USP-APEC RHSC

Center of Excellence (CoE) for Product Quality & Supply Chain Pilot Program:

Securing Medical Product Quality Through the Supply Chain

U.S. Pharmacopeial Convention (USP) | March 28–31, 2017 | USA

Video

Asia-Pacific Economic Cooperation

U.S. Pharmacopeial Convention

Regulatory Harmonization Steering Committee

Life Sciences Innovation Forum

AHC

USP-APEC RHSC

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USP U.S. Pharmacopeial Convention

Regulatory Harmonization Steering Committee
APEC Life Sciences Innovation Forum

AHC APEC Harmonization Center

Welcome

USP-APEC RHSC Center of Excellence Pilot Program
March 28, 2017

Context and Goals for the Pilot Center of Excellence Program

Katherine Bond, ScD
United States Pharmacopeial Convention
Vice President, International Public Policy and Regulatory Affairs

Securing Medicines Quality in the Supply Chain

Goals

- Enhance the implementation and sustainability of the RHSC's Supply Chain Integrity Roadmap best practices with focus on "Securing Medical Product Quality through the Supply Chain"
- Convene diverse group of APEC economy regulators, thought-leaders, academics and industry representatives
- Serve as platform to refine and continually develop the RHSC Supply Chain Tool Kits and identify and address gaps in standards development

Principles

- Holistic approach to the continuum of the pharmaceutical supply chain
- Focus on risk
- Communities of practice, knowledge sharing
- Thought leadership platform

Securing Medicines Quality in the Supply Chain

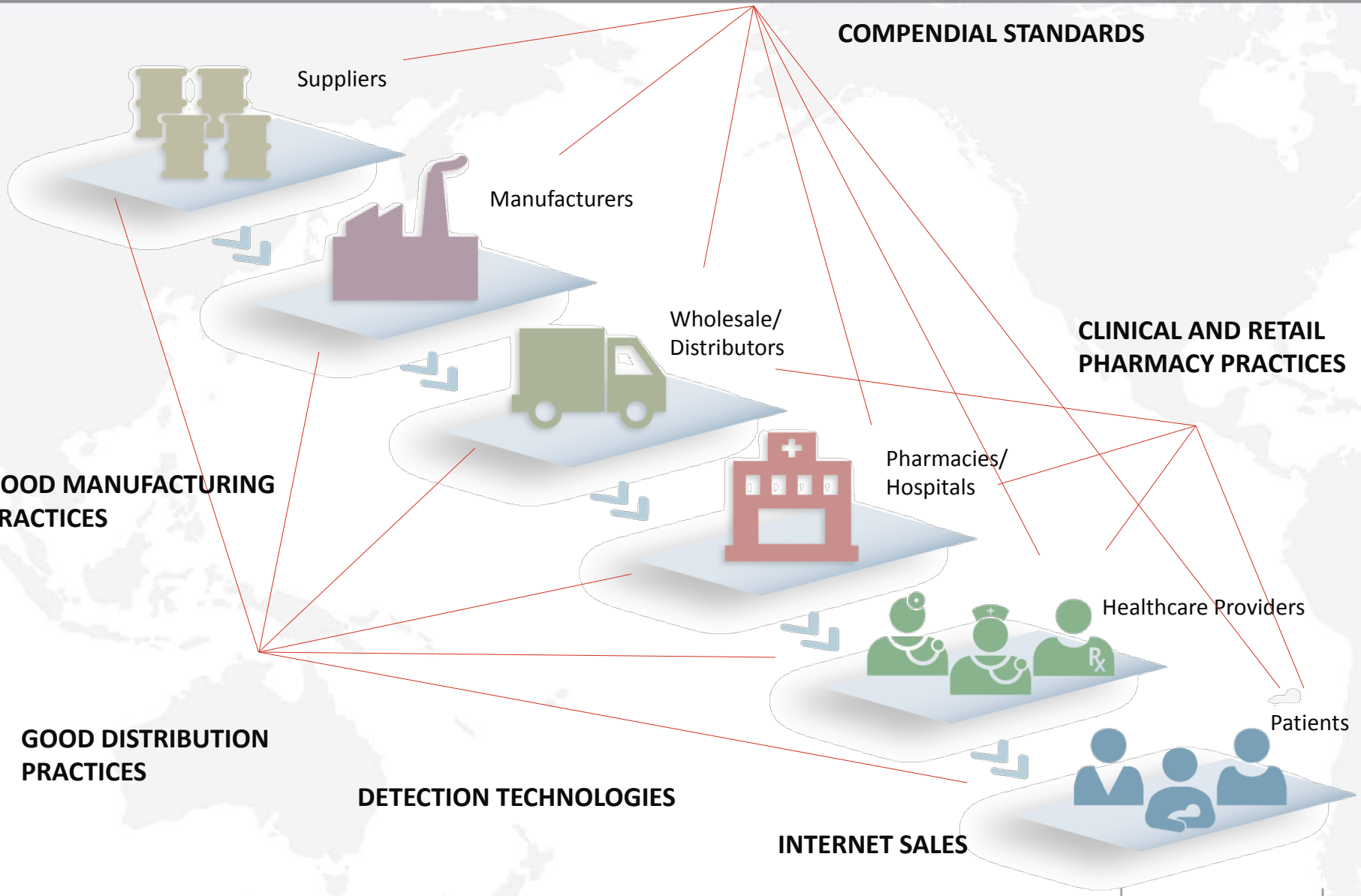
Focus

- Highlight the role of public standards and best practices in addressing quality and supply chain integrity issues
- Target specific aspects of the APEC Supply Chain Roadmap where best practices can have great impact on medicines quality:
  - Good Manufacturing Practices
  - Good Distribution Practices
  - Good Pharmacy Practices
  - Internet Sales
  - Screening and Detection Technologies

Methods

- Keynote talks
- Panel sessions
- Presentations
- Case studies
- Hands-on demonstrations

Roadmap Toolkits



Participants and Speakers

Regulators

Brazil (as presenter)
Chile
People's Republic of China
Chinese Taipei
Indonesia
Republic of Korea
Malaysia
Mexico
Peru
The Philippines
Russia
Singapore
Thailand
Viet Nam
The United States

Other Speakers/ Presenters

APEC Harmonization Center
USP
World Health Organization
USAID
PQM
RX360
School of Health Management and Policy, University of Michigan
University of Maryland School of Pharmacy
Abbvie
Cardinal Health
Jeiven Pharmaceutical Consulting
Merck
APEC Life Sciences Innovation Forum
US Department of Health and Human Services
Bristol-Myers Squibb
Notre Dame

Content Overview Day 1

Plenary Session

- Welcome and Opening Remarks
- Context and Goals of the Pilot CoE Program
- Overview of APEC Supply Chain Roadmap
- Promoting A Quality Culture in the Supply Chain
- The Current Global State of Substandard/Falsified Medicines
- Global Initiatives to Improve the Quality of Medicines
- Public Quality standards: Foundations for Securing Quality in the Global Supply Chain

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Toolkit Application:

- **Good Manufacturing Practices**: **Essentials for Quality**
  - Overview of Gap Analysis and Tool Development
  - GMP case example: Panama Glycerin Case

Content Overview Day 2

GMP Continued

- **Panel Discussion**
  - GMP and Quality: observations across the APEC region
- **Case Study: Exploring GMP from a product quality perspective: Heparin**
  - Discuss facts, alternatives, ways for improvement, and tool kit utilization
  - Reconvene for Group Discussion

Toolkit Application:

- **Good Distribution Practices: Essentials for Quality**
  - Good Distribution Practices and Product Quality
  - APEC RHSC Workstream Efforts and Outcomes
  - GDP case examples
  - Quality Management as a Foundation to GDP Compliance
  - Temperature Control Management Through the Supply Chain Importation

Content Overview Day 3

- **Case Study: GDP from a Product Quality Perspective (Product Returns)**

- **GDP Breakout Session**
  - Case study on Product Returns
  - Reconvene for Group Discussion

Toolkit Applications: Good Retail and Clinical Pharmacy Practices and Internet Sales

- **Panel Discussions**
  - Good Retail and Clinical Pharmacy Practices
  - The Challenges of Internet Pharmacies

Toolkit Applications: Screening and Detection Technologies

- Development and Use
- Screening Technologies in the APEC Toolkit
- Technology show case and marketplace

Content Overview Day 4

- **Screening/Detection Technology Breakout Session**
  - Panel Discussion: Screening Technologies – their value, challenges and future
  - Case Study: Malaria/Diazepam Case Study
- **Tour of USP's Facilities and Museum**

- **Summary of Breakout Sessions**
- **Group Discussion**
  - Reflections
  - Next steps
  - Topics for proposals for future CoE programs
- **Closing and Presentation of Certificates of Participation**

A Special Thanks To

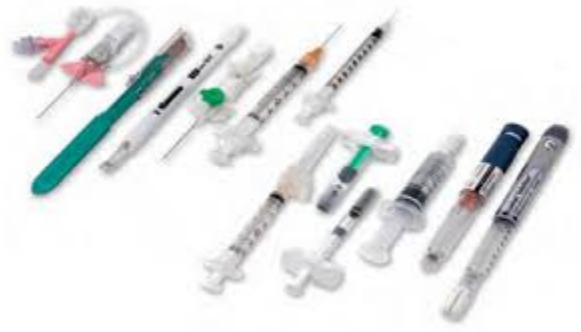
APEC Harmonization Center	APEC LSIF Secretariat	US FDA	USP
Yeowon Sohn Mirinea Kim Helen Jang	Kate Clemans Michael Schmitz	Ilisa Bernstein Michelle Limoli Katharine Neckers	Phillip Nguyen Helen Kharab Stacey Royston John Giannone Desmond Hunt Victor Pribluda Lukas Roth Paul Nkansah Elizabeth Miller Damian Cairatti Jennifer Devine

Questions

Thank You

FDA U.S. FOOD & DRUG ADMINISTRATION

Roadmap to Global Medical Product Quality & Supply Chain Security

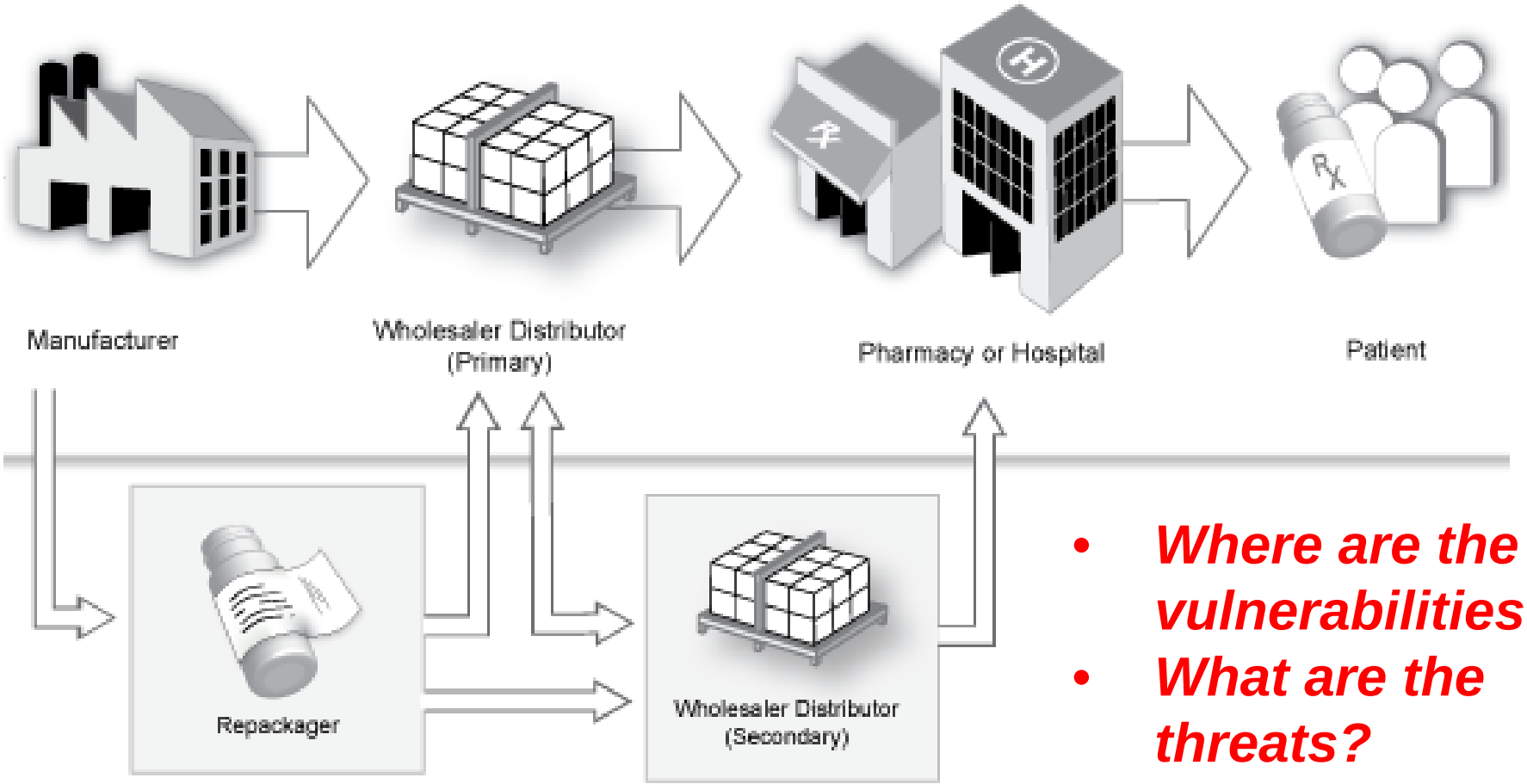


ILISA B.G. BERNSTEIN, Pharm.D., J.D.
U.S. Food and Drug Administration
Presented at: USP APEC Center of Excellence Pilot Program
March 28, 2017

Presentation Overview

- Addressing the Problem
  - The Problem
  - US FDA Approach
  - Collaboration
- APEC Roadmap Project
  - Deliverables
  - Supply Chain Security Toolkit
  - Centers of Excellence

Pharmaceutical Distribution Supply Chain

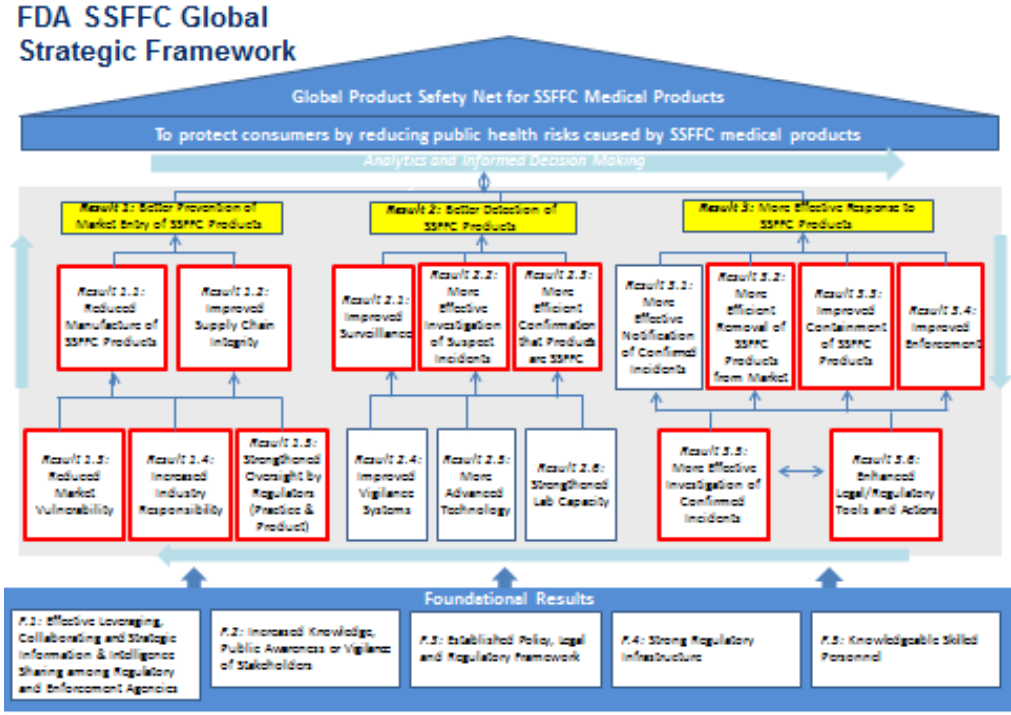


- ***Where are the vulnerabilities?***
- ***What are the threats?***

FDA SSFFC Global Strategic Framework

(SSFFC: Substandard, spurious, falsified, falsely labeled, counterfeit)

- **Prevention**
  - Reduce manufacture of SSFFC products
  - Improve supply chain integrity
- **Detection**
  - Improve surveillance
  - Effective investigation
  - Efficient confirmation of suspect products
- **Response**
  - Increase notification
  - Improve removal from market
  - Containment
  - Improved enforcement



FDA

Drug Supply Chain Security Act

Product Tracing

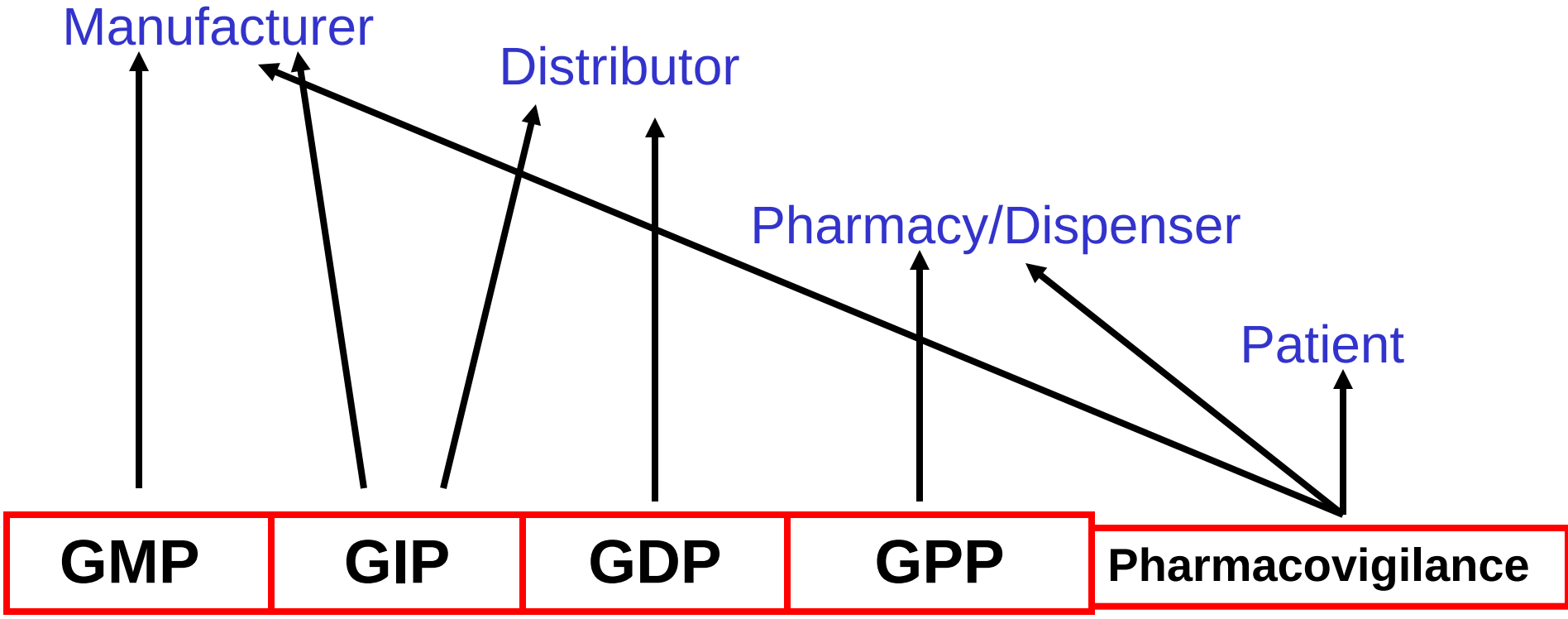
Verification

Product Identification (Serialization)

WDD and 3PL Licensing Standards

Building on GxPs & pharmacovigilance

"Filling in the supply chain holes"

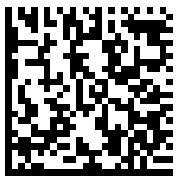


GMP=Good Manufacturing Practice, GIP=Good Importer Practices, GDP=Good Distribution Practice, GPP=Good Pharmacy Practice

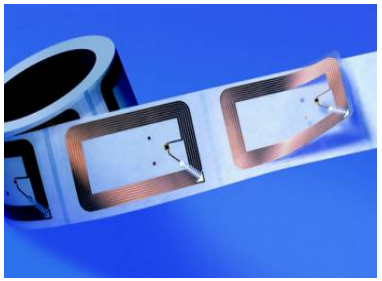
Securing the Product

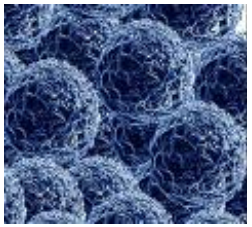
Technology-based Approaches

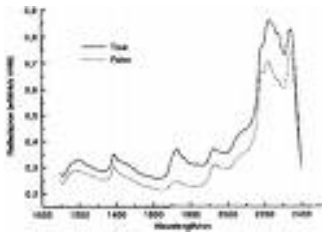
– **Implement track/trace technologies**
  - RFID (radio frequency identification)
  - Barcodes
  - other?



