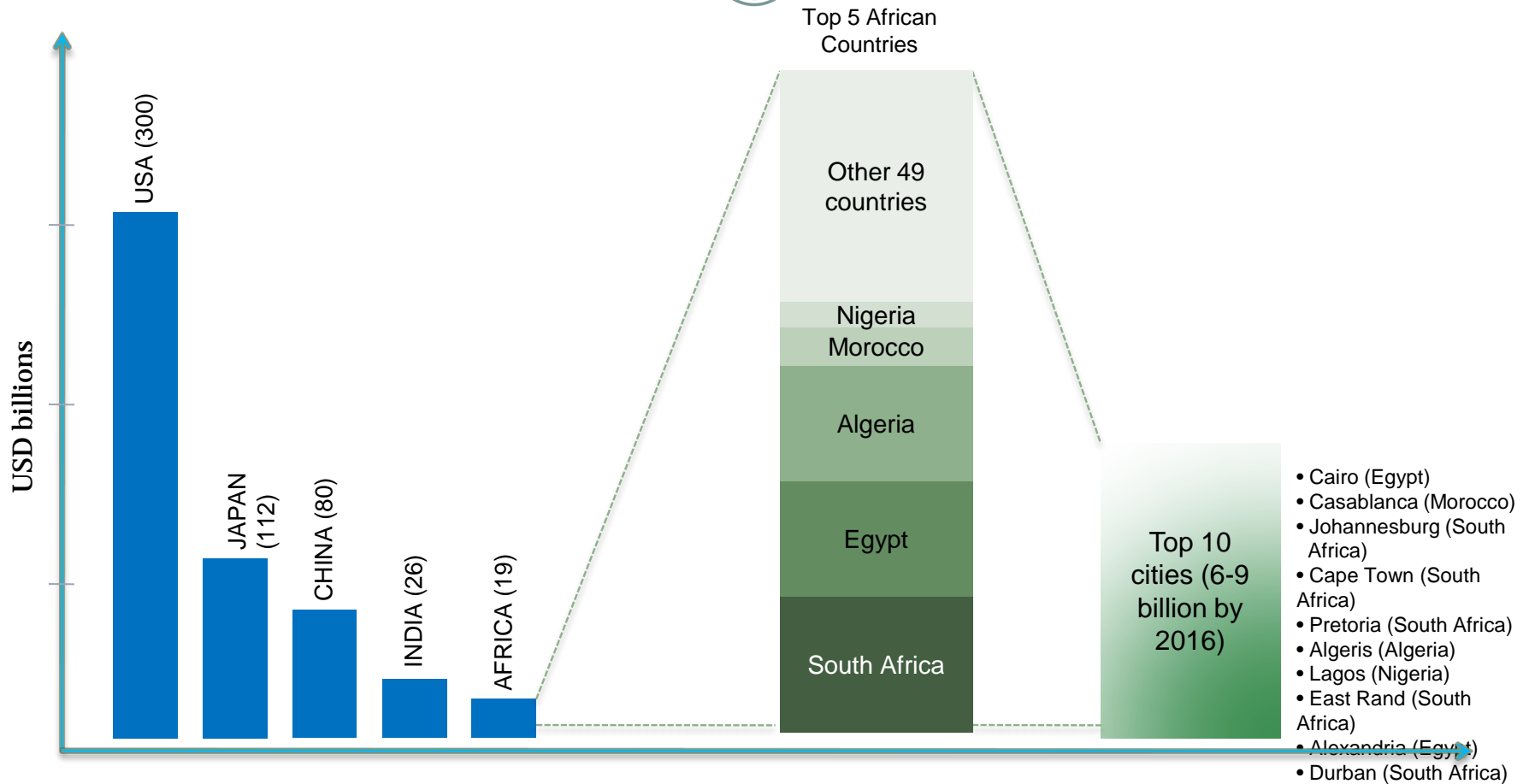
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# World Pharmaceutical Market

