FINAL REPORT: APEC Roadmap to Promote Global Medical Product Quality and Supply Chain Security:
Supply Chain Security Toolkit (7-10-2018)

I.   INTRODUCTION

Member economies of the Asia Pacific Economic Cooperation (APEC) and non-APEC economies alike are adversely impacted by the international movement of substandard and falsified (S & F)[1] medical products. As the medical products industry has become more globalized and specialized, APEC economies must increasingly rely on the global marketplace to provide the medical products needed to keep citizens healthy while ensuring that access to legitimate products is not disrupted. In an effort to address this modern issue, regulators, industry stakeholders, representatives from non-governmental organizations (NGOs), international organizations, and academics from across the globe have come together as members of the "Roadmap to Promote Global Medical Product Quality and Supply Chain Security" ("Roadmap for Supply Chain Security" or "Roadmap") project. This project is a collaborative multi-year project commissioned by APEC with oversight by its Life Science and Innovation Forum (LSIF) and the Regulatory Harmonization Steering Committee (RHSC).

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[1] In 2016, the World Health Organization's Member State Mechanism refined the definition and use of substandard, spurious, falsified, falsely labelled and counterfeit (SSFFC) medical products to substandard and falsified (S & F) medical products. The toolkits for this project were finalized when the term SSFFC was the globally recognized term and were not edited to include S&F term.

The Roadmap for Supply Chain Security covers the entire supply chain and life cycle of medical products (i.e. raw materials to use by patients) and focuses on developing and implementing through training programs processes, procedures, and tools directed at enhancing global medical product quality and supply chain security. Hence, the final report is a living document that may continue to be updated as appropriate and as resources are available. More specifically, the approved project proposal identified three key objectives:

- Develop and implement a strategic plan securing the supply chain of medical products throughout APEC economies, including consideration of regulatory and policy issues related to the distribution chain;

- Enable convergence of regulatory requirements, covering areas as identified in the gap analysis, including, but not limited to: good distribution practices (GDP), pertinent elements of current good manufacturing practices (CGMP) and quality management systems, good import and export practices, product authentication and traceability, related regulatory practices influencing the security of the medical product supply chain, and the evaluation of implementing a single point of contact (SPOC) system by participating economies for the sharing of information related to suspect and non-conforming medical products; and

- Ensure the Supply Chain Security Toolkit ("Toolkit") is developed and implemented with worldwide stakeholder input by conducting a series of workshops intended to facilitate an understanding of current and future best practices for regulators by developing training materials and guidance documents in concert with the APEC Harmonization Center.

To this end, the Roadmap effort is comprised of 10 work groups, each devoted to a component of the supply chain. The specific areas covered by the work groups include:

1.) Good Manufacturing Practices (GMP)

2.) Good Distribution Practices (GDP)

3.) Good Import/Export Practices

4.) Clinical and Retail Pharmacy Practices

5.) Product Security

6.) Detection Technology

7.) Internet Sales

8.) Track and Trace Systems

9.) Surveillance and Monitoring

10.)Single Point of Contact (SPOC)

Between 2013 and 2016, experts participating in these 10 work groups took an in-depth look at the existing standards within their respective subject areas, conducted gap analyses, and developed recommendations for best practices. To capture this information in a useful format, each work group has developed an individual toolkit or set of training materials, which may include best practices, guidance documents, instructional videos, etc., intended to educate regulators, industry stakeholders, and others. This Toolkit is designed to consolidate the work from across the various work groups into one comprehensive resource that is reflective of the global supply chain's interconnectedness and can be navigated based on an economy's particular needs. With the understanding that resources are often limited and progress must be made incrementally, our hope is that regulatory authorities and stakeholders aiming to improve their medical product supply chain infrastructure will be able to identify the supply chain areas most in need of improvements and carve out a feasible path forward.