– **Use authentication/anti-counterfeiting technologies**
  - *Overt* - *e.g.,* holograms, color shifting ink, watermarks
  - *Covert – e.g.,* inks and dyes that fluoresce or absorb UV light, invisible bar codes, some watermarks
  - *Forensic – e.g.,* chemical markers, taggants, other unique chemical features of a substance







We must collaborate!!

- Why?

  It's a global problem, that needs global solutions

- How?
  - Share information
  - Work regionally, multilaterally
    - APEC, WHO, PAHO, others….

Asia-Pacific Economic Cooperation

FDA

- APEC is an international organization with the primary goal of facilitating sustainable economic growth and prosperity in the Asia Pacific Region.
- APEC provides funding for about 100 projects a year, which are open to participation for all 21 APEC member economies.
- The *Roadmap for Global Medical Product Quality and Supply Chain Security* was endorsed by the Life Science and Innovation Forum's Regulatory Harmonization Steering Committee (RHSC) in 2013.

Project Overview

- WHAT is the objective of the Roadmap?
  - Our *Roadmap for Global Medical Product Quality and Supply Chain Security* covers the entire supply chain and life cycle of medical products, from beginning to end (raw materials to patients).

- WHO is involved?
  - Regulators, industry members, academics, and other stakeholders from across the APEC economies, and EU, Africa, and other parts of South America.
  - US FDA is the Roadmap champion.

Project Overview

- WHERE are we in the project?
  - The project was slated for 5 years with APEC funding condensed to 4 years. We have now completed the project, ahead of schedule.
  - The FINAL Project Report and Toolkit was ENDORSED at SOM1 in Vietnam in March 2017

Work Products

- "Final Report: APEC Roadmap to Promote Global Medical Product Quality and Supply Chain Security"
- Supply Chain Security Toolkit
  - Contains training materials intended to educate regulators, industry members, and others on a particular part of the supply chain, including items such as best practices, guidance documents,
  - Internet site:
    - Interactive PDF that pulls together the work from across the various work groups/toolkits into one place on the internet.
    - instructional videos, etc

Work Groups

- Track and Trace Systems
- Good Distribution Practices
- Good Manufacturing Practices
- Good Import/Export Practices
- Clinical and Retail Pharmacy Practices
- Product Security
- Detection Technologies
- Single Points of Contact
- Internet Sales
- Surveillance and Monitoring Systems

APEC

Centers of Excellence (CoE)

- The RHSC has endorsed two pilot programs for supply chain security:
  - United States Pharmacopeial Convention (USP)
    - Training--- that's why you are here!
  - University of Tennessee Health Science Center (UTHSC)
    - "Protecting Patient Safety in the Global Marketplace through GDPs and Product Security Measures"
      - June 27-29th, 2017
      - University of Tennessee Health Science Center, Memphis, Tennessee, USA

Thank You!!!!

Ilisa B.G. Bernstein, Pharm.D., J.D.
U.S. Food and Drug Administration

ilisa.bernstein@fda.hhs.gov

Promoting a Quality Culture in the Supply Chain

Ron Piervincenci, Ph.D.
Chief Executive Officer
U.S. Pharmacopeial Convention (USP)

What is Quality?

- The USP *Quality Institute* defines medicine quality as a balanced, risk-based set of characteristics, systems and requirements that consistently ensure a medicine's delivery of stated and implied clinical outcomes for patients.
- This definition is meant to encompass aspects of a medicine's entire life cycle, including design, manufacturing, supply chain, storage and distribution, as well as falsification. It does not consider the quality of treatment guidelines and practices.

What Happens without Quality?

- The Causes
  1. Products being produced without meeting quality standards, whether inadvertently or intentionally
  2. Products being produced with quality standards but degraded due to inappropriate storage or distribution

- The Impacts
  - Adverse Events
  - Inadequate Treatment
  - Therapeutic Failure
  - Drug Resistance
  - Reduced patient trust

Characteristics of Quality Culture

The Value of Quality

- Increase Provider-Patient Trust
- Increase access to lower cost, quality assured medicines
- Reduce “hidden costs”
- Protect public health

Questions

World Health Organization

Substandard and Falsified Medical Products

Michael Deats
Safety and Vigilance,WHO

Outline

Definitions

- Falsified
- Substandard
- Unlicensed

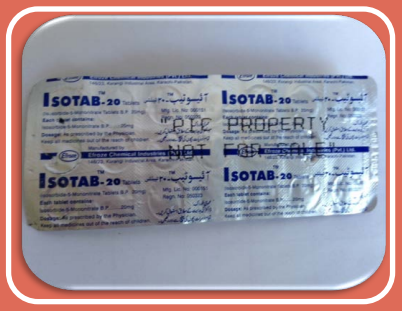
WHO Global Surveillance and Monitoring System

- Objective
- Case Studies
- What is the data telling us?

WHO Member State Mechanism

- Mandate
- Governance
- Activities

Definitions

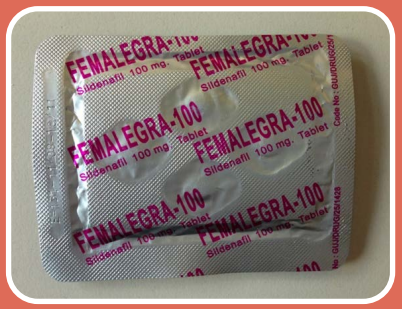


Substandard

- Also called ‘out of specification’, these are authorized medical products that fail to meet either their quality standards or their specifications, or both.

Falsified

- Medical products that deliberately /fraudulently misrepresent their identity, composition or source



Unregistered/Unlicensed

- Medical products that have not undergone evaluation and/or approval by the NRRA for the market in which they are marketed/distributed or used, subject to conditions under national or regional regulation and legislation

WHO Global Surveillance and Monitoring System for substandard and Falsified Medical Products

World Health Organization

WHO Global Surveillance and Monitoring System –rapidalert@who.int

1.Technical Support

- Laboratory Support
- Experts – Specialists Support
- WHO Rapid Alerts
- National Focal points access to WHO database, photo libraries and laboratory reports

2.Strategic Support

- Validated reliable evidence
- Identifies vulnerabilities, weaknesses and products most at risk
- Enables evidence and risk based policy
- Identifies areas for capacity building and investment

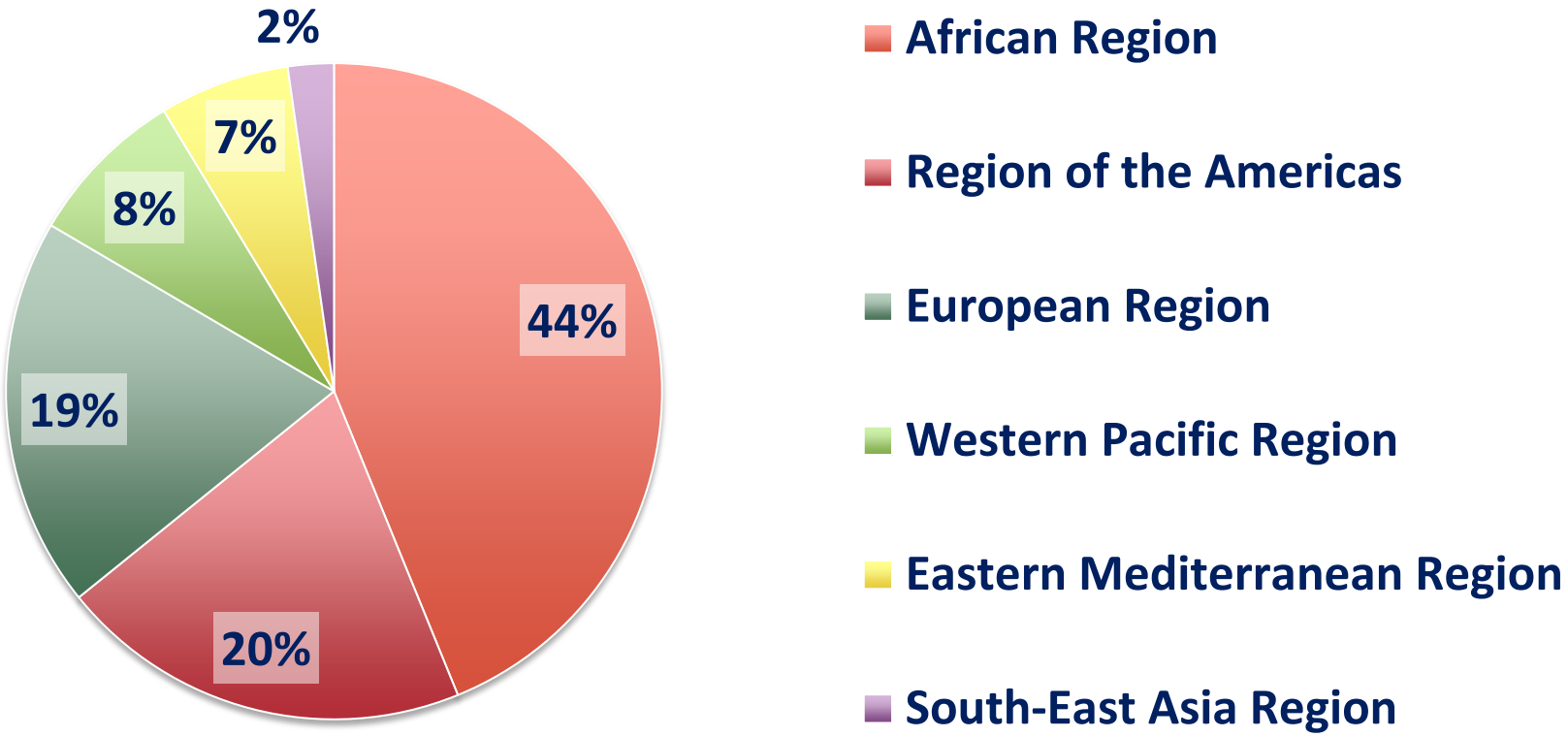
WHO Global Surveillance and Monitoring System

WHO Global Surveillance and Monitoring System – rapidalert@who.int

17 Training events and workshops
126 Member States trained
400 Regulatory personnel trained as focal points
18 large procurement agencies sensitized
1400 Suspect Medical Products Reported
Incidents occurred in 93 countries
17 WHO Global Drug alerts and numerous warnings
WHO Technical Assistance in over 100 Cases

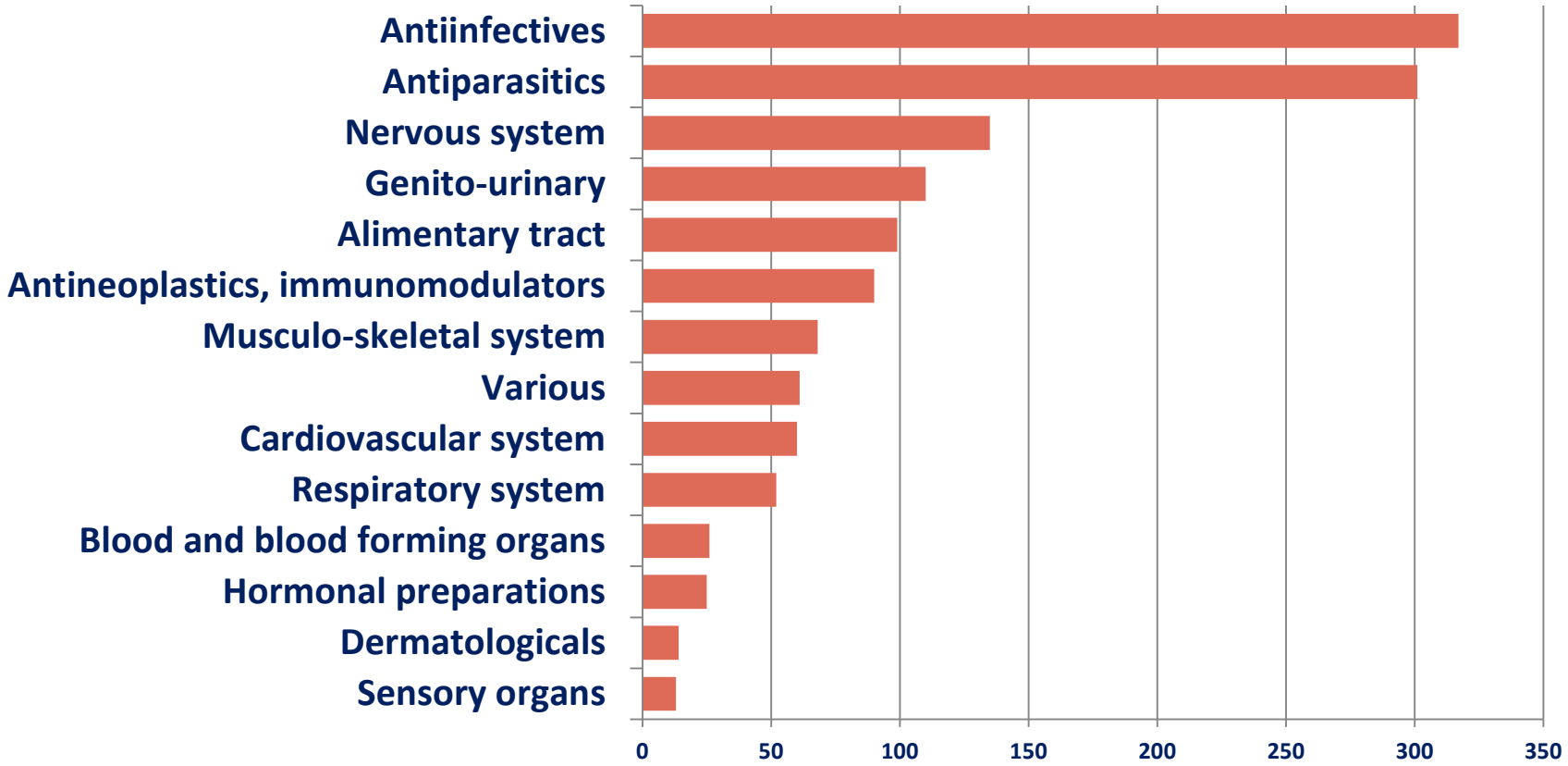
Proportion of reported products to the GSMS, by WHO region

n=1371, data extracted 10 February 2017



Therapeutic Classes of medical product reported to WHO

n=1371 , data extracted 10 February 2017



Hepatitis C - Case Study

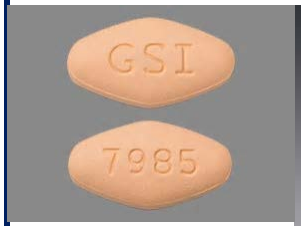
- Liver disease caused by bloodborne Hepatitis C virus
- Infection caused by unsafe injection practices, inadequate sterilization of medical equipment and unscreened blood products
- 130-150 million affected globally
- 350,000-500,000 deaths each year
- Antiviral treatment successful in 50%-90% of cases
- No vaccine available
- Worldwide distribution, but most prevalent in Central and East Asia, and North Africa.