(\$ billions, 2011-12)

6

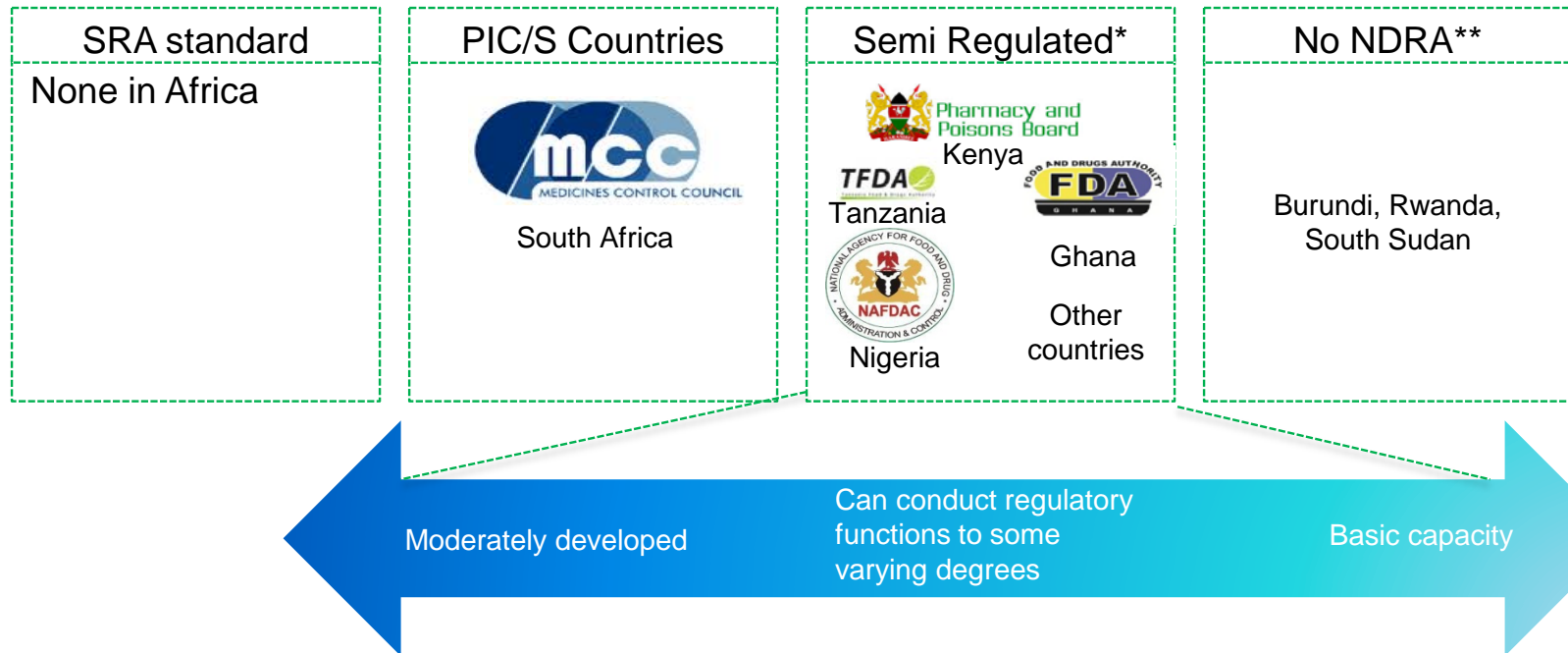


# Africa Pharmaceutical Regulation

7

More Stringent

Less Stringent



**“35% The share of anti-malarial drugs tested in sub-Saharan Africa that were found to be substandard”**

Source: The Lancet Infectious Diseases journal, May 2012

\* Last published data was 2004-2008 \*\* may regulate through some MoH department

# Pharmaceutical Regulatory Environment in Asia (and supplier countries)

8

More Stringent

Less Stringent

## SRA standard

Japan  
USA  
Europe  
Australia  
Canada  
++

## PIC/S Countries



## Semi Regulated





# Prevalence of poor quality drugs in Africa

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## The Deadly World of Fake Drugs



# China Drug Quality – Media Coverage

10

*'Unregulated Chinese companies are exporting pharmaceutical ingredients with few or no quality checks'*

- As published by a UK based international news agency Reuters



## FDA Finding Fuels Indian Crackdown on Sub-standard Drugs

By GUEST BLOGGER | Published: JULY 27, 2011

By Mangesh Sai, Asia Correspondent.