II. BACKGROUND

The Roadmap for Supply Chain Security project officially commenced on January 9, 2013 and was slated to complete within five years, with three years of APEC funding available. As the initial spearhead and champion of the project, the United States Food and Drug Administration (US FDA) has maintained the leadership role known within the APEC community as "project overseer," with logistics support from the APEC Harmonization Center.

The project's objectives, however, could not be achieved without multiple perspectives and insights from all participants and stakeholders working in product quality and supply chain management. As such, this Supply Chain Security Toolkit is the result of collaboration between regulators, industry stakeholders, representatives from NGOs, international organizations, and academics, all of whom generously volunteered their time and expertise. To increase the global reach and perspective, regulators outside of APEC including the European Union, Nigeria, and South America, and organizations including the World Health Organization (WHO), European Directorate for the Quality of Medicines, and United States Pharmacopeial Convention (USP), also participated in this project.

III. PROCESS FOR CREATING THE SUPPLY CHAIN SECURITY TOOLKIT

The Supply Chain Security Toolkit was developed primarily in three different phases: (1) identification of supply chain topic areas to be addressed and the formation of work groups to produce corresponding toolkits, (2) trainings and workshops held during APEC senior officials' meetings (SOMs), and (3) drafting and planning for Toolkit sustainability.

Work Group Toolkits:

Work groups were formed to develop individual toolkits and training materials for each of the 10 specific aspects of the supply chain. Ideally, each work group was formed to develop a balanced membership of regulators, industry members, and other stakeholders; however, the voluntary nature of this project led to some partner imbalances within groups. To account for this imbalance, several opportunities were made available for all Roadmap Project members and outside participants to provide feedback on work group materials.

Work groups used a variety of methods and materials to address their particular subject areas. Most groups conducted surveys or otherwise engaged in a review of the existing regulatory and industry standards for the subject area covered, performed a gap analysis to identify the guidance or training needs in the subject area across the APEC economies, developed standard operating procedures, and recommended best practices. Once this information was acquired or developed, the work groups began developing their training materials for the in-depth presentations they delivered during the following conferences and SOMs:

Workshops:

Between 2013 and 2016, workshops were held to develop the Toolkit and provide training on the subject matter areas:

SOM II, 2014; Qingdao, China: Good Clinical and Pharmacy Practices, Single Point of Contact (SPOC), Good Manufacturing Practices (GMP), Internet Sales, and the Product Security work groups provided in-depth trainings on their toolkits.

SOM I, 2015; Clark, Philippines: Good Distribution Practices (GDP), Single Point of Contact (SPOC), and the Product Security work groups provided in-depth trainings on their toolkits.

SOM III, 2015; City of Cebu, Philippines: Internet Sales, Good Manufacturing Practices (GMP), Track and Trace Systems, and the Detection Technologies work groups provided in-depth trainings on their toolkits.

SOM I, 2016; Lima, Peru: All 10 work groups presented executive summaries of their individual toolkits and participated in in a two-day discussion regarding the creation of the comprehensive Supply Chain Security Toolkit and sustainability of the Roadmap Project's deliverables.

All training materials are available for use on the APEC Harmonization Center's website: http://www.nifds.go.kr/apec/SupplyChain/APEC_SupplyChainToolkit_170317.pdf.

Supply Chain Security Toolkit Creation & Roadmap Sustainability Planning:

A five-day workshop during SOM I 2016 in Lima, Peru, served as a turning point in the life of the project. While workshops at previous SOMs centered around in-depth trainings on the various work group documents and individual toolkits, this workshop shifted gears toward the creation of the comprehensive Supply Chain Security Toolkit. In order to produce a Supply Chain Security Toolkit that would pull together the individual toolkits and trainings of the 10 work groups and demonstrate how all components of the supply chain fit together, the workshop was divided into two parts: (1) executive overviews from each work group, and (2) an open work group leaders meeting to discuss the final Roadmap Project's deliverables.

During the workshop, a core drafting group comprised of volunteers from across all work groups was established to generate this final project report, and leads were designated to manage feedback and suggested revisions from the larger group.

