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
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

- Suppliers
- Manufacturers
- Wholesale/Distributors
- Pharmacies/Hospitals
- Healthcare Providers
- Patients

GOOD DISTRIBUTION PRACTICES

GOOD MANUFACTURING PRACTICES

DETECTION TECHNOLOGIES

INTERNET SALES

COMPENDIAL STANDARDS

CLINICAL AND RETAIL PHARMACY PRACTICES

Securing Medical Product Quality Through the Supply Chain
<table>
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<th>Participants and Speakers</th>
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<td><strong>Regulators</strong></td>
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<tr>
<td>Brazil (as presenter)</td>
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<tr>
<td>Chile</td>
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<td><strong>Other Speakers/Presenters</strong></td>
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<td>Bristol-Myers Squibb</td>
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<td>Notre Dame</td>
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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

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

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Toolkit Applications: Good Retail and Clinical Pharmacy Practices and Internet Sales
• Panel Discussions
  • Good Retail and Clinical Pharmacy Practices
  • The Challenges of Internet Pharmacies

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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

<table>
<thead>
<tr>
<th>APEC Harmonization Center</th>
<th>APEC LSIF Secretariat</th>
<th>US FDA</th>
<th>USP</th>
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<td>Yeowon Sohn</td>
<td>Kate Clemans</td>
<td>Ilisa Bernstein</td>
<td>Phillip Nguyen</td>
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Thank You
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
Product Tracing

Product Identification (Serialization)

WDD and 3PL Licensing Standards

DRUG SUPPLY CHAIN SECURITY ACT

Verification

Regulations
 Standards
 Compliance
Building on GxPs & pharmacovigilance
“Filling in the supply chain holes”

Manufacturer ➔ Distributor ➔ Pharmacy/Dispenser ➔ Patient

GMP | GIP | GDP | GPP | Pharmacovigilance

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....
• 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

YAY!!!!
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

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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

- Shared Interest
- Identify and Sharing Best Practices
- Transparency
- Effective Process
- Data and Learning
The Value of Quality

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

You can use this page to choose to report an SSFC medical product(s), search the WHO database and access various resources.

Navigate the page by using the tabs on the top ribbon.

When submitting a report of a new SSFC medical product(s), and if you have completed the mandatory questions for each sub section, draft versions of your report will be automatically saved as you navigate through the pages.

To submit a new report, go to the tab “Submit a report” and click on “New report”. You can save a draft of the report which is accessible under “All draft reports”.

You will receive a PDF copy of your submitted report in the email confirming receipt.

Some of the Frequently Asked Questions (FAQs) are content aging, that is, if you point for more info,
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

- African Region: 44%
- Region of the Americas: 20%
- European Region: 19%
- Western Pacific Region: 8%
- Eastern Mediterranean Region: 7%
- South-East Asia Region: 2%
Therapeutic Classes of medical product reported to WHO

n=1371, data extracted 10 February 2017

- Antiinfectives
- Antiparasitics
- Nervous system
- Genito-urinary
- Alimentary tract
- Antineoplastics, immunomodulators
- Musculo-skeletal system
- Various
- Cardiovascular system
- Respiratory system
- Blood and blood forming organs
- Hormonal preparations
- Dermatologicals
- Sensory organs
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

Thefts of Medicines

- Medicines are a valuable commodity
- Thefts from Healthcare facilities across the world are 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

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)

1995 Niger
- Meningitis
- 2500 Deaths

2015
- Meningitis
- Shortage
- Public Supply

2010 Cameroon
- Meningitis
- High prices
- Stock Shortage

2010 China
- Rabies
- 1 Death
- 8 Arrests

2013
- Rabies
- 10,800 Doses
- 17 Arrests

2009 Philippines
- Influenza

2013-2016
- Tetanus
- Rabies
- Vaccine Clinics

2016 Indonesia
- Hepatitis B
- Tuberculosis
- Polio
- Tetanus
- 23 Arrests

2016 Bangladesh
- Yellow Fever
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

GOVERNANCE

1 Chair (Spain)
11 vice Chairs
Regional rotation

PURPOSE

International collaboration from a public health perspective on sub-standard and falsified medical products
MS Mechanism Steering Committee

WHO regions

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. Colored and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization Map Production: Health Statistics and Information Systems (HSI) World Health Organization © WHO 2013 All rights reserved.
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
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
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

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Group Lead, Safety and Vigilance,
Essential Medicines and Health products
World Health Organization
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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 a suite of awards that focuses on procurement of health commodities and provides technical assistance to the supply chain.