A routine monthly inspection carried out by the Food and Drugs Administration (FDA) authorities in the state of Maharashtra, India, last month noted an increase in the number of sub-standard drug samples raising apprehensions about the availability of safe and genuine drugs in the state. Officials pointed out that 26 drug samples were found to be spurious, compared with the 16 samples that were not-of-standard quality detected in May and 20 in April. Reportedly, some Ampicillin and Amoxycillin formulations did not have any active ingredients, while others had 6% to 30%. Thiamine tablets with Vitamin B1 and diclofenac sodium, Paracetamol and Magnesium Trisilicate tablets were also found to be sub-standard, officials said.

While some of the offenders are well-known drug manufacturers (like Alkem Laboratories for omeprazole capsules and Venus Biosciences for Odicin-200), many are small drugmakers, such as Affy Pharma for levocetirizine tablets, Medipol Pharmaceuticals India for clauvmentin dry syrup, Endolabs for paracetamol tablets, Softsule for DIAX OD, Therachem Laboratories for Metflo, Medopharm for Milclav dry syrup, amoxycillin and potassium CLA S, Biocin Healthcare for Thyomin tablets and Nuclotec Remedies for Digizyme syrup.

Sub-standard drugs from India has been a major issue for some time now, though the FDA says its crackdown has ensured a significant drop in the number over the past six months. \* In a bid to



## India says its drugs safe despite Ranbaxy generics fraud

Agence France-Presse | Updated: June 03, 2013 16:23 IST



**New Delhi:** India, known as the "pharmacy to the world", today defended its lucrative generic drug industry as safe and strongly regulated after the nation's biggest drug firm pleaded guilty to US charges of making adulterated medicines.

In a bid to defend its generic export sector, the government also charged that "isolated reports" of spurious drugs found in global markets and alleged to be from India were "desperate attempts" by other countries hurt by "the strength of the Indian pharma industry".

India's "pharmaceutical sector is a highly regulated one and the exports are heavily guided by various regulatory regimes of the importing countries", the government said in a statement.

The statement came after New Delhi-based Ranbaxy Laboratories, India's largest drug company by sales, pleaded guilty in the United States to criminal charges of making adulterated medicines and agreed to a 500 million dollar (around ₹ 2833 crore) settlement.

Organization



## Fake drug racket: One more held

Dwaipayan Ghosh, TNN Jul 27, 2011, 04:55am IST



**NEW DELHI:** Days after three persons were arrested for running one of the largest drug rackets from Delhi and NCR, the crime branch made a fourth arrest after raiding a factory in the Naraina industrial area in southwest Delhi.

DCP (crime) Ashok Chand confirmed the arrest. The accused, Afroz Alam, was involved in preparing fake aluminium foil which was used to package the fake drugs.



## India, Africa to check fake drug menace

Anirban Bhattachik, New Delhi, DHNS:

Medicines from China being off-loaded as Indian products in Ghana, South Africa and Ivory Coast

With Chinese counterfeit medicines being pushed into Africa with fake "Made-in-India" labels, New Delhi is in favour of close interaction between Indian drug regulators and their African counterparts to jointly fight against the menace.

Keen to make it sure that mischief by some pharmaceutical companies based in China does not have any adverse impact on India's growing business interests in Africa, New Delhi took up the issue with Beijing and requested it to take action against the fake drug makers.