Hepatitis C –Innovator Medicines

HARVONI

(Ledipasvir 90mg and Sofosbuvir 400mg)

- Average price $32,138 for 28 Tablets
- 1 Tablet per day, usually 8-12 week course of treatment $64,276 - $96,414



SOVALDI

(Sofosbuvir 400mg)

- Average price $29,756 for 28 tablets bottle
- 1 Tablet per day, usually 12 week course of treatment $89,268

Japan - Falsified Innovator Version of Harvoni

- Harvoni packaging containing vitamin pills

- Harvoni packaging containing Sovaldi

Israel – Falsified Innovator version of Harvoni

- **Sovaldi stolen from hospital in Pakistan**
- **Repackaged as Harvoni**
- **Traded through Hong Kong, India, Switzerland and Israel**
- **Israeli patient recognises that tablets are not the usual shape and colour**

Swiss Medic Alert . https://www.swissmedic.ch/aktuell/00673/03287/index.html?lang=en

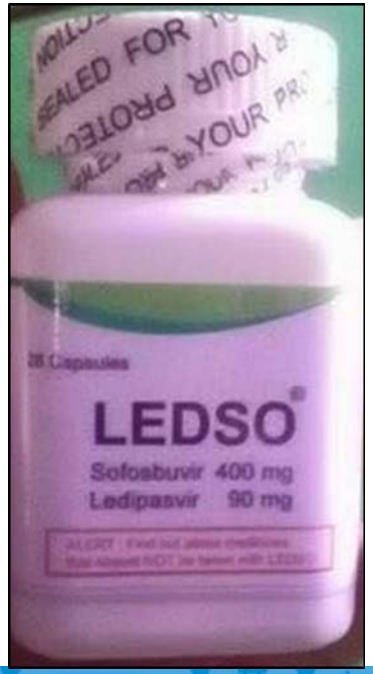
Thefts of Medicines

- **Medicines are a valuable commodity**
- **Thefts from Healthcare facilities across the world ae common**
- **In low and middle income countries healthcare workers are frequently involved**
- **Medicines can be traded for life essentials**
- **Thefts also occur in high income countries**

Theft of medicines from Italian Hospitals http://www.transcrime.it/wp-content/uploads/2014/03/Pharma-Theft-Report.pdf

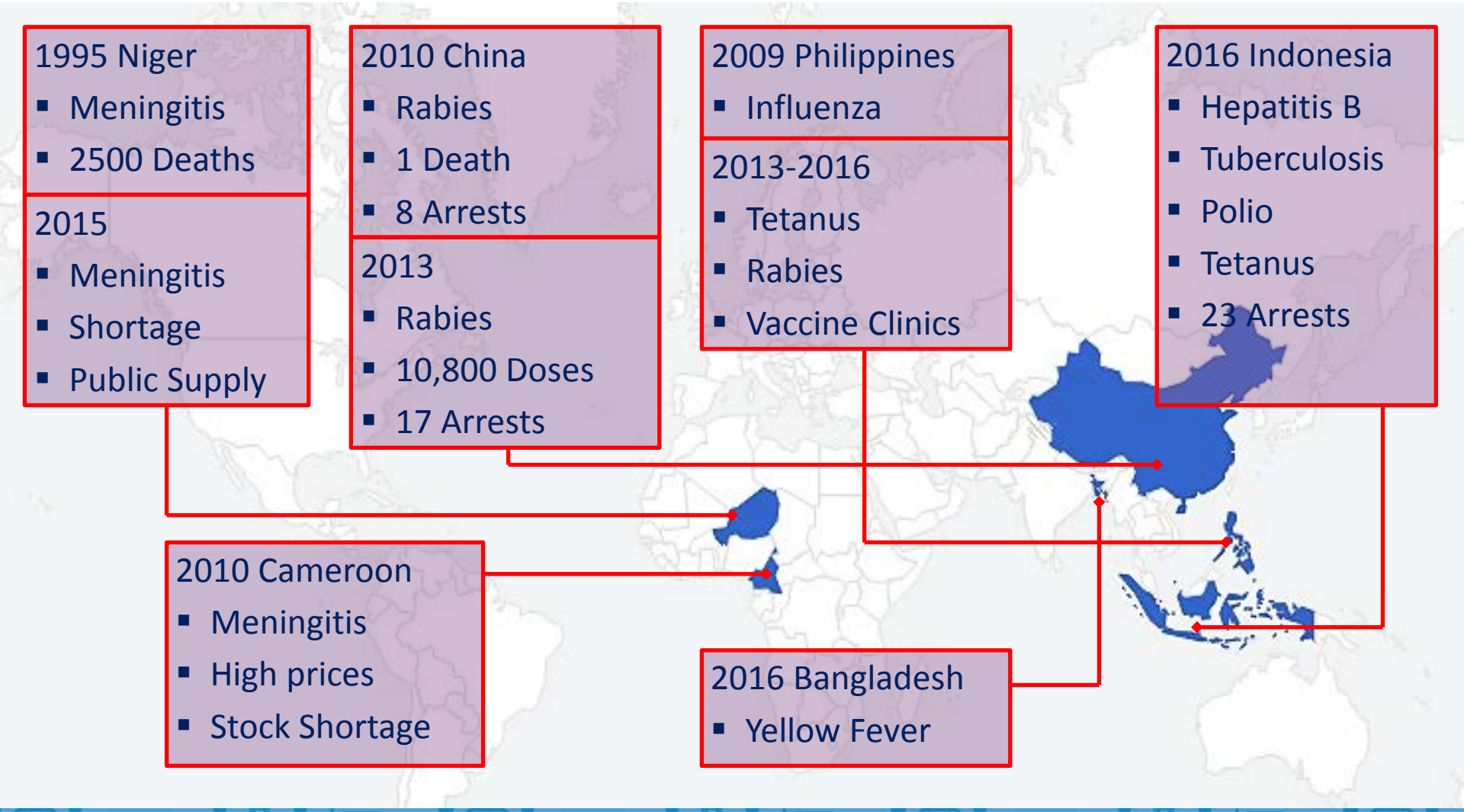
Myanmar – Falsified Generic Versions of Harvoni

- Pharco Corporation, do not manufacture this product
- Circulating in Health facilities in Myanmar for $900 per bottle of 28 tablets
- WHO Alert issued February 2016



Falsified Vaccines

(Source: National Ministries of Health Alerts and Govt Press releases)

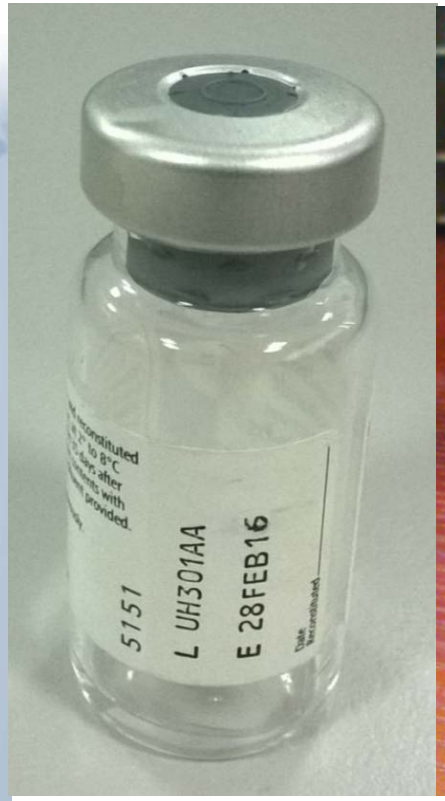


Falsified Yellow Fever Vaccine - 2016

- Falsified vaccines discovered in Bangladesh
- Local wholesaler supplied by a bogus employee pretending to work for the genuine manufacturer
- No antigens present
- Global WHO Alert Issued

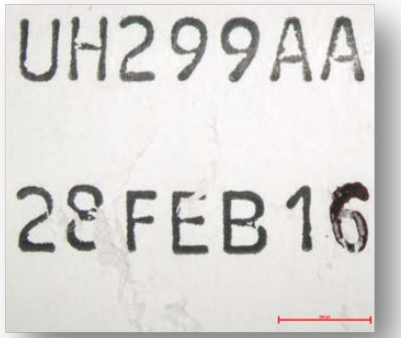
Falsified Meningitis Vaccines – May 2015

- **Largest outbreak of Meningitis C in Africa – Niger 2015**
- **Shortage of vaccines**
- **Falsified versions of Mencevax and Menomune**
- **Niger Focal point informs WHO Surveillance and monitoring system**
- **2 WHO Global medical product alerts issued**



Falsified Meningitis C Vaccine

- Seasonal outbreak could be expected
- Shortage could be identified
- Clear link between shortages and emergence of falsified vaccines
- Vigilance and awareness can be increased in these circumstances
- It is very easy to undermine confidence in an immunization campaign



What is the Data telling us?

- Poor governance, lead to SF medical products
- Shortages and stock outs lead to falsified products entering the supply chain
- Weak regulatory oversight of the supply chain- last mile to the patient
- Identification of the Medicines most at risk – Antibiotics and anti- malarials
- Risk based inspection and post market surveillance is generally weak
- Weak coordination with other stakeholders especially Customs
- Low reporting to NMRA's from public and healthcare workers
- Weak laboratory capacity in LIC's

WHO Member State Mechanism substandard and Falsified Medical Products

Member State Mechanism

MANDATE

World Health Assembly 65.19

2012

PURPOSE

International collaboration from a public health perspective on sub-standard and falsified medical products

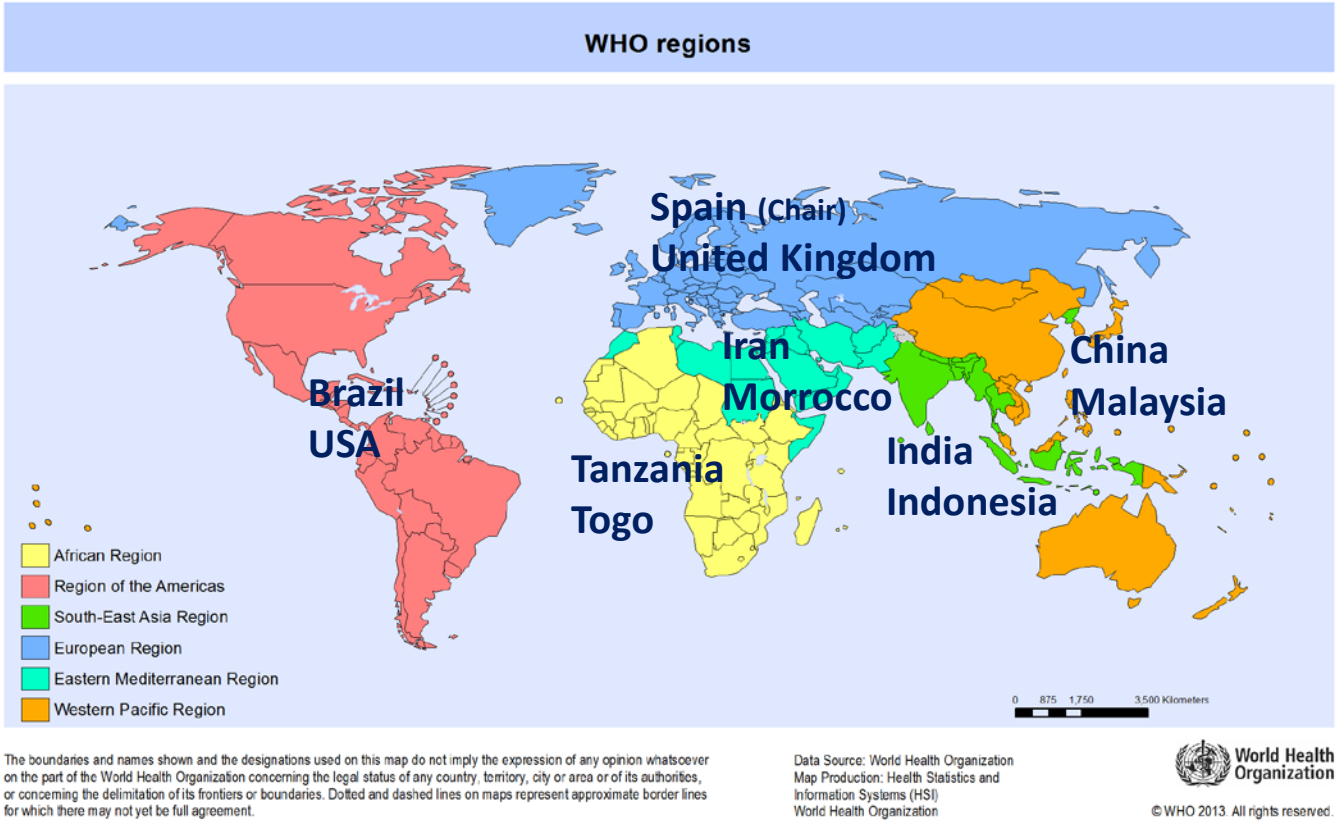
GOVERNANCE

1 Chair (Spain)

11 vice Chairs

Regional rotation

MS Mechanism Steering Committee



MS Mechanism Activities

Developing National Strategies

- Prevention, Detection, Response (WHA 2017)
- Training Material Survey

Global Focal Point Network

- National Regulatory Authority network of focal points TOR's (WHA 2016)
- Linked to existing WHO Surveillance and monitoring system (WHO 2013)

Technology

- Track and Trace (WHA 2016), Authentication (WHA 2017)
- Field Detection technologies

MS Mechanism Activities

Access to medicines

- Availability, Acceptability and Affordability
- Linkage to substandard and falsified medical products

Communication

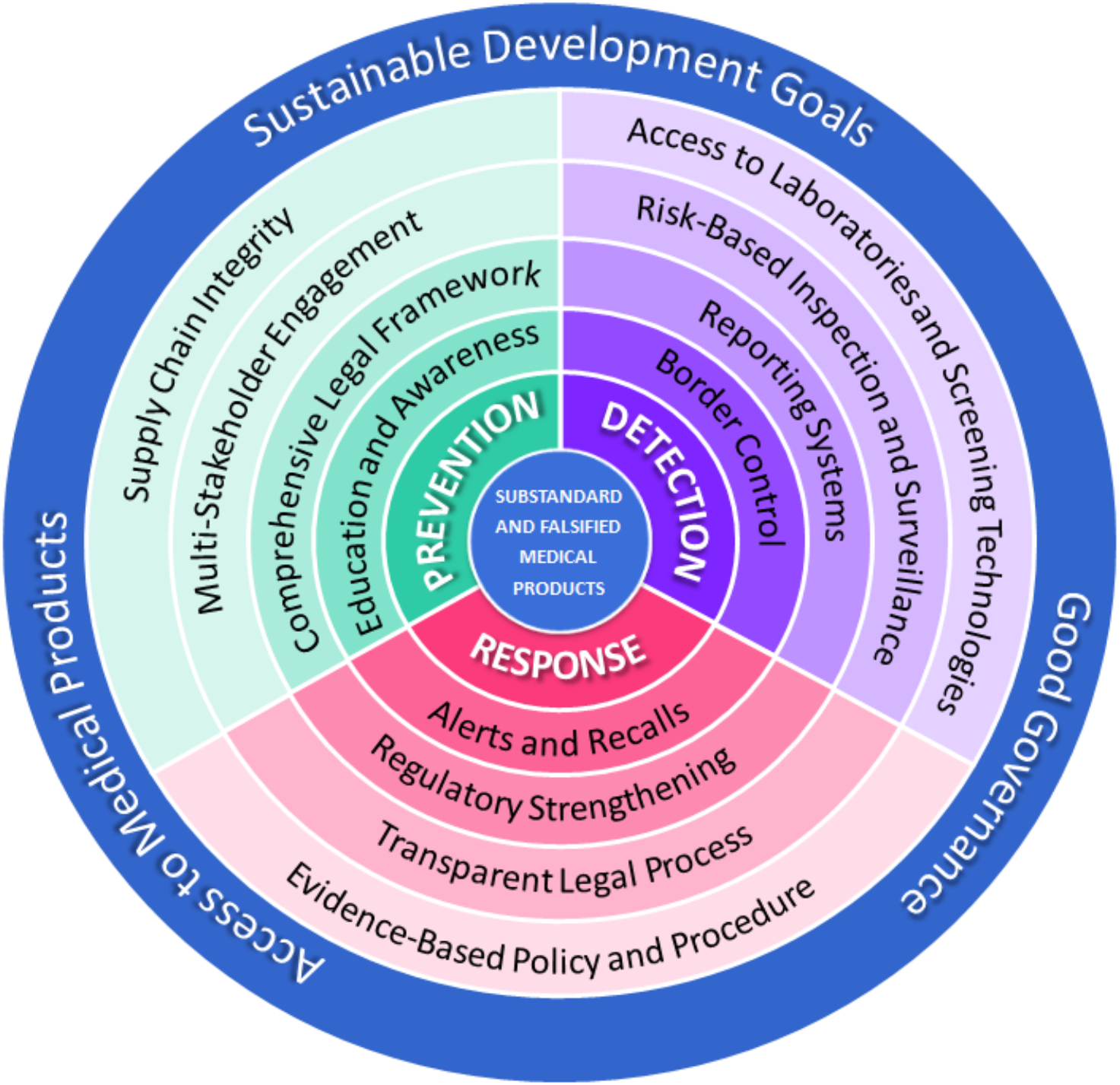
- Education and awareness
- Risk Communication

Public Health and Socio Economic Impact Study

- Prevalence
- Cost

Vulnerabilities

Access	• Affordability • Availability • Acceptability
Governance	• Poor Procurement • Corruption • Unethical practice
Supply Chain Integrity	• Porous Borders • Weak Regulatory oversight • Medical Products On-line


Sustainable Development Goals
Access to Laboratories and Screening Technologies
Risk-Based Inspection and Surveillance
Reporting Systems
Border Control
DETECTION
Supply Chain Integrity
Multi-Stakeholder Engagement
Comprehensive Legal Framework
Education and Awareness
PREVENTION
SUBSTANDARD AND FALSIFIED MEDICAL PRODUCTS
RESPONSE
Alerts and Recalls
Regulatory Strengthening
Transparent Legal Process
Evidence-Based Policy and Procedure
Access to Medical Products
Good Governance

www.who.int/medicines/regulation/ssffc

updates

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World Health Organization

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Essential medicines and health products

- Medicines and health products
- About us
- Access
- Innovation
- Regulation
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- News
- Contacts

Substandard, Spurious, Falsely labelled, Falsified and Counterfeit (SSFFC) Medical Products

The existence of substandard, spurious, falsely labelled, falsified and counterfeit (SSFFC) medical products is an unacceptable risk to public health. They affect every region of the world, and medicines from all major therapeutic categories have been reported, including vaccines and diagnostics. They harm patients and undermine confidence in medical products, healthcare professionals and health systems. WHO is working with stakeholders to minimize the risks from SSFFC medical products by collecting data and transferring knowledge and good practices to countries.

- SSFFC Medical Products - Background
- WHO Medical Product Alerts – Background
- Full List of WHO Medical Product Alerts
- Fact Sheet - Updated January 2016

SSFFC Medical Products Activities

Thank You

Michael Deats

Group Lead, Safety and Vigilance,

Essential Medicines and Health products

World Health Organization

deatsm@who.int

www.who.int/medicines/regulation/ssffc

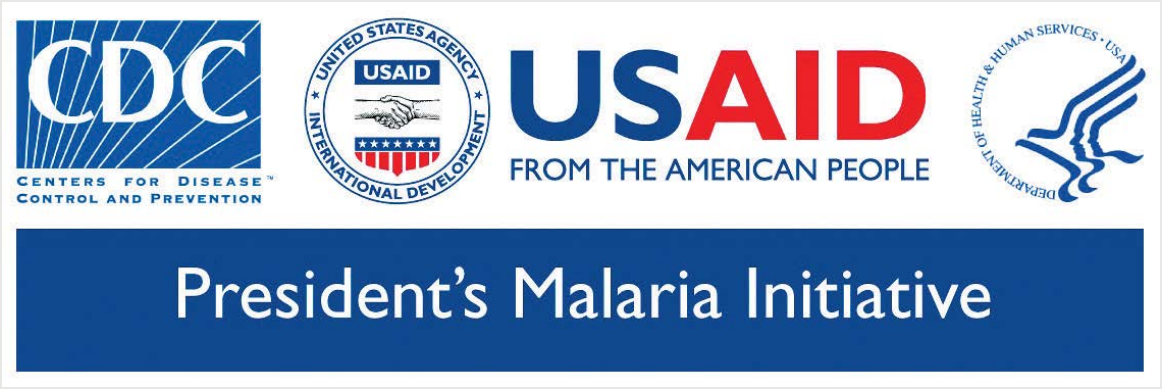
Christine Y. Malati, PharmD
Pharmaceutical Advisor Bureau for Global Health

cmalati@usaid.gov

USP pilot APEC Center of Excellence

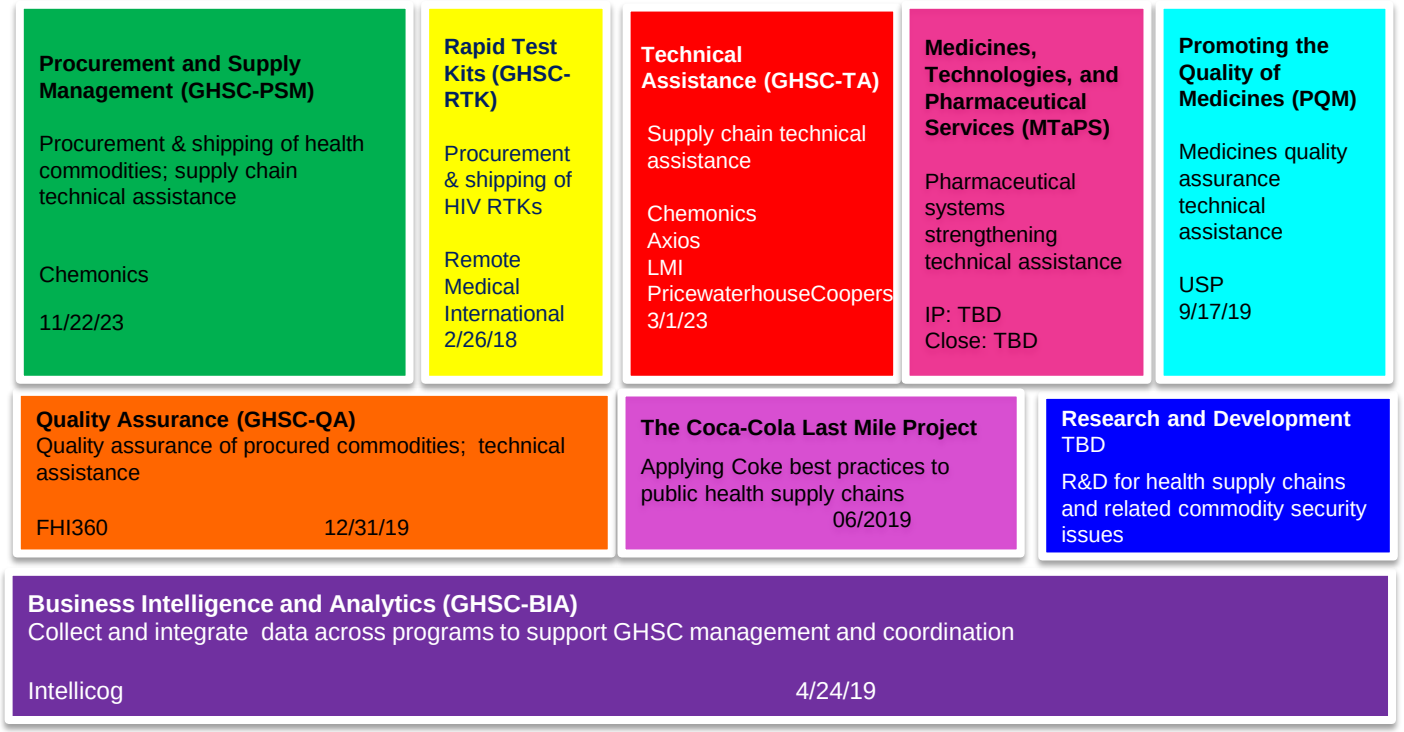
March 28, 2017

There is a delicate balance between health system strengthening and disease eradication.