**Global Health Supply Chain Program**

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<tr>
<th>Award</th>
<th>Description</th>
<th>Partner(s)</th>
<th>Start/End Date</th>
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<tr>
<td>Procurement and Supply Management (GHSC-PSM)</td>
<td>Procurement &amp; shipping of health commodities; supply chain technical assistance</td>
<td>Chemonics</td>
<td>11/22/23</td>
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<tr>
<td>Rapid Test Kits (GHSC-RTK)</td>
<td>Procurement &amp; shipping of HIV RTKs</td>
<td>Remote Medical International</td>
<td>2/26/18</td>
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<tr>
<td>Technical Assistance (GHSC-TA)</td>
<td>Supply chain technical assistance</td>
<td>Chemonics Axios LMI PricewaterhouseCoopers</td>
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<td>Medicines, Technologies, and Pharmaceutical Services (MTaPS)</td>
<td>Pharmaceutical systems strengthening technical assistance</td>
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<td>Promoting the Quality of Medicines (PQM)</td>
<td>Medicines quality assurance technical assistance</td>
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<td>The Coca-Cola Last Mile Project</td>
<td>Applying Coke best practices to public health supply chains</td>
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<td>06/2019</td>
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<td>Business Intelligence and Analytics (GHSC-BIA)</td>
<td>Collect and integrate data across programs to support GHSC management and coordination</td>
<td>Intelicog</td>
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The Coca-Cola Last Mile Project
Applying Coke best practices to public health supply chains
06/2019

The Global Health Supply Chain Program is a suite of awards that focuses on procurement of health commodities and provides technical assistance to the supply chain.
BGH revealed to the FDA the impact of their work in our partner countries.

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<td>2017</td>
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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
Promoting the Quality of Medicines (PQM)

Jude Nwokike, Director
U.S. Pharmacopeial Convention
March 28, 2017
Substandard and Counterfeit Medicines
A Systematic Review of Literature

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

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

**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.

Tariq Almuzaini, Imti Choonara, Helen Sammons
## Quality Of Oxytocin Available In Low- And Middle-Income Countries: A Systemic Review Of The Literature

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Year</th>
<th>Study</th>
<th>Total of samples assayed</th>
<th>Country of manufacturer (N of samples)</th>
<th>Provenience of sample (N of samples from central or facility level setting and public or private sector outlets)</th>
<th>Tests performed</th>
<th>Percent failed samples**</th>
<th>Stated problem</th>
<th>Percent inadequate API fails***, % (n)</th>
<th>Percent low API fails****, % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stanton (2012)</td>
<td>NI</td>
<td>2012</td>
<td>1</td>
<td>46</td>
<td>46 facility level settings</td>
<td>API</td>
<td>76.1</td>
<td>76.1 (35)</td>
<td>Inadequate API</td>
<td>76.1 (35)</td>
<td></td>
</tr>
<tr>
<td>Karlkar (2013)</td>
<td>China (141), Pakistan (4), Switzerland (3), NI (21)</td>
<td>2013</td>
<td>2</td>
<td>169</td>
<td>162 facility level, 7 central level settings</td>
<td>API, sterility tests (only 40 samples)</td>
<td>55.6 (API)</td>
<td>97.5 (API or sterility or both, n = 40)</td>
<td>Inadequate API or not sterile or both</td>
<td>55.6 (94)</td>
<td>55.6 (94)</td>
</tr>
<tr>
<td>Stanton (2014)</td>
<td>India (193)</td>
<td>2014</td>
<td>3</td>
<td>193</td>
<td>193 private sector facility level settings</td>
<td>API</td>
<td>35.7</td>
<td>35.7 (69)</td>
<td>Inadequate API</td>
<td>35.7 (69)</td>
<td>29.5 (57)</td>
</tr>
<tr>
<td>Hegerzeil (1992)</td>
<td>Zimbabwe (UC)</td>
<td>1992</td>
<td>4</td>
<td>5</td>
<td>Unclear ('imported')</td>
<td>API</td>
<td>80.0</td>
<td>80.0 (4)</td>
<td>Inadequate API</td>
<td>80.0 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Pribiuda (2012)</td>
<td>Indonesia (LMIC)</td>
<td>2012</td>
<td>7</td>
<td>110</td>
<td>Indonesia (110)</td>
<td>API, identity, contaminant or strange particle matters</td>
<td>11.8</td>
<td>11.8 (13)</td>
<td>Inadequate API or no API or contaminants</td>
<td>11.8 (13)</td>
<td>9.1 (10)</td>
</tr>
</tbody>
</table>