"The health of our brothers and sisters in Africa are as important for the Indian government as that of our own citizens," said Gurjit Singh, Joint Secretary in the East and Southern Africa Division of the Ministry of External Affairs. "It is now clear that the fake drugs being sold in Africa with 'Made in India' tag are not produced in India, but elsewhere," he said.

Singh did not specify in which country the fake medicines were actually being produced. But probes by drug controlling authorities in Nigeria and other African countries over the past few years proved that the counterfeit medicines were in fact produced in China. The National Agency for Food and Drug Administration and Control of Nigeria in 2009 seized a large consignment of counterfeit anti-malarial generic medicines with "Made in India" labels and later found that the fake drugs had in fact been produced in China.



## India agrees to help Nigeria tackle the import of fake drugs

Abiodun Raufu

Additional article information

India, one of the largest exporters of fake and substandard drugs to Nigeria, has agreed to take measures to tackle the problem. It is concerned about Nigeria's threat to ban the import of all drugs from countries that export fake drugs to its shores.

The Indian minister of state for commerce and industry, Mr Shri Rajiv Pratap Rudy,



## BMJ Group Blogs



BMJ Group

## Amir Attaran and Marvin Shepherd: Denialism and India's risky medicine

24 Jan, 13 | by BMJ Group



Governments that lie are dangerous to public health [1]. South Africa's shameless denial that HIV causes AIDS delayed treatment for millions, and many needlessly died.



Now India's government is doing something similarly brazen by denying that India exports fake medicines to Africa. It is an untruth for which India must apologize and which it must correct.

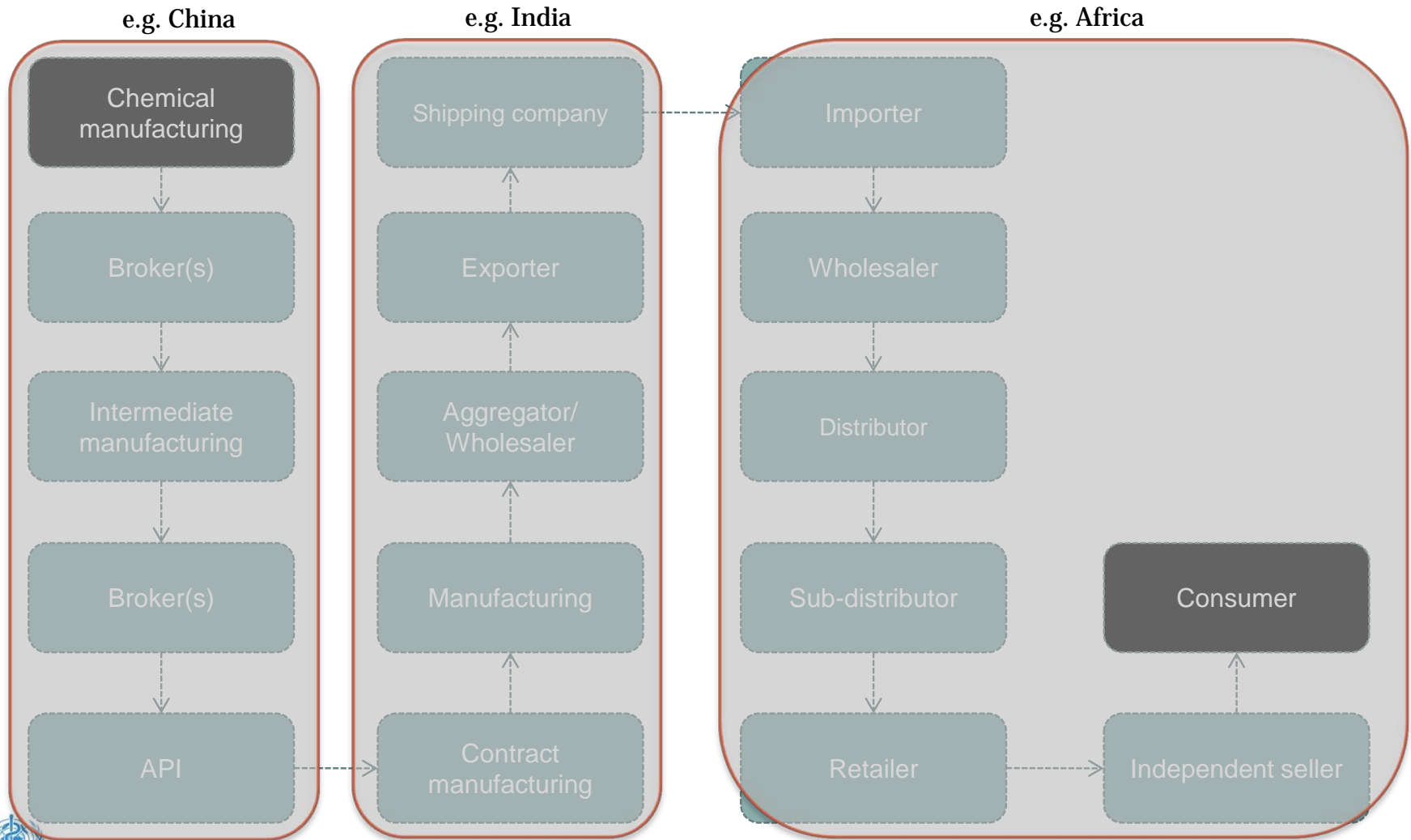
In December 2012, the Guardian reported that Africa is awash with falsified or substandard lania medicines and that it is suspected these 'come from China and India.' India's Ministry of External Affairs denounced the Guardian's report in a widely issued statement. "The Government of India," it reads, "would like to state categorically that the report is totally incorrect. No fake medicines have been sent from India to the continent of Africa."