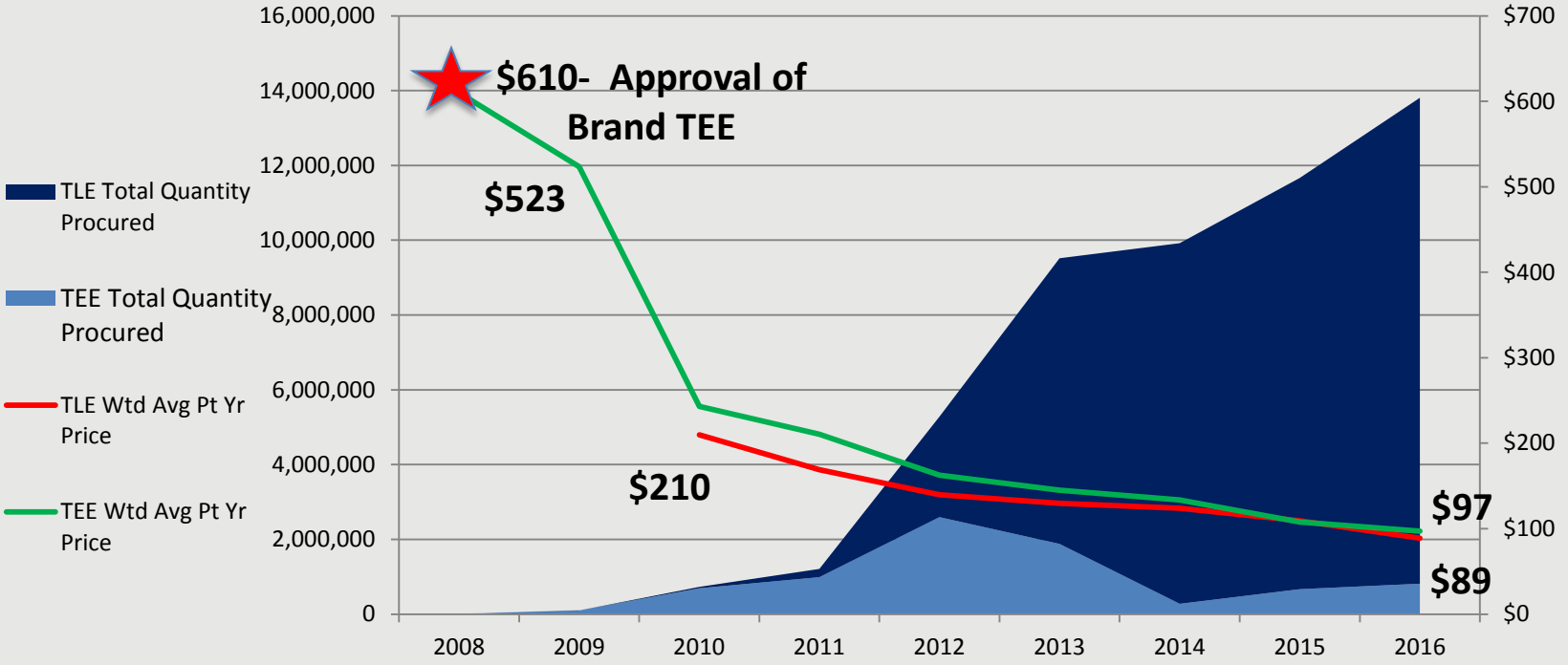


The Global Health Supply Chain is suite of awards that focuses on procurement of health commodities and provides technical assistance to the supply chain.

Global Health Supply Chain Program



BGH revealed to the FDA the impact of their work in our partner countries.



	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
BRAND (TEE)	1	1	1	1	1	1	1	1	1	1
GENERIC (TEE)	0	1	1	2	3	5	6	6	6	6
GENERIC (TLE)	0	1	1	1	2	4	5	5	4	4

Country Scenarios.

- Country 1 – Product rejection due to short shelf life
  - Acceptance of short product due to conversation with MOH
- Country 2 – Product rejection due to preference for national products
  - Certain manufacturers request preferential treatment when evaluating RFQs.
- Country 3 – Product rejection due to different results in quality control testing.
  - Extremely delayed shipment of HIV RTKs and resulted in stockouts in clinics
- Multiple countries – Drug recall involving most common ARV
  - MOU between FDA and USAID to facilitate data exchange

Quality and accessibility are important attributes for pharmaceuticals used in developing countries.

QUALITY – Muhimibili University of Health and Applied Sciences

- HPLC vs. HPTLC

Registration – Tanzania Food and Drug Authority

Accessibility – Local Wholesalers with stock on hand

South to South

Zambia, Ethiopia, Nigeria

High-performance thin layer chromatography to pharmaceutical product quality

Eliangiringa Kaale[1], Vicky Manyanga[1], Narsis Makori[2], David Jenkins[3], Samuel Michael Layloff[5]

1 *Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania*
2 *Supply Chain Management System, Dar es Salaam, Tanzania*
3 *FHI360, Durham, NC, USA*
4 *United States Agency for International Development, Washington, DC, USA*
5 *Supply Chain Management System, Arlington, VA, USA*

Abstract OBJECTIVE To assess the sustainability, robustness and economic advanta
thin layer chromatography (HPTLC) for quality control of pharmaceutica
METHOD We compared three laboratories


Kenya, Malati, 2013

Promoting the Quality of Medicines

Promoting the Quality of Medicines (PQM)

Jude Nwokike, Director
U.S. Pharmacopeial Convention
March 28, 2017

USP U.S. Pharmacopeial Convention

USAID FROM THE AMERICAN PEOPLE

Substandard and Counterfeit Medicines

A Systematic Review of Literature

Table 2 Frequency of six different issues reported concerning the quality of the medicines tested

Stated problem	Frequency of studies containing samples with stated problem	Per cent
Inadequate amount of active ingredient	14	93
No active ingredient	7	47
Excessive amount of active ingredient	6	40
Dissolution failure	5	33
Wrong ingredient	4	27
Impurity	2	13

Key messages

- The prevalence of substandard/counterfeit antimicrobials is high throughout Africa and Asia in lower income countries and lower middle-income countries.
- The prevalence of substandard/counterfeit medicines was significantly higher in the unlicensed markets.
- Inadequate amounts of active ingredients were the largest problem identified

BMJ open

Tariq Almuzaini, Imti Choonara, Helen Sammons

Oxytocin *Tracer Medicine?*

Quality Of Oxytocin Available In Low- And Middle-Income Countries: A Systemic Review Of The Literature

BJOG An International Journal of Obstetrics and Gynaecology

% inadequate API Fails

76.1

55.6

35.7

WHO 2015 survey – 64%

Reference	Country	Year	Study	Total of samples assayed	Country of manufacturer (N of samples)	Provenience of sample (N of samples from central or facility level setting and public or private sector outlets)	Tests performed	Percent failed samples**	Stated problem	Percent inadequate API Fails***, % (*n*)	Percent low API fails****, % (*n*)
Stanton (2012[17]				46	NI	46 facility level settings 33 private, 12 public sector, 1 NI	API	76.1	Inadequate API	76.1 (35)	76.1 (35)
Karikari (2013)[14,****]				169	China (141) Pakistan (4) Switzerland (3) NI (21)	162 facility level, 7 central level settings 90 public, 79 private sector	API, sterility tests (only 40 samples)	55.6 (API) 97.5 (API or sterility or both, *n* = 40)	Inadequate API or not sterile or both	55.6 (94)	55.6 (94)
Stanton (2014)[18]				193	India (193)	193 private sector facility level settings	API	35.7	Inadequate API	35.7 (69)	29.5 (57)
Hogerzeil (1993)[5,*****]	Zimbabwe (LIC)	1992	4	5	Undear ('imported')	5 public facility level settings	API	80.0	Inadequate API	80.0 (4)	0
Pribluda (2012)[16,*****]	Indonesia (LMIC)	2011	7	110	Indonesia (110)	91 facility level, 19 central level settings 110 public sector settings	API, identity, contaminant or strange particle matters	11.8	Inadequate API or no API or contaminants	11.8 (13)	9.1 (10)

Table 2. Main characteristics and findings of eight studies on quality of oxytocin samples from LMC countries

Promoting the Quality of Medicines (PQM)

Funded by USAID and implemented by USP, the PQM program provides **technical leadership** to help **build local capacity** in medicine quality assurance systems, support manufacturers to **increase the supply** of quality-assured priority medicines and **ensure the quality and safety of medicines globally**.

PQM works **in 34 countries** through funding by:

- **20** country missions
- **2** regional missions
- **4** core health elements
- **1** cross-bureau program

PQM Promoting the Quality of Medicines

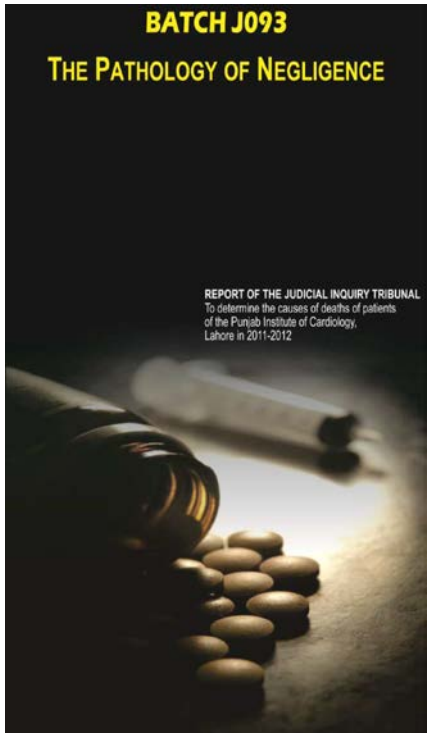
IR1

Medical Products Quality Assurance Systems Strengthened

When Systems Fail

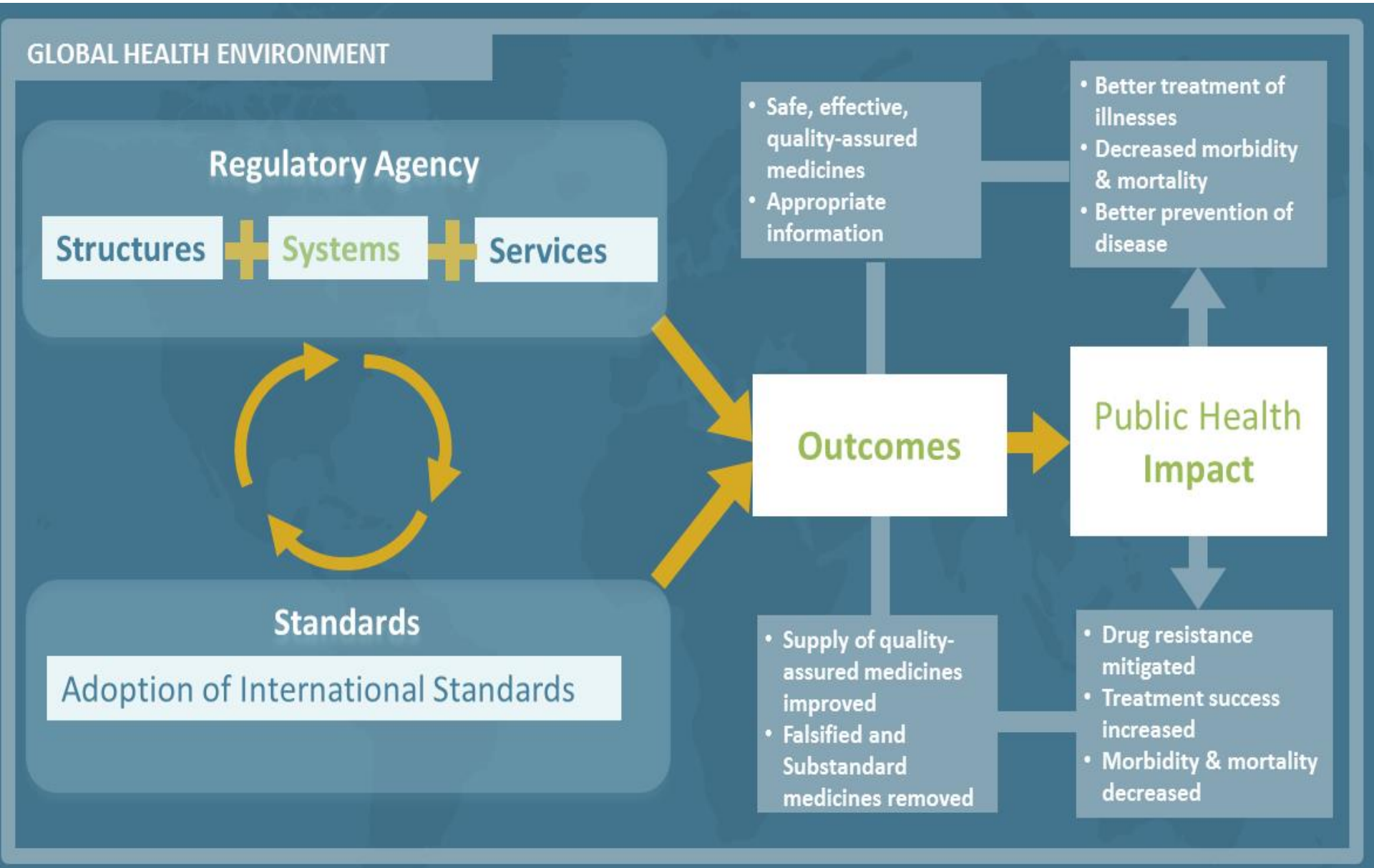
Batch J093: The Pathology of Negligence

There was either **collusion, gross negligence or carelessness** on the part of the concerned officials at PIC who failed to detect that the **consignment consisted of six different batches instead of two mentioned in the delivery challan**. That said, information was **mechanically, and without any counterchecking, entered into the registers**. Even the **Inspection Committee of the hospital failed to notice**, detect and point out this glaring discrepancy.



Report of the Judicial Inquiry Tribunal to determine the causes of death of patients of the Punjab Institute of Cardiology, Lahore in 2011-2012

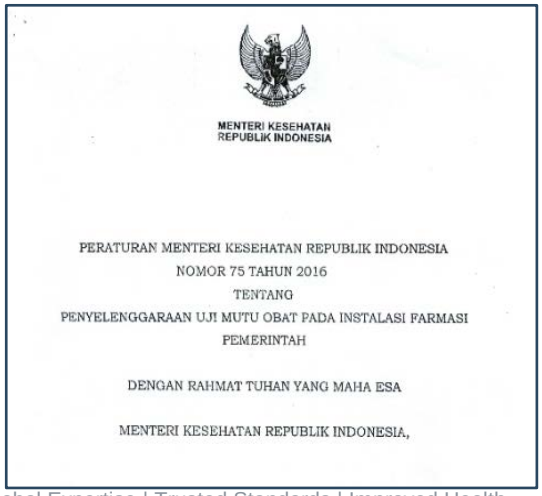
Functional Regulatory Systems and their Outcomes



Advancing Quality Systems in Indonesia

Objectives

Protect and promote public health by strengthening QA/QC systems through strategic technical assistance and collaboration



MENTERI KESEHATAN
REPUBLIK INDONESIA

PERATURAN MENTERI KESEHATAN REPUBLIK INDONESIA
NOMOR 75 TAHUN 2016
TENTANG
PENYELENGGARAAN UJI MUTU OBAT PADA INSTALASI FARMASI PEMERINTAH

DENGAN RAHMAT TUHAN YANG MAHA ESA

MENTERI KESEHATAN REPUBLIK INDONESIA,

PQM Initiatives

New MOH quality surveillance regulation for government pharmacy/storage facilities nationwide

Initiated WHO PQ project with national QC laboratory with the goal of meeting prequalification requirements this year

GF direct procurement grant to leverage TB funds to support capacity building of 12 govt. QC laboratories

National Accreditation Body changed scope of accreditation from product to method-based at the national QC laboratory

Outcomes

3 official revisions of MOH policy reflecting MOH-BPOM discussions

60 SOPs developed with PTBB lab, LIF compiled, multiple analytical trainings, infrastructure upgrades

$3 million in procurement funds leveraged via GF TB

WHO PQ program initiated with two provincial govt. QC labs

Ethiopia as New Model for Africa

Objectives

- Protect and promote public health

PQM Initiatives

- Proclamation No. 661/2009
- Adoption of international regulatory guidelines and quality management systems
- Building of a foundation for growth of the local pharmaceutical industry
- Strengthening of the regulatory and quality assurance workforce

Outcomes

- 12 recalls of five products, including 69 million condoms
  - tens of thousands of infections prevented
- Reduction of approval time for key medicines from 24 to 4.5 months
  - millions of people able to begin treatment earlier