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
IR1
Medical Products Quality Assurance Systems Strengthened
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.
Functional Regulatory Systems and their Outcomes

GLOBAL HEALTH ENVIRONMENT

Regulatory Agency
- Structures
- Systems
- Services

Outcomes
- Safe, effective, quality-assured medicines
- Appropriate information

Public Health Impact
- Better treatment of illnesses
- Decreased morbidity & mortality
- Better prevention of disease

Standards
- Adoption of International Standards
- Supply of quality-assured medicines improved
- Falsified and Substandard medicines removed
- Drug resistance mitigated
- Treatment success increased
- Morbidity & mortality decreased
### Objectives

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

### 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
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
## Working with Manufacturers

*Targeting local needs and exports in Nigeria*

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

### 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

**Pharmaceutical Sector Profile: Nigeria**
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
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
Thank You
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
- Hikai
- 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
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 Ergometrine.

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 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.

1. Rx-360 Membership
2. Participate in an Rx-360 Audit
3. Ask your customers to license the Rx-360 audit

More time to devote to customer needs
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 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
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
Additional Audit Initiatives

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

- **Medical Device**
  - ISO 13485

- **Supply Chain Security and Good Distribution Practices** (Adopted from C-TPAT, EU/WHO GDP (Both are already in practice)

- **Contract Laboratories**
  - (cGMP, ICH: in early development)
Joint Audit Process

1. Rx-360 member contacts Supplier asking them to accept an Rx-360 audit.
2. Rx-360 members enters audit request into auditsPLUS.
3. Reports PCO to Sponsors; Sponsors address PCO directly with Supplier, separately.
4. Auditor submits audit report and corresponding documents to auditsPLUS for Supplier review.
5. Sponsors review report; Auditor sends final report and establishes CAPA plan.
6. Auditor reports any Potentially Critical Observations (PCO) to Rx-360 within 24 hours.
7. Once minimum number of sponsors is satisfied, audit request is sent to supplier.
8. Audit coordinator contacts Supplier; conducts pre-audit questionnaire; develops audit plan.
9. Audit coordinator selects and assigns auditor.
10. Audit coordinator contacts supplier; conducts pre-audit questionnaire; develops audit plan.
11. Audit coordinator follows up and closes out CAPA’s, Supplier reports CAPA follow-ups to Rx-360.
12. Audit Reports stored in auditsPLUS.
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
Transitioning to a More Robust Program

Enhanced Coordination
Critical Mass

Joint Audits
The Rx-360 Audit Report & CAPA
A detailed response
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
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.
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
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)
Let’s not forget the licensing program…

• 88 in 2015

• 184 invoiced by December 31st

• 26 licenses processed on one site audited last year.
Serving patients is a privilege that comes with responsibilities...
Extra Slides