de from the strangeness of the comment—how would the Indian government know it exits its borders?—India's categorical denial is false. The UN Office of Drugs and Crime rightly identifies a "consensus, increasingly backed by forensic research ... that



# The Long and Winding Multi-country Pharmaceutical Supply Chain

## From Chemical to Consumer





# Importer and Wholesale market in Onitsha, Nigeria

13



Ever busy Onitsha Main Market

Drugs being sold  
in the open market



# African Private Sector Importers and QA



	QUALITY ASSURANCE CONTINUUM		
Quality indicators	More stringent	In - between	Less stringent
Do you conduct Audits/inspection?			
Do you conduct Audits/inspection for Indian suppliers?			
Do you conduct Audits/inspection for Chinese suppliers?			
Frequency of audits			
Pre-shipment testing			
Laboratory used			
Post-shipment testing			
Post-marketing surveillance			
<div><div><div></div><div>YOHA International</div></div><div><div></div><div>Dominion Pharmaceuti</div></div><div><div></div><div>Veteran pharmaceuticals</div></div><div><div></div><div>Caroga Pharma</div></div></div>			

# African Private Sector Importers and QA



	QUALITY ASSURANCE CONTINUUM		
Quality indicators	More stringent	In - between	Less stringent
Do you conduct Audits/inspection?	Yes	Not for all suppliers	No
Do you conduct Audits/inspection for Indian suppliers?	Yes	Not for all suppliers	No
Do you conduct Audits/inspection for Chinese suppliers?	Yes	Not for all suppliers	No
Frequency of audits	Annual	2-5 years	No re-inspections
Pre-shipment testing	Yes	In some cases	No
Laboratory used	WHO Prequalified	ISO certified	Any other laboratory
Post-shipment testing	Yes	In some cases	No
Post-marketing surveillance	Yes	In some cases	No