Philippines – Improved surveillance of the local market

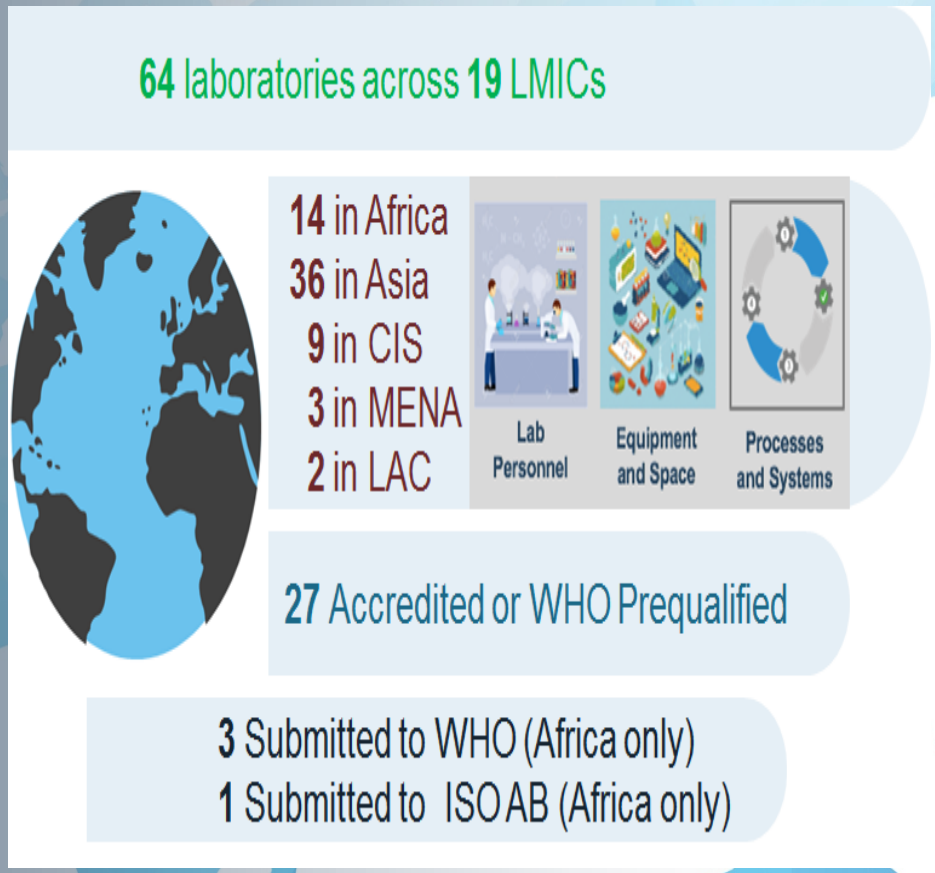
- Expanded skills in regulatory inspection of pharmaceutical distribution chains

- Strengthened PMS – product quality surveillance data informed FDA's advisory 2016-100 and regulatory action

Global Outcomes

Replicating Best Practices in other Countries

- Supported 16 NRAs to implement new guidelines/SOPs
- Strengthened quality surveillance in 12 countries
- Improved capacity of 64 labs



Sustaining Efforts

Components of effective and sustainable system for containment of substandard and falsified medical products:

- Country specific structures and systems
  - Quality Assurance Policy
  - Regulations
  - Guidelines (GDP)
- Risk-based approach to PMS
- Enforcement actions

IR2

Supply of Quality Assured Priority Medicines Increased

Promoting the Quality of Medicines

Supply of Quality Assured Priority Medicines Increased

Activities that increase the supply and access to a steady supply of essential, locally produced, quality-assured medicines, targeting USAID priority health programs. Delivering targeted and customized technical assistance to local manufacturers to address quality-related issues.

- GMP
- GLP
- GCP

IR2

Working with Manufacturers

Targeting local needs and exports in Nigeria

Objectives

- Supply 70% of domestic needs through local drug manufacturers *(2008 Target)*

Pharmaceutical Sector Profile: Nigeria

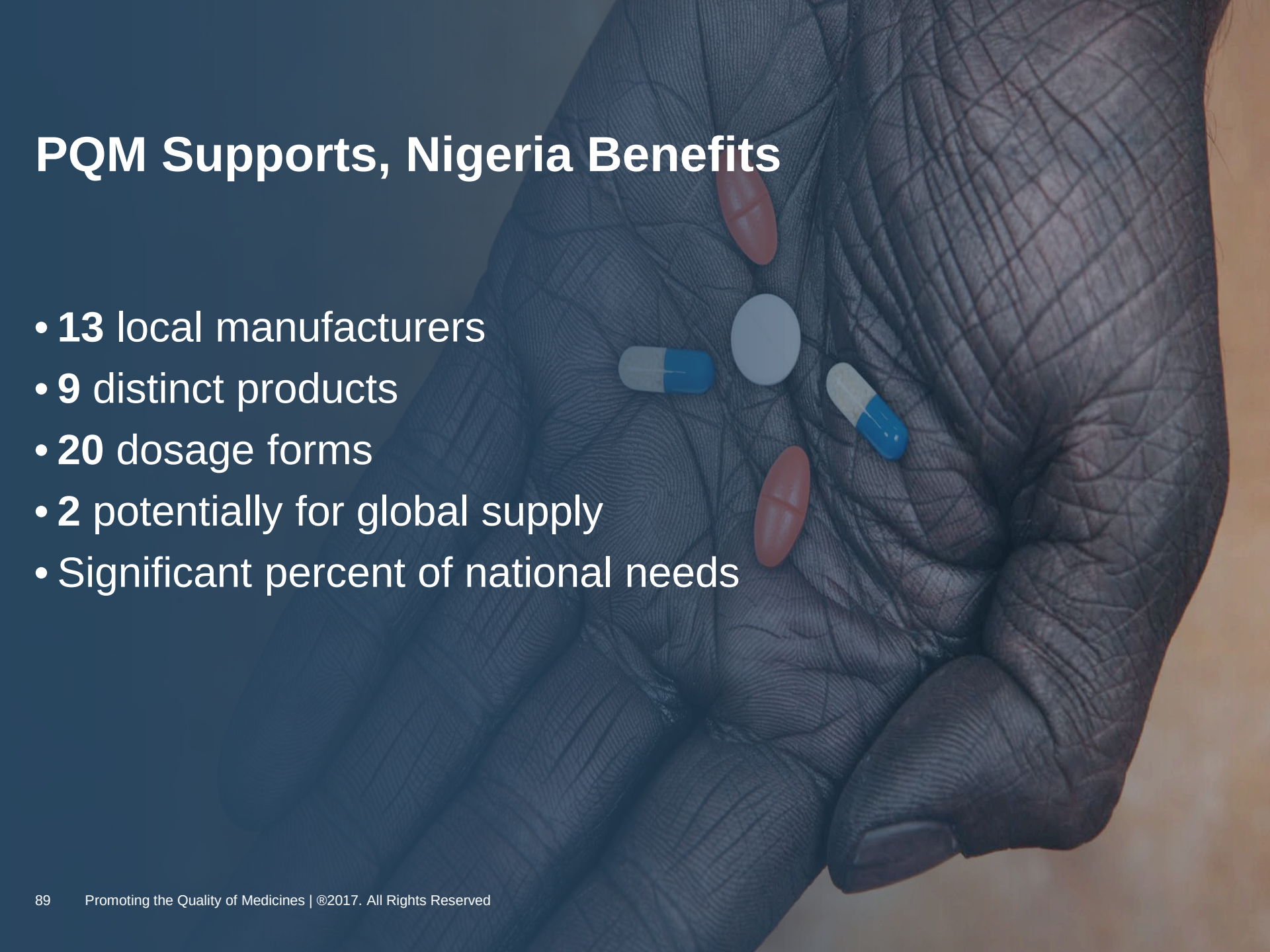
PQM Initiatives

- Increasing confidence in local industry
- Targeting for local needs and global supply by 13 local manufacturers
- Supply to UNICEF
- WHO Prequalification status anticipated
- Policy advocacy for local procurement
  - cost of quality study
  - ROI

Outcomes

- Chlorhexidine gel
  - tens of thousands of infections averted
  - adverse events prevented
- Improved essential medicines supply security for millions of people

PQM Supports, Nigeria Benefits



- **13** local manufacturers
- **9** distinct products
- **20** dosage forms
- **2** potentially for global supply
- Significant percent of national needs

Examples from Asia

- **Indonesia** - Supported government and private sector manufacturers towards WHO PQ, anticipating 2 submissions this year

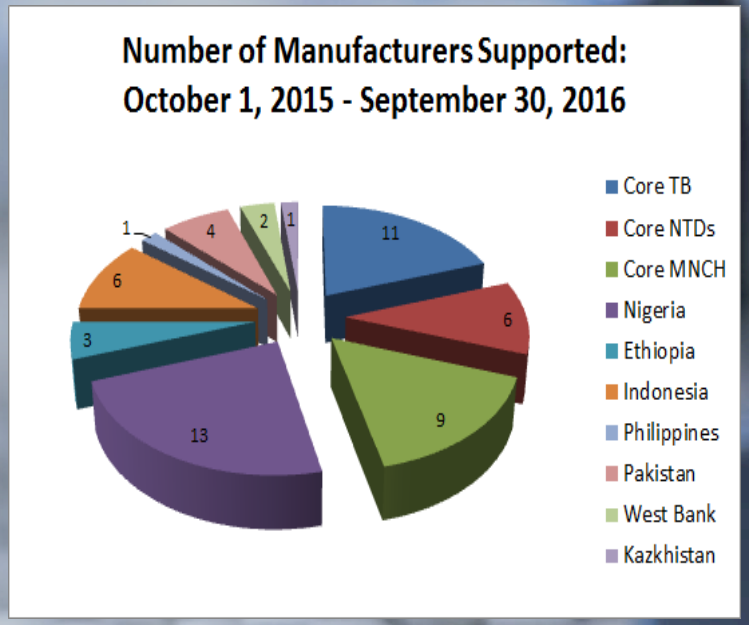
  Vietnam - Trained 55 representatives from local manufacturers on WHO GMP in support to the MOH and DAV

  Philippines - Supported trainings, mock audits, and dossier review for local manufacturers interested in WHO PQ

PQM Promoting the Quality of Medicines

Global Outcomes

Replicating Best Practices



- Supported 51 local manufacturers of essential medicines
- Improved approval of 18 TB API/FPP products
- Supported NTD, MCH, and PMI products

Sustaining Our Efforts

- Rethink regulation as enabler of access
- Build manufacturing capacity closer to the disease burden
- Reward investments in quality upgrades and adoption of international standards

Promoting the Quality of Medicines

Thank You

This document is made possible by the generous support of the American people through the United States Agency for International Development (USAID). The contents are the responsibility of the Promoting the Quality of Medicines program and do not necessarily reflect the views of USAID or the United States Government.

USP U.S. Pharmacopeial Convention

USAID FROM THE AMERICAN PEOPLE

Rx-360 and Audit Program Overview

28 March 2017

Mark Paxton, CEO

Membership

Broad and Inclusive

- Global – most regions
- Small and large pharma companies
- Branded and generic
- Manufacturers of APIs, excipients, medical products
- Regulatory agencies, standard setting bodies, and industry organizations participate as Observers

Current Rx-360 Membership

Members

Manufacturers (27)

- AbbVie
- Amgen
- AstraZeneca
- Baxter
- Bayer
- Bend Research
- Biogen Idec
- Boehringer Ingelheim
- BMS
- Daiichi Sankyo Co., Ltd.
- Eli Lilly
- Forest Laboratories
- Roche/Genentech
- GSK
- Impax Laboratories Inc.
- Johnson & Johnson
- Merck & Co.
- Merz Aesthetics
- Mylan Inc.
- Novartis
- Pfizer
- Pharmaceutics International, Inc.
- Procter & Gamble
- Sanofi-Aventis
- Takeda
- Teva
- UCB Pharma S.A.

Suppliers (30)

- AMPAC Fine Chemicals LLC
- Ash Stevens
- Aurisco
- Avantor Performance Materials, Inc.
- BASF
- Cambridge Major Laboratories, Inc.
- Cardinal Health
- Contemporary Graphic Solutions
- DSM Nutritional Products Ltd.
- FUJIFILM Diosynth Biotechnologies U.S.A., Inc.
- GE Healthcare
- Hikal
- Hovione
- Imperial Health Sciences
- Labochim
- LifeConEx
- Ligand
- Merck KGaA
- Neuland Laboratories Limited
- Novozymes
- OSO BioPharmaceuticals Manufacturing LLC
- Resilinc
- Sartorius AG
- Sigma Aldrich
- Spectrum Chemical Mfg. Corp.
- TempTime
- Thermo Fisher
- VWR
- West
- York Container

Observers

Auditors (13)

- Auckerman Consulting
- blue inspection body GmbH
- BSI Supply Chain Solutions
- MPC Consulting LLC
- PharmaPact Consulting Services
- PSC Biotech Corp.
- Regulatory Compliance Associates
- Rephine Ltd.
- RMC Pharmaceutical Solutions Inc.
- Safis Solutions LLC
- SQA Services Inc.
- STS Consulting
- The Weaver Group, Inc.

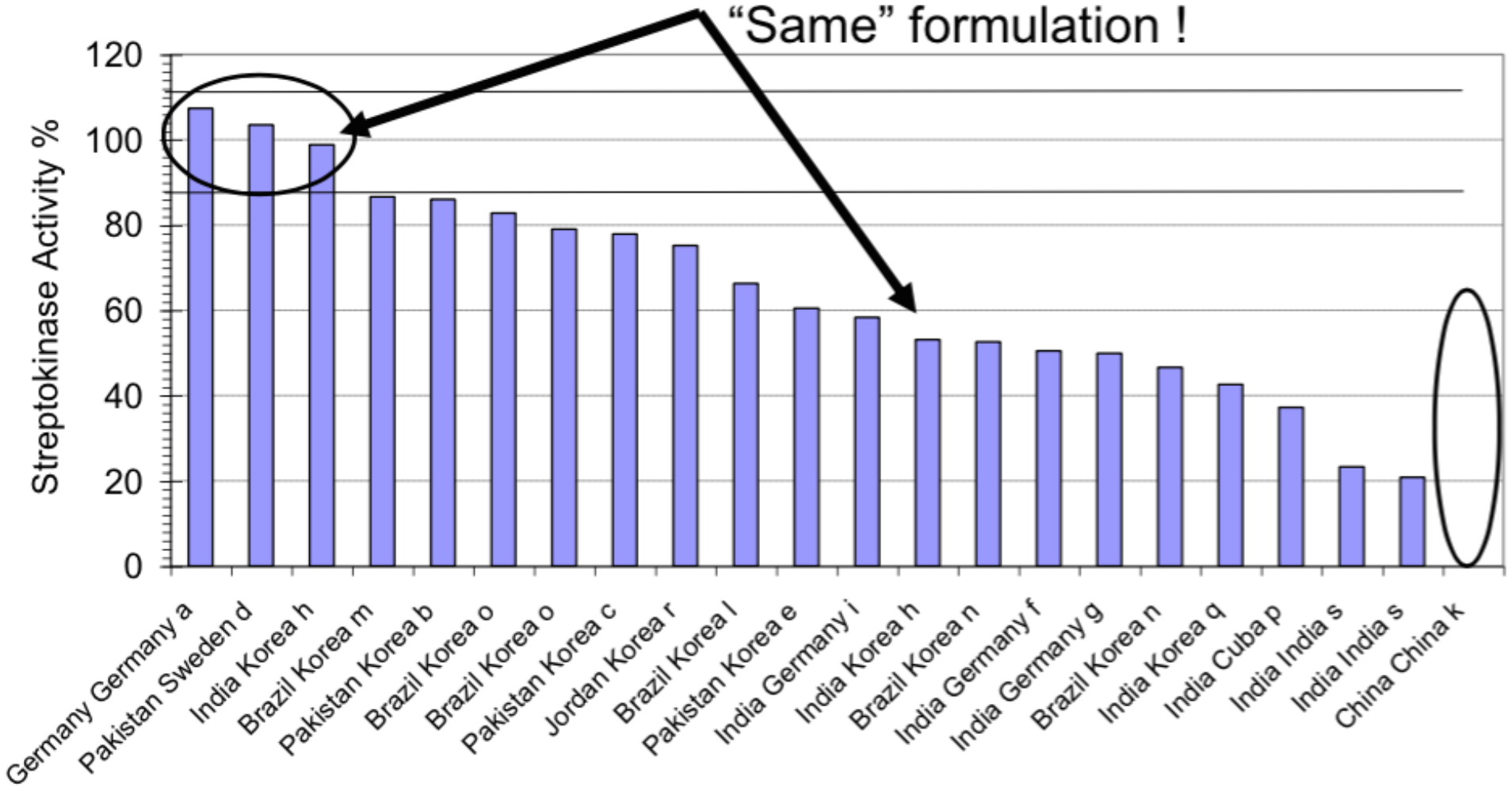
Associations (20)

- Alliance for Safe Online Pharmacies
- ANSI-ASQ National Accreditation Board
- APIC
- Bulk Pharmaceutical Task Force
- Consumer Healthcare Products Association (CHPA)
- Council for Responsible Nutrition
- European Fine Chemicals Group (EFCG)
- European Generic Medicines Association (EGA)
- EXCiPACT
- Health Distribution Management Association (HDMA)
- International Society for Pharmaceutical Engineering (ISPE)
- IPEC Americas
- IPEC Europe
- NSD Bio Group
- Parenteral Drug Association (PDA)
- Pharmaceutical Quality Group (PQG)
- Pharmaceutical Research & Manufacturers of America (PhRMA)
- Pharmaceutical Supply Chain Initiative (PSCI)
- Rx Response
- USDM Life Sciences, LLC

Audit Programs

Sharing the cost of audits while enhancing the security of the supply chain and improving patient safety

Streptokinase activity



Hermintin et al, European Heart Journal (2005) 26, 933-940

100% of Ergometrine tablets fail assay

USAID FROM THE AMERICAN PEOPLE | USP
PROMOTING THE QUALITY OF MEDICINES

POST-MARKET QUALITY SURVEILLANCE PROJECT
MATERNAL HEALTHCARE PRODUCTS
(OXYTOCIN AND ERGOMETRINE)
ON THE GHANAIAN MARKET

FOOD AND DRUGS AUTHORITY FDA GHANA

REPORT OF FIRST ROUND

Post-marketing quality surveillance was carried out to assess the quality of uterotonics (Oxytocin and Ergometrine) on the Ghanaian market between August and September 2012. A total of 303 samples— 185 Oxytocin injection, 103 Ergometrine injection, and 15 Ergometrine tablets—were sampled from both public and private hospitals, clinics, medical stores, pharmaceutical outlets, and the informal sector across the ten regions of Ghana.

Eighty-six percent (86%) of the Oxytocin samples found on the market were manufactured in China, whereas 90.68% of Ergometrine samples were manufactured in India. Of those collected and tested, 8.11% of Oxytocin samples and 57.63% of Ergometrine samples had been issued marketing authorizations: Two companies supplying Oxytocin and one company supplying

Out of the 169 Oxytocin samples assayed, 55.62% failed. Of the 99 Ergometrine injection samples, 73.74% failed, and all of the 11 (100%) Ergometrine tablets tested failed assay. Two (2) samples of Oxytocin injection and three (3) samples of Ergometrine tablets (two of the three Ergometrine tablets had the same batch number) were determined to be counterfeit products.