Another outcome of the SOM I workshop in Lima, Peru was the decision to move the Roadmap Project's deliverables into APEC Regulatory Harmonization Steering Committee (RHSC) Centers of Excellence (CoEs) at the conclusion of the multi-year project, sustaining development with oversight by RHSC. The RHSC has currently endorsed two pilot CoE programs on supply chain security— one by the University of Tennessee Health Science Center (UTHSC) and another by the United States Pharmacopeial Convention (USP).

IV. ROADMAP PROJECT WORK GROUPS

1.) Good Manufacturing Practices (GMP):

Background and Current Status: Appropriate manufacturing is essential for global medical product quality and supply chain security. As such, the Good Manufacturing Practices Work Group (GMP WG) was formed as part of this Roadmap with the primary objectives of: 1) evaluating the existing GMP standards across the APEC economies, 2) identifying best practices related specifically to medical supply chain security, and 3) setting forth GMP recommendations for regulatory authorities for supply chain security.

The GMP WG identified and evaluated current good manufacturing practices (CGMP) applicable to both active pharmaceutical ingredients (APIs) and finished medical products across and beyond the APEC economies. This evaluation focused specifically on practices to ensure greater supply chain security (e.g. the appropriate qualification of contract manufacturers and re-packagers, methods to identify and avoid the use of shadow manufacturers, etc.). Based on this assessment, the GMP WG made recommendations for best practices to reduce divergent practices and minimize opportunities for the introduction of S & F medical products into the global supply chain. To capture this information, the GMP WG developed two resources:

- A gap assessment to identify the differences in CGMP requirements related to supply chain security across and beyond the APEC economies (including requirements from Brazil, China, EU, International Council for Harmonisation's (ICH) Q7 Good Manufacturing Practice, India, Japan, USA, WHO) and the impact, both economic and in terms of patient safety, of these differences on APEC economies; and

- A GMP Toolkit comprised of training materials including best practice documents and slide presentations, which was initially drafted based on information collected in the GMP evaluation and gap assessment and was further refined based on the feedback received during the 2015 training program in Cebu, Philippines.

Toolkit Summary: The Good Manufacturing Practices Toolkit defines the CGMP elements relevant to supporting medical product quality and supply chain security. The Toolkit includes the training material used in presentations covering best practices in four areas: regulatory oversight, manufacturing itself, supply chain management, and related considerations along the supply chain. With respect to each of

these four categories, our primary objective is to converge CGMP requirements related to supply chain security across APEC economies.

One of the GMP WG's first tasks was to come up with best practices for regulatory operations aimed at supervising manufacturers. These best practices include meeting necessary licensing and registration requirements to sufficiently inform authorities and establishing local laws to allow adequate regulatory oversight and enforcement.

With regard to manufacturing itself, the control of yields and reconciliations is critical to tracking the volume of legitimate material produced and ready for entry into the supply chain. Unanticipated changes serve as an important indicator that the supply chain may have been compromised, thus, a yield should be established for each production operation and deviations from the expected yield must be investigated and explained.

Qualification and verification activities are also critical to supply chain management. To support these activities, materials and suppliers should be classified and assessed based on the perceived risk to quality they present. Complementing the qualification of products as "fit for use," the verification of incoming goods is the last line of defense for ensuring medical product quality. Verification is intended to detect both inadvertent errors and willful adulteration of goods entering a pharmaceutical facility and the greater supply chain. Incoming goods must be verified to be the correct material of the specified quality prior to release for use in pharmaceutical manufacturing or for repackaging and relabeling. Other related considerations along the supply chain include the control of rejected and returned materials. The disposition of rejected material is important to prevent rejected or substandard material from being introduced into the supply chain. With regard to outsourcing activities, all supply chain participants are responsible for product quality.