YOHA International
 Dominion Pharmaceuti
 Veteran pharmaceuticals
 Caroga Pharma

# Pharmaceutical manufacturing sites in India and relative quality standards

9,000-10,000 manufacturing sites

1,000-1,500 manufacturing sites

**Highest  
Standard**

**Schedule M**  
**(Approval by any one of India's State Drug Regulatory Authority)**

**Indian  
State DRA  
Approved  
Standard**

**Source:** CDSCO; Pharmexcil data 2012; IDA, WHO PQP, Empower analysis



# Pharmaceutical manufacturing sites in India and relative quality standards

9,000-10,000 manufacturing sites

1,000-1,500 manufacturing sites

WHO PQP

SRA

Highest  
Standard

International procurement  
agents

Approval by PIC/S and other  
NDRAs

Approval by Central and State  
(WHO cGMP)

**Schedule M**  
**(Approval by any one of India's State Drug Regulatory Authority)**

Indian  
State DRA  
Approved  
Standard

Source: CDSCO; Pharmexcil data 2012; IDA, WHO PQP, Empower analysis

# Variation in API Quality Standards

	Drug Master File (DMF)	Non - DMF	
		Detailed API information	Little /no API information

Source: Empower research

# Variation in API Quality Standards

	Drug Master File (DMF)	Non - DMF	
		Detailed API information	Little /no API information
Relative quality (purity, impurities, categorisation)			
Relative cost			
Regulatory requirements			
NDRA inspections			
Filing requirements if change in API source made			

Source: Empower research

# Variation in API Quality Standards

	Drug Master File (DMF)	Non - DMF	
		Detailed API information	Little /no API information
Relative quality (purity, impurities, categorisation)	High	Medium	Low
Relative cost	10	4	1
Regulatory requirements			
NDRA inspections			
Filing requirements if change in API source made			

Source: Empower research

# Variation in API Quality Standards

	Drug Master File (DMF)	Non - DMF	
		Detailed API information	Little /no API information
<b>Relative quality (purity, impurities, categorisation)</b>	High	Medium	Low
<b>Relative cost</b>	10	4	1
<b>Regulatory requirements</b>	SRA and only South Africa in African continent; International procurement agents also submit DMF	Nigeria, Zimbabwe, Tanzania, Uganda (now)	Most of francophone Africa, Sudan, Liberia and others
<b>NDRA inspections</b>			
<b>Filing requirements if change in API source made</b>			