Audit Programs

Two offerings

In keeping with the Rx-360 Mission, two audit programs were developed:

1. The Joint Audit Program
2. Audit Report Licensing

Rx-360 Audit Programs

Rx-360 Can Assist with Suppliers Meeting Regulatory Needs

- With new regulations in effect, the need to conduct audits is greater than ever.
- However, the ability for suppliers to meet the auditing needs of their customers decreases further.
- Three steps can assist with this conundrum while building a more comprehensive quality program

Joint Audits- Requesting Audits

Concept

- Audits are conducted at the request of members. Rx-360 does not define the frequency of audits, but does schedule the audits

- Audits may be requested by (for example):
  - Pharmaceutical/biotech manufacturer member to audit a supplier
  - Supplier member to audit their own “up-stream” suppliers

Rx-360 Audit Programs

Rx-360 Joint Audit Program

Qualification of Auditors

- BSI (British Standards Institution) has partnered with Rx-360 to conduct Joint Audits on behalf of the members www.BSI.com
- Auditors register with the consortium via Rx-360 Website
- The Rx-360 Audit Operations Group regularly reviews auditor qualifications to ensure they are in keeping with Rx-360 standards
- Auditors are assigned to an audit based on qualifications and location

quirement	Description	Auditor meets minimum requirement Yes / No
EDUCATION	Has, as a minimum, a Bachelor's Degree from an accredited university (a minimum of three years).	☐ Yes ☐ No
PROFESSIONAL EXPERIENCE	Has a minimum of five years of GMP operational pharmaceutical experience with a minimum of 3 years of that experience in a quality related function. Operational experience includes those skills and competencies gained while working within a pharmaceutical GMP environment.	☐ Yes ☐ No
REGULATORY KNOWLEDGE	Is knowledgeable about pertinent regulatory and best-practices requirements (*e.g.* ICH Q7 for APIs, CFRs for USA, IPEC guidelines for excipients). The training and assessments must be fully documented. ☐ API ☐ Excipients ☐ Basic Chemical/Raw Material ☐ Packaging ☐ Chromatography Resins ☐ GDP	☐ Yes ☐ No
AUDITOR TRAINING	The provider of auditing services the auditor is associated with has a quality systems approach that includes training and refresher training of auditors	☐ Yes ☐ No

Rx-360 Audit Programs

Rx-360 Joint Audit Program

Audit Guidelines

API and Registered Intermediates
- ICH Q7

Excipients
- EXCiPACT GMP

Basic Chemicals/Raw Materials
(including Chromatography

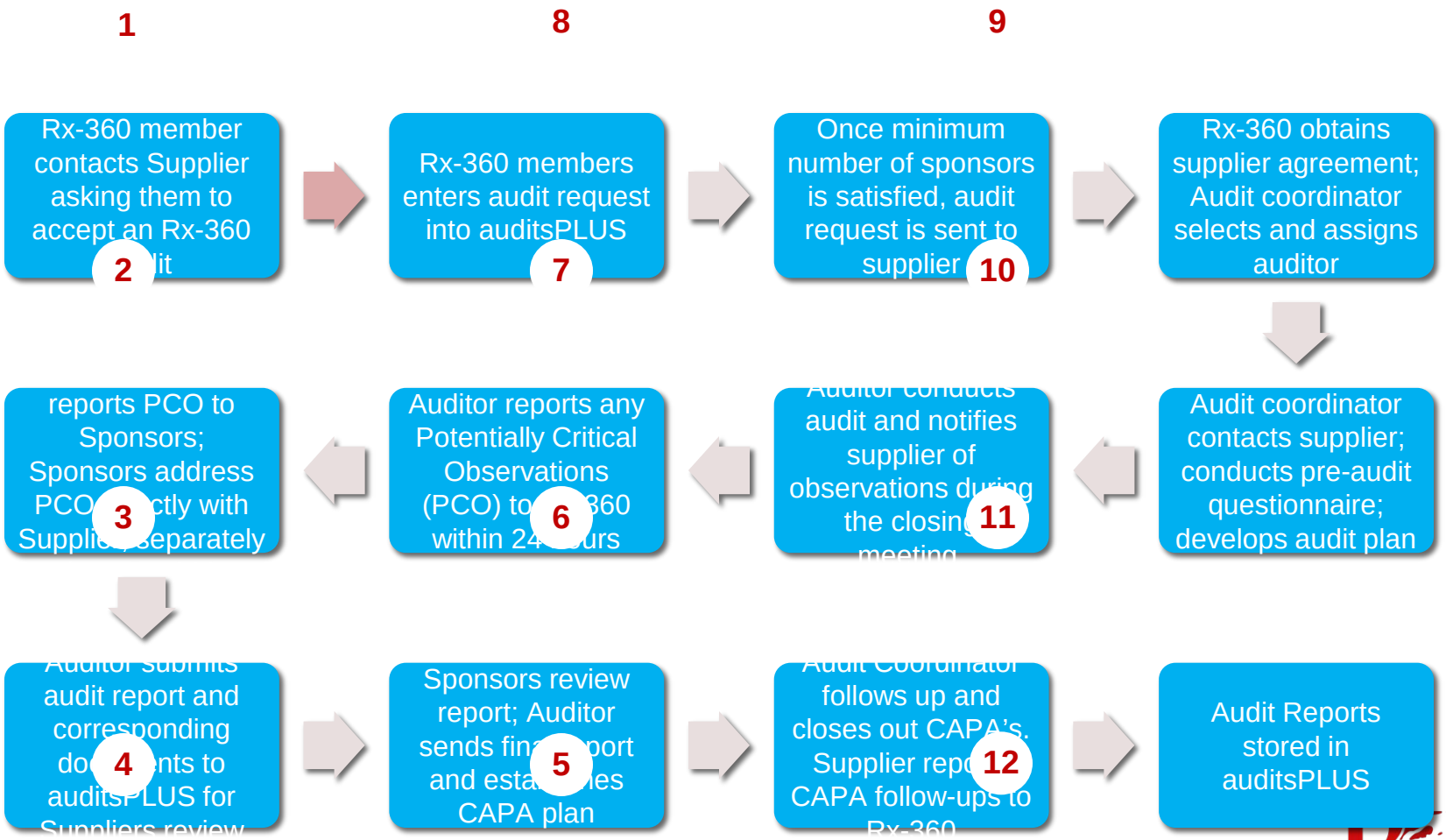
Packaging/Printed Materials
- ISO 15378

Rx-360 Audit Programs

Additional Audit Initiatives

The Rx-360 Joint Audit Program has branched out to include the following:

Joint Audit Process



Rx-360 Joint Audit Program

Observations

- Rx-360 Audit reports use two types of Observations

Potentially Critical

- A deficiency that indicates a critical system failure that may pose an immediate risk to patient safety or health, or may result in

Other

- A deficiency against the Rx-360 audit standards, guidelines, checklists, but that are not potentially critical

Rx-360 Audit Programs

Transitioning to a More Robust Program

Enhanced Coordination
Critical Mass

Joint Audits

The Rx-360 Audit Report & CAPA

A detailed response

Audit Programs

An International Supply Chain Organization
www.Rx-360.org

Document Name: FORM 7 – Joint Audit Report Template Rx-360 API
Document Number: 61765240v3

RX-360 AUDIT REPORT – API's

Company audited	
Name	Location & Contact Details

Products/Materials/Services within scope of audit	Dates of Audit

Audit Report Number	Standards used (as applicable)
[INSERT AUDIT REFERENCE #]	• *Rx-360 Audit Guideline for APIs* • *Rx-360 Supply Chain Security Checklist*

Auditors			
	Print	*Signature*	*Date*
Name of Auditing Company			
Name of Lead Auditor			

Distribution	
Supplier Contact Name and email address	
Rx-360 Coordinator" Name and email address	

Rx-360 will also distribute to member companies and others as agreed by Supplier. Recipient company names are withheld here for purposes of confidentiality.

Document Name: FORM 7 – Joint Audit Report Template Rx-360 API
Document Number: 61765240v3

Scope of the Audit

Summary

summary paragraph for the audit.

detailed comment for any **POTENTIALLY CRITICAL** observations]

OTENTIALLY CRITICAL OBSERVATION FOR THE PURPOSE
UDITS: A deficiency that indicates a critical system failure that diate risk to patient safety or health, or may result in adverse dentity, strength or purity of a product. The Potentially Critical objectively verifiable based upon documentation, facts, and

sess all observations for criticality with respect to their

h system/subsystem are provided with the observations ort.

Observations

dered as "OTHER" unless otherwise identified. ons by Quality System, with the most serious listed first.)

rvations of which X were classified as Potentially and supplier's response details are available in chment).

Audit Programs

Rx-360
An International Supply Chain Organization
www.Rx-360.org

Document Name: FORM8 – QA Audit ObservationCAPA Implementation Form
Document Number: 61472636v3

CAPA Implementation Form

Supplier:
Site:
Product (if specific product implicated):
Audit performed by:
Date of QA audit:
Audit #

Observation No.	Finding	Response	Completion Date	Current Status	Auditor Agree Y/N	Comments
1.						
2.						
3.						

CAPA plan reviewed by: _____
Auditor Signature

Audit Company:
Date:

Rx-360 | An International Supply Chain Organization • Washington, D.C. • www.rx-360.org

The Rx-360 Audit Report & CAPA

A list of the documents from the audit

1. Statement of Work
2. Pre-audit questionnaire
3. CVs of lead and co-auditors
4. Qualification form for auditors
5. Audit Report with observations, if any
6. CAPA from Supplier
7. Documented CAPA updates until CAPA is closed
8. Close out letter from Rx-360/BSI

Rx-360 Audit Licensing Program

- Audit reports originating from the Joint Audit Program may be licensed to **both members ($2500) and non-members ($5000)** for a fee
- A list of reports available for licensing can be found on the Rx-360 website www.Rx-360.org
- Suppliers determine which organizations may license an audit report through an addendum to the original CDA
- Members are provided access to the reports and corresponding materials through auditsPLUS system
- Non-Members are sent the documents by the Rx-360 Secretariat

Rx-360 Audit Programs

Critical Mass….

Rx-360 Consortium

More members, more engagement…

Historically and currently, the most inefficient problem results from matching audit requests among a relatively few number of companies.

- Rx-360 has tried a number of internal processes to improve the matching opportunities, including direct reach outs to other members after an initial audit request is put into the system, and

- Asking members to compile and deliver to Rx-360 their current an at least 3-year audit plans.

Rx-360 Audit Programs

The Same Site/Time Problem

- Information on Member Audit Plans are the singular issue to determining what a Critical Mass needed for success looks like ….
- Consider a single company's audit plan. Then add another, and another …….
- Differences are sites and times

Rx-360 Audit Programs

Perspective: What we are starting to look like…

Rx-360 Consortium

2016 was a fair increase in audits performed over 2015 and prior years …..

86 completed…Contextually, not so many, right?

But….

- 67 requests made through Feb, 2017
- Gates Foundation support
- Prepaid programs by Members (total ~ $750K)

Rx-360 Audit Programs

Let’s not forget the licensing program…

- 88 in 2015
- 184 invoiced by December 31st
- 26 licenses processed on one site audited last year.

Rx-360 Audit Programs

Summary

Privilege & Responsibilities

Serving patients is a privilege that comes with responsibilities...

Extra Slides

Rx-360 Consortium

Regulatory Acceptance

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

…This should normally provide sufficient assurance that the results of an audit carried by the third party are credible thus waiving the need for an audit conducted by the manufacturing authorization holder itself….

FDA

"FDA is very much in favor of industry's cooperative efforts, such as Rx-360…" Rick Friedman

Rx 360

More from Regulators

Medicines & Healthcare products Regulatory Agency

API audits by 3rd Party Auditors are regarded as suitable by MHRA on the following basis:

- The scope of the audit must be clearly defined and must include appropriate/defined elements of the supply chain.
- Auditors must be appropriately qualified.
- A 3rd party auditor may provide audit reports to multiple Manufacturing Authorisation holders. Manufacturing Authorisation holders may make use of such a report as far as the scope is fully pertinent to the APIs in question.

USP-APEC RHSC Center of Excellence Pilot Program
March 28, 2017

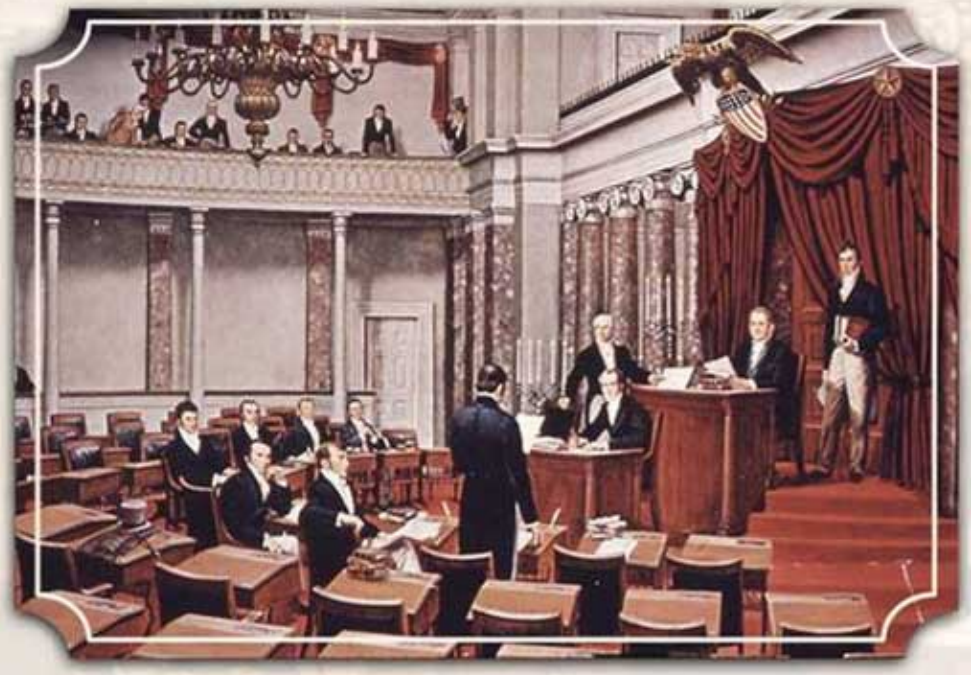
Public Quality Standards: Foundations for Securing Quality in the Global Supply Chain

Jaap Venema, Ph.D.
United States Pharmacopeial Convention
Chief Science Officer & Chair, Council of Experts

Agenda

- Quality Standards: A Long History of Harmonization
- Our Standards-Setting Process
- Quality Standards in the Global Supply Chain

The Founders - USP's Original "Harmonization" Team



1820

Spalding

Bigelow

Mitchill

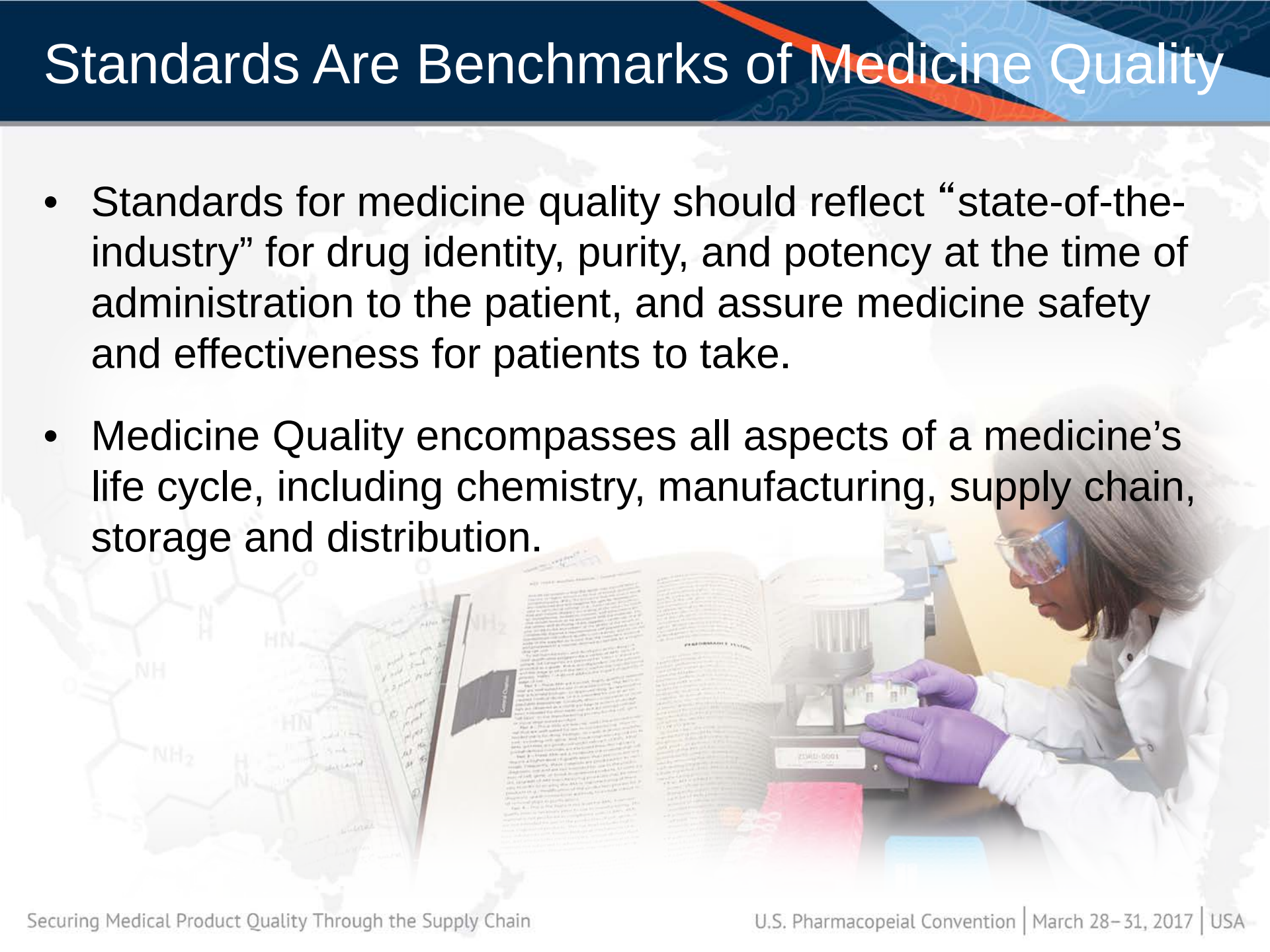
USP was founded in 1820 by 11 physicians, in Washington, D.C.