Rx-360 Consortium
Regulatory Acceptance

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

…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….
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.
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
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

RESEARCH
- Example: Identity standards in monographs

DEVELOPMENT
- Example: Excipient and ingredient standards
- Regulatory systems strengthening

DISTRIBUTION
- Example: Good distribution practices
- Regulatory systems strengthening

MANUFACTURING
- Example: Elemental impurity standards

HEALTHCARE PROVIDERS
- Example: Safe medication use, prescription labeling, hazardous drug—practitioner handling

QUALITY ASSURED
- Pharmaceuticals, foods, & dietary supplements

PATIENTS & CONSUMERS (BENEFICIARY)
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%)

Securing Medical Product Quality Through the Supply Chain

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

- Expert Committees
  - USP Convention
  - USP Staff
    - Advisory Bodies
    - Stakeholder Forums and Project Teams
  - Council of Experts
    - Joint Standards-Setting Subcommittees
      - Subcommittees
      - Expert Panels

- = Election of Experts
- = Recommendation
- XXXX = Recommendational body
- XXXX = Decisional body
### Council of Experts

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](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

- 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

876 Scientific Experts—Volunteers and Government Liaisons

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

Current Expert Committee Members By the Numbers

- 76% U.S. based
- 26% Non-U.S. based
- 11% Practitioner and Government
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

GOOD DISTRIBUTION PRACTICES

GOOD MANUFACTURING PRACTICES

DETECTION TECHNOLOGIES

INTERNET SALES

COMPENDIAL STANDARDS

CLINICAL AND RETAIL PHARMACY PRACTICES

Suppliers

Manufacturers

Wholesale/Distributors

Pharmacies/Hospitals

Healthcare Providers

Patients
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

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

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 and Good Distribution Practices for Bulk Pharmaceutical Excipients, and the previously proposed general chapter Good Distribution Practices—Supply Chain Integrity. 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, Environmental Conditions Management, Good Importation and Exportation Practices, and Supply Chain Integrity and Security—highlighting best practices and principles.

(GCPS: D. Hunt.) Correspondence Number—C139771
## Examples from Case Studies: Heparin

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<td><strong>STAGE 1</strong></td>
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<td><strong>NY TIMES</strong></td>
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<td>MARCH</td>
<td>Soliciting methods from industry</td>
<td>FDA requests continued optimization of monograph methods</td>
<td>FYI: Worldwide round-robin studies to investigate impurities methods and molecular weight determinations procedure</td>
<td>Stage 3 revised Heparin Sodium monograph is published in USP37-NF32</td>
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<td>APRIL-MAY</td>
<td>Validation of methods</td>
<td>USP develops methods</td>
<td>FYI: Stage 3 revision proposal of Heparin Sodium monograph: Optimization of $^1$H NMR, anion-exchange HPLC procedure, revised protein impurities with tighter specification, new nucleotidic impurities procedure with tighter specification. USP releases 2 new RSs.</td>
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<td>JUNE</td>
<td>Soliciting batch data to support specifications</td>
<td>NOVEMBER 1, 2012</td>
<td>FYI: Stage 2 revised Heparin Sodium monograph becomes official</td>
<td>MAY 1, 2014</td>
<td>Stage 3 revisions become official</td>
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<td>MARCH</td>
<td>FDA seeks USP collaboration to improve heparin standards</td>
<td>NOVEMBER 2012-MARCH 2013</td>
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<td>MARCH</td>
<td>USP strengthens Heparin monograph in its entirety: Identification, Potency, Organic Impurities, Absence of OSCS. USP releases 5 new RSs.</td>
<td>Standards open for public comment</td>
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<td>OCTOBER 1</td>
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Examples from Case Studies: Glycerin

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

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

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

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

**Delivered to Panama manufacturing facility**
- Test incoming material
- insufficient test
Examples from Case Studies: Oxytocin

USP 40

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.

Official Monographs / Oxytocin 5541

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:

\[ C \left( \frac{r_U}{r_S} \right) \]

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.
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