Source: Empower research

# Variation in API Quality Standards

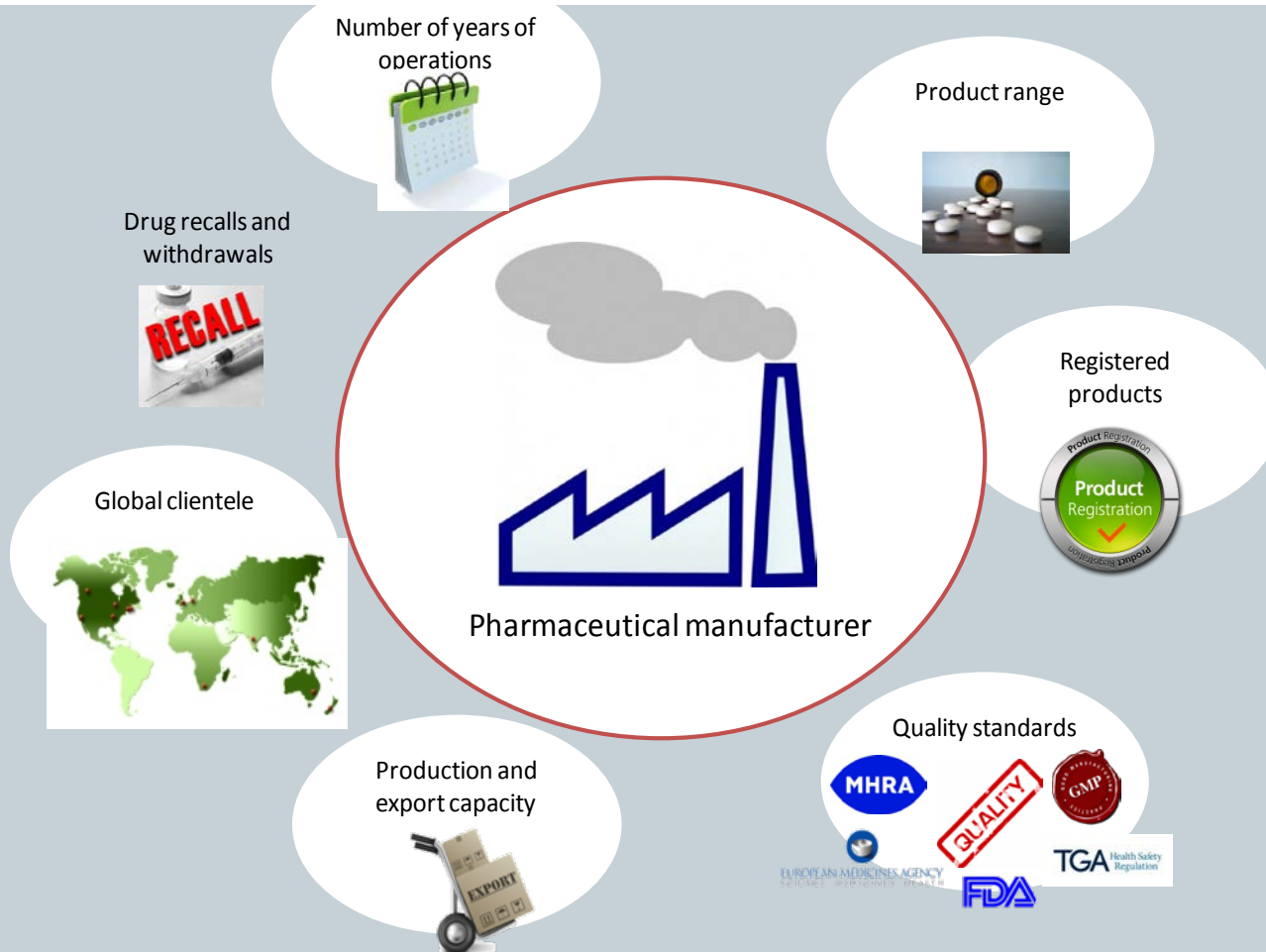
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<b>Regulatory requirements</b>	SRA and only South Africa in African continent; International procurement agents also submit DMF	Nigeria, Zimbabwe, Tanzania, Uganda (now)	Most of francophone Africa, Sudan, Liberia and others
<b>NDRA inspections</b>	Yes	No	No
<b>Filing requirements if change in API source made</b>	Need to file a type II (major variation) which requires new stability studies of FPP to ensure it complies with original specifications of regulatory approval		Minimal requirements

Source: Empower research

# Searching for Quality Manufacturers

(23)

## DATA VARIABLES OF PHARMACEUTICAL MANUFACTURERS



# Pharmaceutical Production and WHO PQ

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China has fewest number of WHO Prequalified finished products when compared to India and Africa

and Africa

HIV medicines

Name	PQ sites in India										PQ sites in China					PQ sites in Africa									
[Lamivudine + Zidovudine] + Nevirapine																									
[Tenofovir disoproxil fumarate + Lamivudine] + Atazanavir (as sulfate) + Ritonavir																									
[Tenofovir disoproxil fumarate + Lamivudine] + Nevirapine																									
Abacavir																									
Abacavir (as sulfate)																									
Abacavir (as sulfate) + Lamivudine																									
Abacavir (as sulfate) + Lamivudine + Zidovudine																									
Abacavir + [Lamivudine + Zidovudine]																									
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Atazanavir (as sulfate) + Ritonavir																									
Azithromycin																									
Ciprofloxacin																									
Darunavir (as ethanolate)																									
Didanosine																									
Efavirenz																									
Efavirenz + [Lamivudine + Stavudine]																									
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Efavirenz + Emtricitabine + Tenofovir disoproxil fumarate																									
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Emtricitabine																									
Emtricitabine + Tenofovir disoproxil fumarate																									
Ganciclovir																									
Indinavir																									
Lamivudine																									
Lamivudine + Nevirapine + Stavudine																									
Lamivudine + Nevirapine + Zidovudine																									
Lamivudine + Stavudine																									
Lamivudine + Tenofovir disoproxil fumarate																									
Lamivudine + Zidovudine																									
Lopinavir + Ritonavir																									
Nevirapine																									
Nevirapine + [Lamivudine + Stavudine]																									
Nevirapine + [Lamivudine + Zidovudine]																									
Ritonavir																									
Stavudine																									
Tenofovir disoproxil fumarate																									
Zidovudine																									