Agenda

- Quality Standards: A Long History of Harmonization
- Our Standards-Setting Process
- Quality Standards in the Global Supply Chain

Standards Are Benchmarks of Medicine Quality

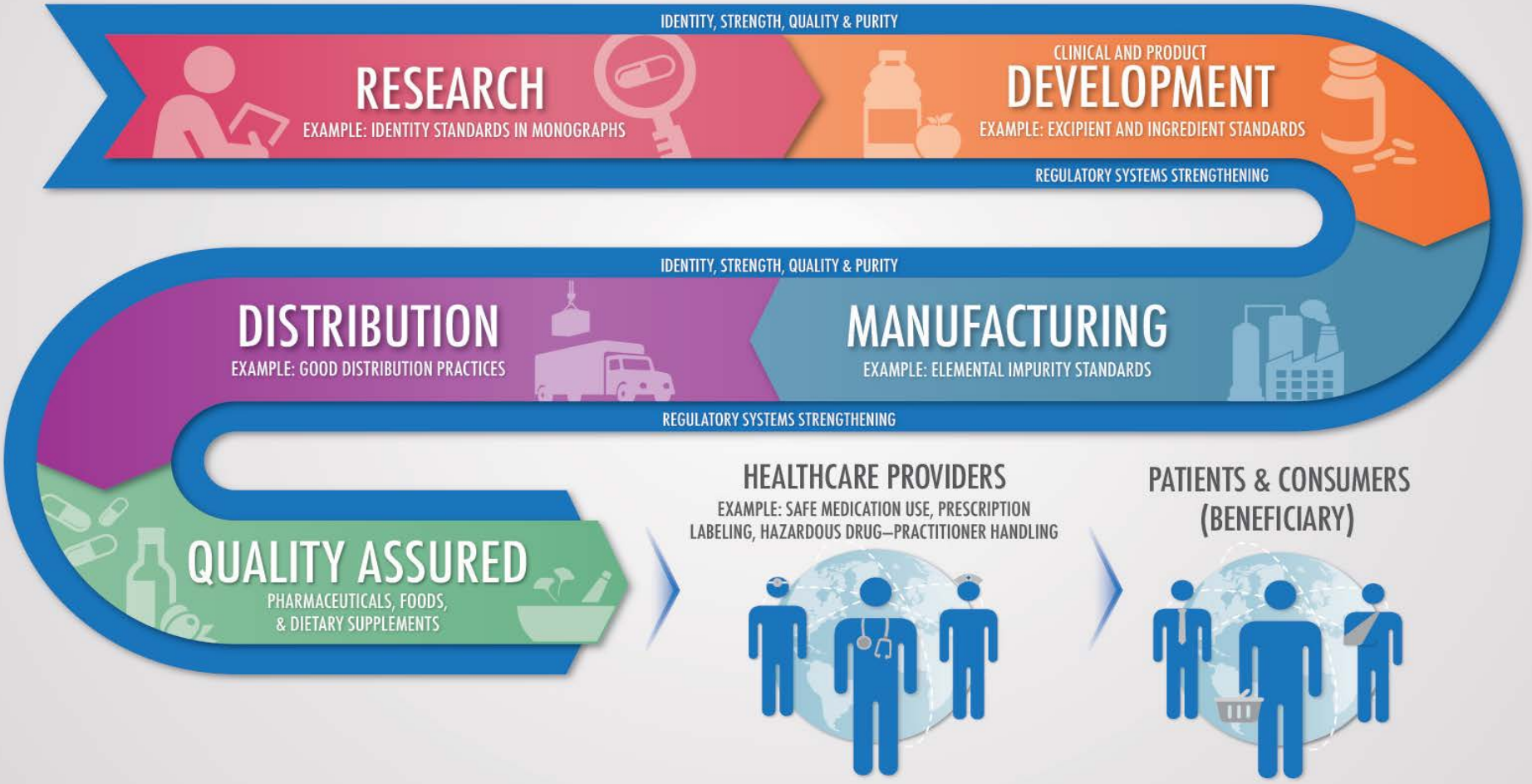
- Standards for medicine quality should reflect “state-of-the-industry” for drug identity, purity, and potency at the time of administration to the patient, and assure medicine safety and effectiveness for patients to take.
- Medicine Quality encompasses all aspects of a medicine’s life cycle, including chemistry, manufacturing, supply chain, storage and distribution.



Standards Ensure Quality Medicine Reaches Every Patient

1 INCREASE AVAILABILITY OF QUALITY PRODUCTS

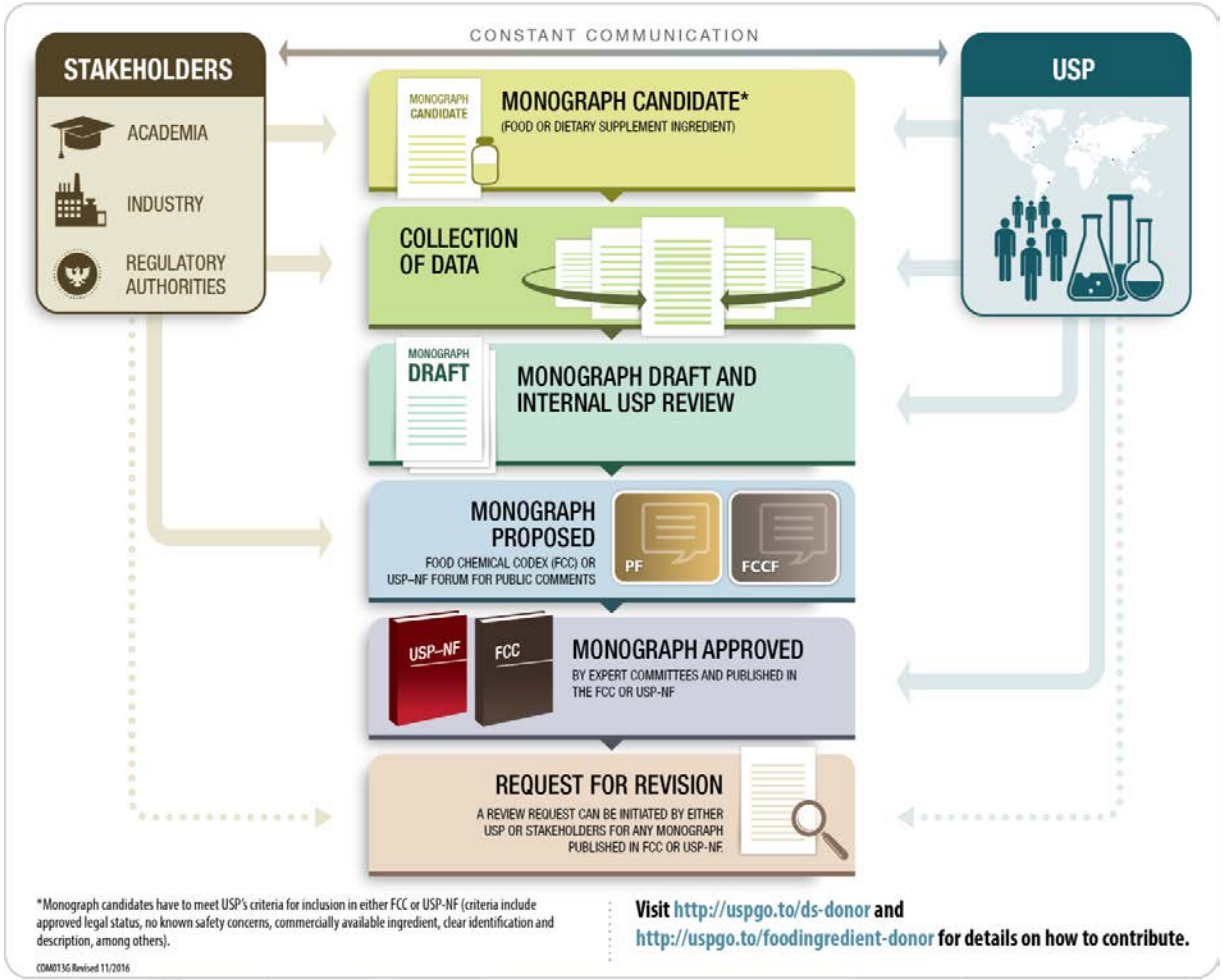
2 PROTECT PEOPLE FROM HARMFUL, POOR QUALITY PRODUCTS



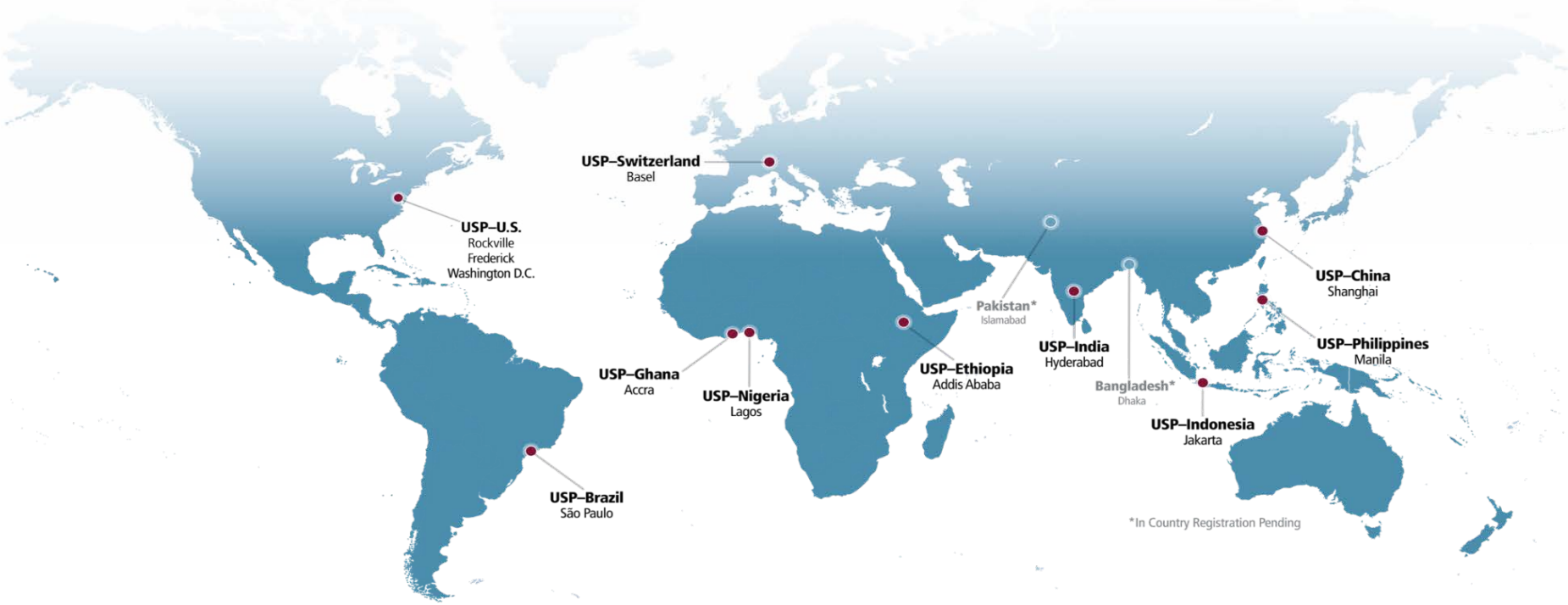
Science is the Base of Standards-Setting

The USP standard setting process includes independent experts from industry, government, and academia. Monographs set forth article's name, definition, specification, and requirements for packaging, storage and labeling.

Opportunity for participation in the process



Collaborative Testing Laboratories Ensure Methods are Robust



USP–U.S.

- Reference Standard
- Compendial Development R&D
- Biologics
- Dosage Form Performance
- Reference Standard Production (Packaging, Distribution)
- 65,000 sq. ft.
- Scientific Staff: 256 of 660 (39%)

USP–Brazil

- Compendial Development R&D
- 6,400 sq. ft.
- Scientific Staff: 27 of 36 (75%)

USP–Ghana

- Third Party Testing
- 1,000 sq. ft.
- Scientific Staff: 5 of 7 (71%)

USP–India

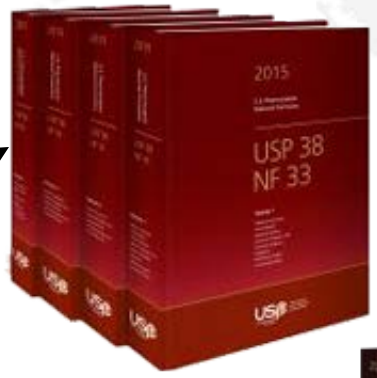
- Reference Standard
- Compendial Development R&D
- Biologics
- Dosage Form Performance
- Microbial Testing, Synthetic Chemistry
- 55,000 sq. ft.
- Scientific Staff: 108 of 142 (76%)

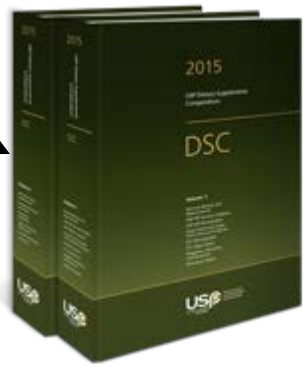
USP–China

- Reference Standard
- Compendial Development R&D
- Biologics
- Dosage Form Performance
- Microbial Testing
- GCoE for Food
- 58,000 sq. ft.
- Scientific Staff: 54 of 77 (76%)

USP Monographs are Connected to Reference Standards

The reference materials relate directly to methods in the USP publications:





Types of USP Standards

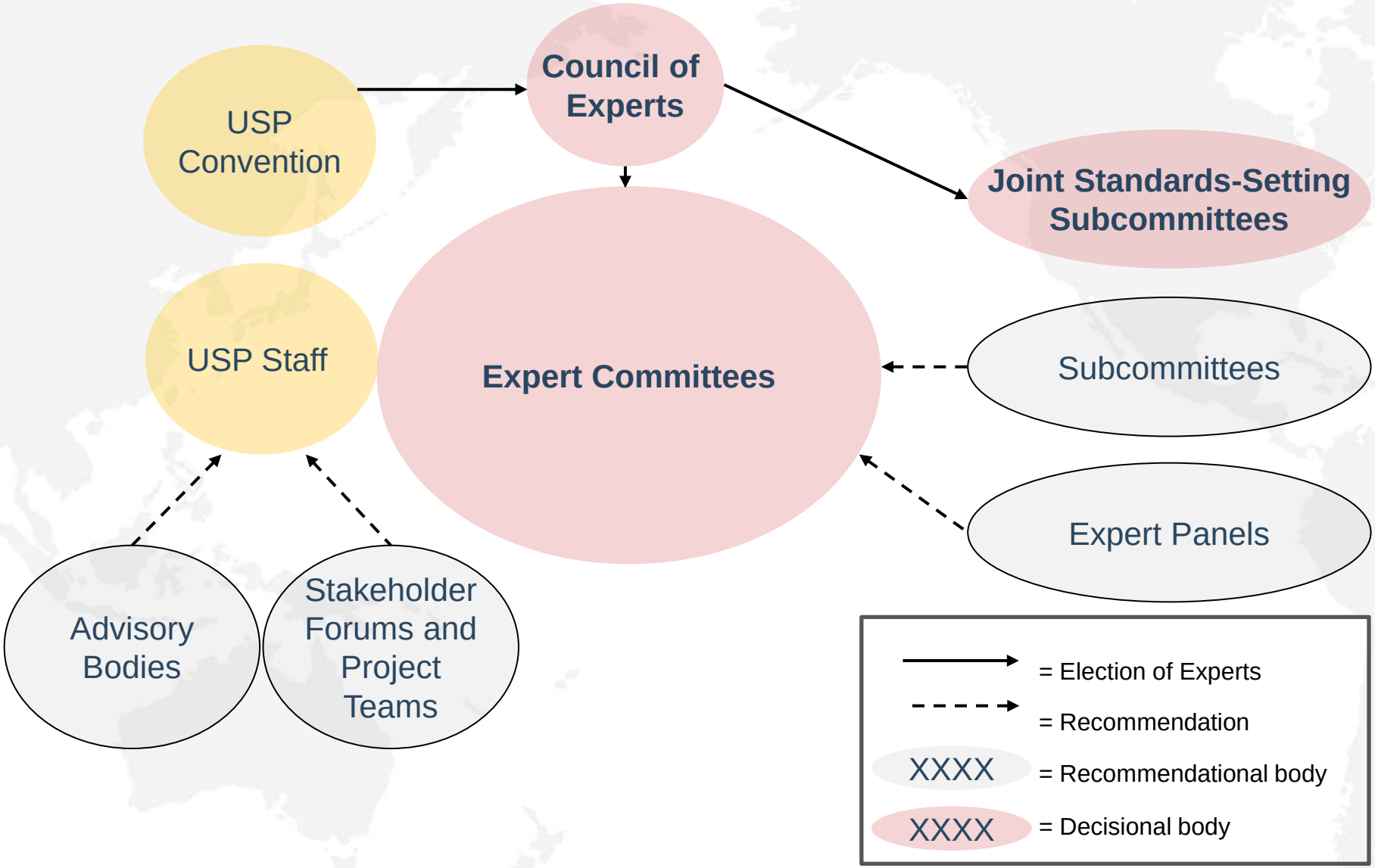
- General Notices
  - Key information supporting use of standards
  - Required unless noted otherwise in monograph
- General Chapters
  - Required when monograph cites them (numbered <1000)
  - Some are informational ONLY (numbered 1000-1999)
  - Support monographs by centralizing methods and procedures
- Monographs
  - Specifications for pharmaceutical articles in commerce (from release through product shelf life), linked through name
  - Specifications – Tests, assays and acceptance criteria needed to demonstrate the article meets required quality standards
- Physical Reference Materials
  - Provide traceable standards to demonstrate broad-based acceptability of procedures

Uses of USP Reference Standards

There are two main types of USP Reference Standards:

- Standards with Quantitative Applications
  - Assays (for drug substances and for formulations)
  - Limit tests (e.g., Impurity Reference Standards)
- Standards with only Qualitative Applications
  - Identification tests
  - Elution markers
  - System Suitability tests

Standards-Setting is a Transparent and Collective Effort



2015-2020 Council of Experts and Expert Committees

Council of Experts consists of the 25 EC Chairs and oversees scientific and standards-setting decisions

Expert Committees (ECs):

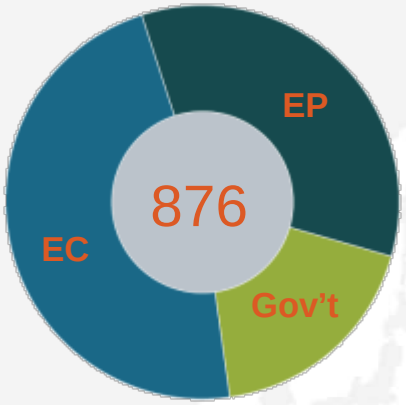
- Elected by CoE for duration of cycle
- Each is specific to a different area of standards
- Develop and revise standards that comprise USP's compendia
- Review public comments
- Adhere to strict confidentiality and conflict of interest provisions
- Members serve as individual experts and not any outside interest
- Expert Panels formed to provide additional expertise on a particular compendial topic, supplementing EC expertise

More information on each EC is available at http://www.usp.org/expert-committees

Expert Panels Provide Additional Expertise

- Formed to provide additional expertise on a particular compendial topic, supplementing EC expertise
- Members may participate with conflict of interest if disclosed
- Launched at any time and operate until fulfillment of charge
- Examples:
  - Compounding with Hazardous Drugs
  - Elemental Impurities
  - Food Adulteration
  - Modern Microbiological Methods
  - Modernization of Identification Tests
  - Quality Standards for Pharmaceutical Continuous Manufacturing

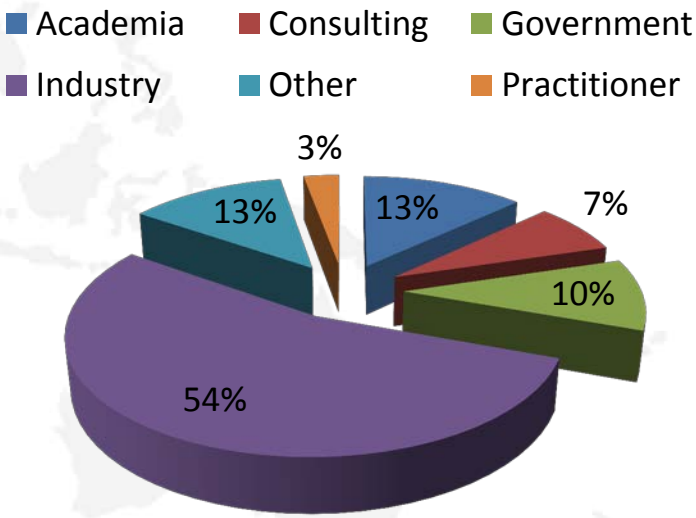
Diverse Expertise Behind Our Standards



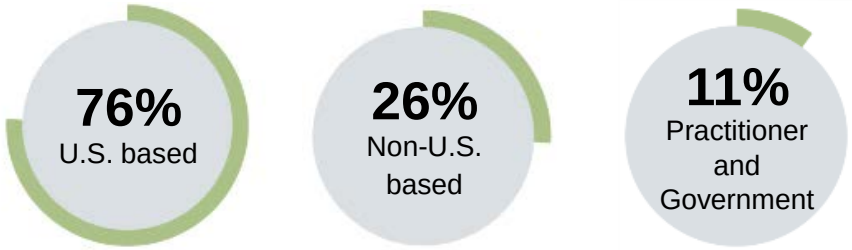
876 Scientific Experts–Volunteers and Government Liaisons

- 416 EC Members
- 301 EP-Only Members
- 159 Government Liaisons

- Leaders in their respective fields in industry, academia, healthcare, regulatory affairs
- Together they contribute to standards development through Expert Committees and Expert Panels
- Government Liaisons also contribute to the process



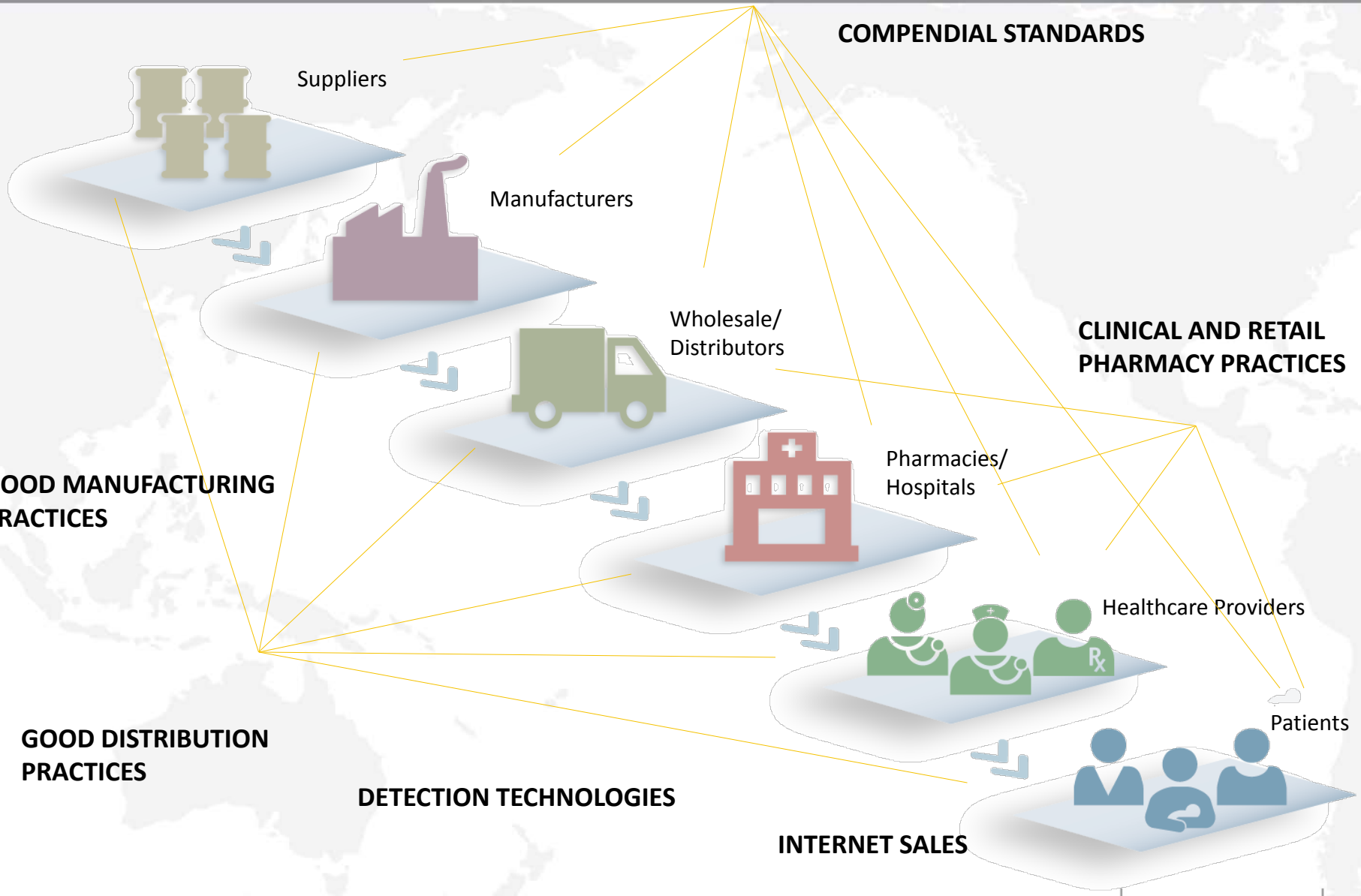
Current Expert Committee Members By the Numbers



Agenda

- Quality Standards: A Long History of Harmonization
- Our Standards-Setting Process
- Quality Standards in the Global Supply Chain

Public Quality Standards Apply Across the Supply Chain



Raw Materials Lack Consistent Definitions

- ICH Q7: Starting materials, reagents, and solvents intended for use in the production of intermediates or APIs
- However, the term could cover materials beyond this definition:
  - Starting or source materials
  - Cell lines, viral or bacterial stocks
  - Crude API
  - In-process materials (resins, buffers)
  - Ancillary materials
  - Formulation components, e.g. excipients, stabilizers
  - Implantables and delivery devices
  - Containers, closures, and inks
- Raw Materials may or may not remain in final therapeutic product as active substances or as excipients

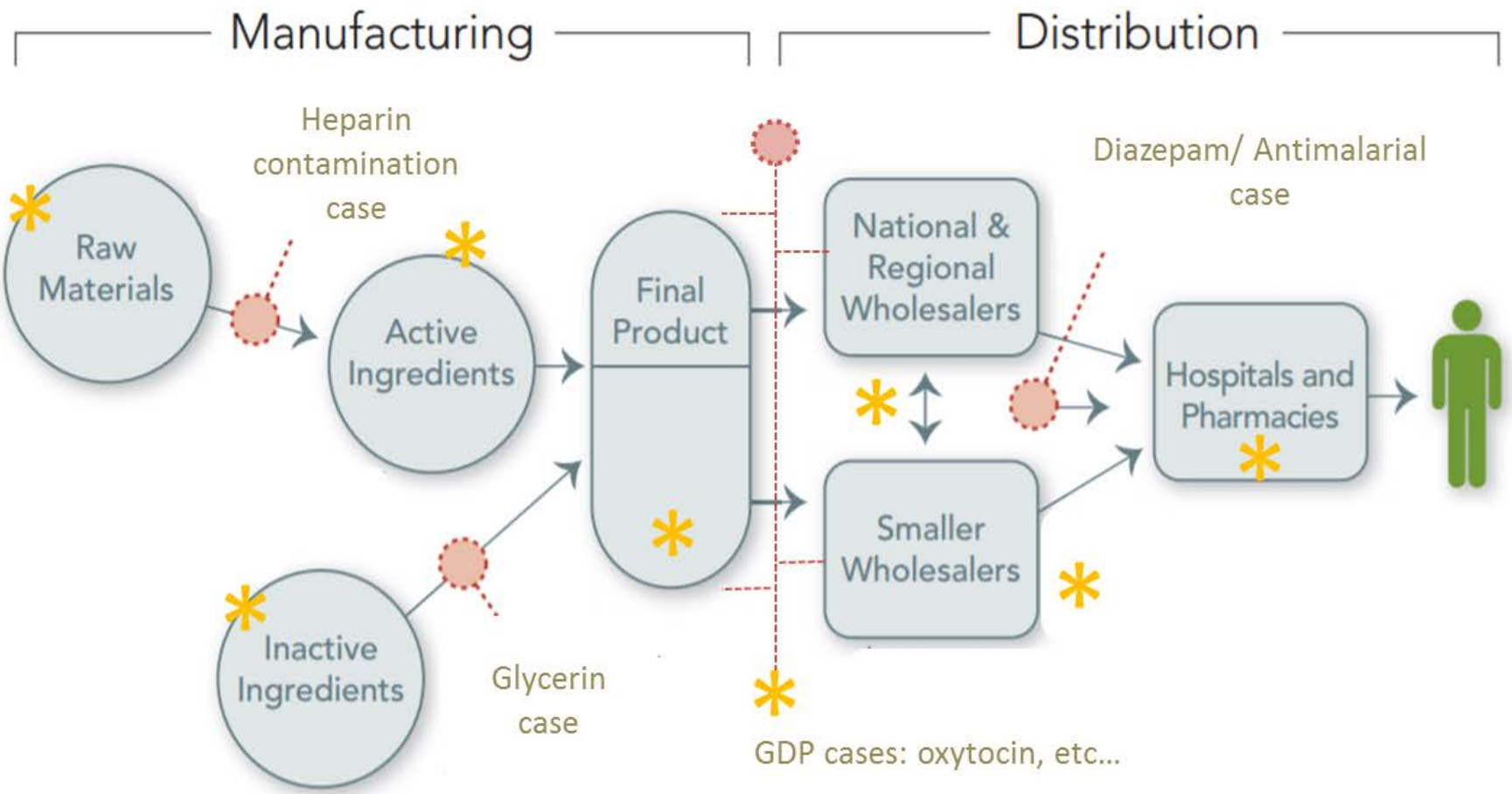
Raw Materials Can Cause Quality Concerns

- Specifications during the product lifecycle are heavily focused on active ingredient and the final product
- However, failures of products can be caused by non-active raw materials
- Raw material quality concerns have been amplified by recent materials supply issues (Glycerin, Heparin, Melamine)
- Some components are more critical than others, so risk assessment strategies are required to ensure quality

Quality Approaches for Raw Materials

- GMP vs. non-GMP raw materials
  - GMP-compliant materials: process and final product are controlled and reproducible
- Compendial or non-compendial raw materials
  - Materials meeting monograph requirements
  - Alternatives to monographs - when not available
- Reliance on Suppliers
  - Specifications: lot to lot consistency and materials for multiple use
  - Validity and validation of test methods
  - Certificate of Analysis (CoA) and testing beyond CoA
  - Pharmacopeial procedures
- Risk-based approaches for critical raw materials
  - Use of multi-suppliers materials
  - Impact of materials on final product
  - Define failures mode -use of quantitative tools- and mitigate risk

Public Quality Standards Apply Across the Supply Chain



* Public Quality Standards

Graphic adapted from: “After Heparin: Protecting consumers..” PEW Health Group White Paper. 2012. The Pew Charitable Trust. <http://magazine.pewtrusts.org/~/media/assets/2012/12/pew_heparin_final_hr.pdf?la=en>

Healthcare Quality & Safety Focus Areas

- ↑ **Safe Use of Medication & ↓Medication Errors**
  - Errors caused by **Drug Names / Pronunciation**
  - Unsafe sterile and nonsterile **Compounding Practices**
- ↓ **Hazardous Drug Exposure** to healthcare providers and patients
- ↑ **Patient Health Literacy** related to prescription drugs

Impact across distribution channel and across the continuum of care

Manufacturers
>200 Manufacturers
>40 new drugs approved/year

Institutions
5,627 Hospitals
15,600 SNF
67,000 Pharmacies

Healthcare Providers
300K Pharmacists
380K Pharmacy techs
2.7M Nurses
1M MDs

Patients
33M hospital admissions
1.7M patients in SNF
4B prescriptions

Examples from Case Studies: Good Distribution Practices

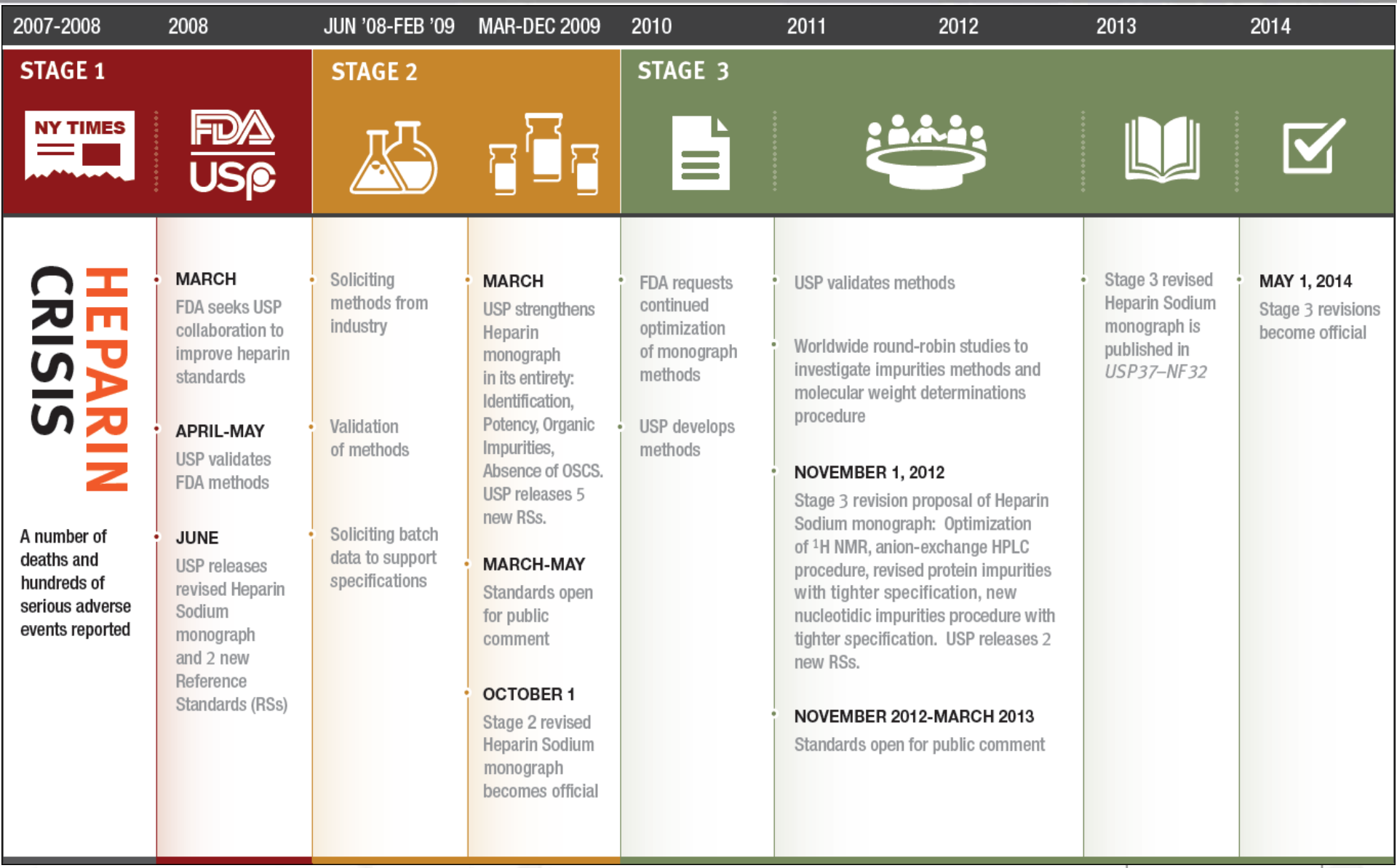
BRIEFING

〈 1083 〉 **Good Distribution Practices,** *PF* 38(2) [Mar.–Apr. 2012]. A new series of informational chapters describing various aspects of the pharmaceutical supply chain replaces that which appeared as an *In-Process Revision* in *PF* 38(2) but since then has been canceled. USP is proposing this new series of Good Distribution Practices (GDP) general chapters, which were developed based on a review of two existing general chapters, *Good Storage and Distribution Practices for Drug Products* 〈 1079 〉 and *Good Distribution Practices for Bulk Pharmaceutical Excipients* 〈 1197 〉, and the previously proposed general chapter *Good Distribution Practices—Supply Chain Integrity* 〈 1083 〉. These three general chapters provide information related to the storage, shipment, distribution, and transportation of pharmaceutical components and products. The review showed overlapping and complementary items among these general chapters and highlighted the need to revisit *USP* chapters on GDP from an overarching perspective. These new general chapters will cover material flow beginning with initial procurement and continuing throughout the supply chain to delivery to the end user for pharmaceutical components and products, medical devices, and dietary supplements. The chapters will address four main GDP topics—*Quality Management System* 〈 1083.1 〉, *Environmental Conditions Management* 〈 1083.2 〉, *Good Importation and Exportation Practices* 〈 1083.3 〉, and *Supply Chain Integrity and Security* 〈 1083.4 〉—highlighting best practices and principles.

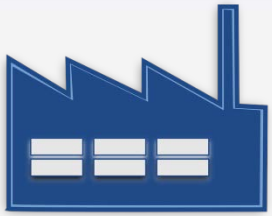
(GCPS: D. Hunt.) Correspondence Number—C139771

General Chapters: Good Distribution Practices Updates

Examples from Case Studies: Heparin



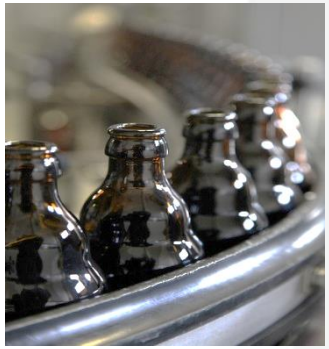
Examples from Case Studies: Glycerin



TD Glycerin
- NOT Compendial glycerin
- NOT for Pharmaceuticals
- NOT licensed

Cough syrup manufactured and released
- Inadequate release testing
- Insufficient tests

Resold, relabeled and new paperwork as pharma glycerin.
- Unknown history
- Changed to “Glycerin”



Delivered to Panama manufacturing facility
- Test incoming material
- insufficient test

Purchased by the Panama Government
- Clear requirements
- Understanding of Supply Chain

Examples from Case Studies: Oxytocin

peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively; *V* is the volume of sample solution in which the sample was dissolved; and *W* is the amount, in mg, of oxytocin dissolved in the sample solution.

Oxytocin Injection

» Oxytocin Injection is a sterile solution of Oxytocin in a suitable diluent. Each mL of Oxytocin Injection possesses an oxytocic activity of not less than 90.0 percent and not more than 110.0 percent of that stated on the label in USP Oxytocin Units.

Packaging and storage—Preserve in single-dose or multiple-dose containers, preferably of Type I glass or in suitable plastic containers.

Labeling—Label it to indicate its oxytocic activity in USP Oxytocin Units per mL. Label it also to state the animal source if naturally derived, or to state that it is synthetic.

USP Reference standards ⟨11⟩—
USP Endotoxin RS
USP Oxytocin RS

Bacterial Endotoxins Test ⟨85⟩—It contains not more than 35.7 Endotoxin Units per USP Oxytocin Unit.

pH ⟨791⟩: between 3.0 and 5.0.

Particulate Matter in Injections ⟨788⟩: meets the requirements for small-volume injections.

Other requirements—It meets the requirements under *Injections and Implanted Drug Products* ⟨1⟩.

Assay—Proceed as directed for *Oxytocin* except to use undiluted Injection as the *Assay preparation* and to allow not less than 25 minutes between injections. Calculate the potency, in USP Oxytocin Units per mL, by the formula:

$$C(r_U / r_S)$$

in which *C* is the concentration, in USP Oxytocin Units per mL, of the *Standard preparation;* and r_U and r_S are the mean values of the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Monograph: Oxytocin

Summary

- Public quality standards apply across the entire supply chain
- Holistic view and risk-based approach are necessary to establish appropriate quality and regulatory check points
- Standardization of raw materials allows to control consistency in manufacturing of finished products
- Pharmacopeial standards can provide tools for compliance with regulatory requirements

Questions

Thank You