Source: WHO PQ, UNFPA



# Pharmaceutical Production and WHO PQ

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China has fewest number of WHO Prequalified finished products when compared to India and Africa

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Ritonavir																								
Stavudine																								
Tenofovir disoproxil fumarate																								
Zidovudine																								

Name	Anti-TB medicines												PQ sites in India	PQ sites in China	PQ sites in Africa
Amikacin (as sulfate)															
Cycloserine															
Ethambutol															
Ethambutol + Isoniazid															
Ethambutol + Isoniazid + Pyrazinamide + Rifampicin															
Ethambutol + Isoniazid + Rifampicin															
Ethambutol hydrochloride															
Ethambutol hydrochloride + Isoniazid															
Ethambutol Hydrochloride + Isoniazid + Pyrazinamide + Rifampicin															
Ethambutol hydrochloride + Isoniazid + Rifampicin															
Ethionamide															
Isoniazid															
Isoniazid + Pyrazinamide + Rifampicin															
Isoniazid + Rifampicin															
Levofloxacin															
Moxifloxacin (as hydrochloride)															
Ofloxacin															
Para-aminosalicylate sodium															
Protionamide															
Pyrazinamide															

# Pharmaceutical Production and WHO PQ

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China has fewest number of WHO Prequalified finished products when compared to India and Africa

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HIV medicines														
Name	PQ sites in India							PQ sites in China	PQ sites in Africa					
[Lamivudine + Zidovudine] + Nevirapine														
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Abacavir														
Abacavir (as sulfate)														
Abacavir (as sulfate) + Lamivudine														
Abacavir (as sulfate) + Lamivudine + Zidovudine														
Abacavir + [Lamivudine + Zidovudine]														
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Atazanavir (as sulfate) + Ritonavir														
Azithromycin														
Ciprofloxacin														
Darunavir (as ethanolate)														
Didanosine														
Efavirenz														
Efavirenz + [Lamivudine + Stavudine]														
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Lamivudine														
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Tenofovir disoproxil fumarate														
Zidovudine														

Anti-TB medicines												
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Amikacin (as sulfate)												
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Ethambutol + Isoniazid												
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Ethambutol hydrochloride												
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Ethionamide												
Isoniazid												
Isoniazid + Pyrazinamide + Rifampicin												
Isoniazid + Rifampicin												
Levofloxacin												
Moxifloxacin (as hydrochloride)												
Ofloxacin												
Para-aminosalicylate sodium												
Protonamide												
Pyrazinamide												

Anti-malarials												
Name	PQ sites in India				PQ sites in China				PQ sites in Africa			
Amodiaquine												
Amodiaquine (as hydrochloride) + Artesunate												
Artemether + Lumefantrine												
Artesunate												
Artesunate + [Sulfadoxine + Pyrimethamine]												
Artesunate + Mefloquine (as hydrochloride)												

# Conclusions

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- Sourcing QA pharmaceuticals is a major challenge
- Ensuring QA during the procurement process is a major challenge
- Ensuring QA in the supply chain is a major challenge
- Ensuring QA APIs is a major challenge
- Ensuring all the above for Orphan drugs with small markets compounds all the challenges as there are only 1-2 alternative suppliers
- NDRAs and DNDi have to play a key role in ensuring sustainable and consistent QA medicines are available for patients