Communication among all stakeholders is essential. Each party that performs a function is responsible for ensuring that it is performed in full compliance and should not rely on others for quality control. Quality agreements cannot negate an individual's basic responsibility to follow CGMPs. Quality agreements should be considered standard practice, as they protect both patients and businesses. Last but not least, stakeholders should be on the lookout for potential show and shadow factories.[2] When selecting a manufacturer, companies should seek information about suppliers from other companies and regulatory authorities. Good supplier-customer relationships should be established so that suspicions may be reported and investigated through unannounced audits or notification to regulatory authorities.

Interdependencies, Gaps, and Related Initiatives: CGMPs provide a baseline for appropriate procedures in all areas of the medical product supply chain, and therefore complement all of the APEC work groups. More specifically, issues addressed by other work groups relating to CGMPs include: Good Distribution Practices (GDPs) regarding the storage and distribution of active pharmaceutical ingredients

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[2] In an effort to mislead clients and regulators, some companies will "show" immaculate, state of the art facilities and represent that such facilities are where they manufacture their products, while in fact the facilities where they actually manufacture products remain in the "shadows," hidden from regulatory oversight.

(APIs) and finished drug products; Internet sales of unregulated sources of APIs; Good Import/Export Practices relating to potentially unregulated manufacturing activities in free trade zones; the Clinical and Retail Pharmacy focus on large scale re-packaging or re-labeling and preparation of compounded medicines; S & F Surveillance and Monitoring needed for prevention, detection and response; and the need for oversight of API and drug products to begin with the original manufacturer.

Regulatory authorities within the APEC economies can use the best practices in the GMP Toolkit as a guide when updating their CGMP's best practices or when providing training to stakeholders, as appropriate. Furthermore, manufacturers should endeavor to implement best practices to the fullest extent possible in their day-to-day operations, regardless of whether the standards recommended exceed those of the regulatory framework under which they operate.

2.) Good Distribution Practices (GDP):

Background and Current Status: To ensure supply chain security and integrity and maintain product quality, GDPs should be followed by all stakeholders as medical products move through the supply chain. There is now a widespread expectation by national medical regulatory authorities (NMRA) that GDPs and supply chain controls be a part of the Quality Management Systems (QMS) for pharmaceutical and device manufacturers. To assist supply chain stakeholders in meeting these expectations, a GDP work group was formed from wholesalers, manufacturers, and regulators from NMRAs. The work group's objective was to develop recommendations for the standardization and of GDPs, focusing on supply chain security across industry while accounting for the applicable and evolving regulations.

Overview and Guidance Document Summary: The GDP Toolkit explores the purpose and requirements of GDPs, as well as how they overlap and fit together with CGMPs and Good Import/Export Practices. To this end, the GDP Toolkit includes several spreadsheets to help evaluate current regulations in each market, divided into six "pillars" or program areas. The first pillar covers GDPs as they pertain to marketing authorization, licenses control, Quality Through Assessment (QTA), and destruction. The second pillar discusses cold chain requirements (also referred to as "end-2-end temperature management") and manufacturing temperature management. The GDP toolkit's third pillar covers import/export requirements pertaining to trade controls, as set forth in Title VII of the U.S. Food and Drug Administration Safety and Innovation Act. The fourth pillar describes Track and Trace, and serialization requirements using guidance from the U. S. Drug Supply Chain Security Act (DSCSA) and the European Union's Falsified Medicines Directive (FMD). Also based on FMD guidance, the fifth pillar discusses product protection, including tamper-evident packaging, counterfeit protection, and diversion/theft controls. Lastly, the sixth pillar focuses on device controls, specifically the Unique Device Identifier and Global Unique Device Identification Database (GUDID).

Interdependencies, Gaps, and Related Initiatives: The GDP work group tracked regulatory changes pertaining to GDPs and the medical product supply chain.

3.) Good Import/Export Practices:

Background and Current Status: Trade allows for the global distribution of new medical products, providing health benefits to patients around the world. However, inadequate and ineffective regulatory controls facilitate the movement of S & F medical products and have detrimental public health consequences.

The workgroup identified several factors facilitating the movement of S & F medical products, including but not limited to:

- Inadequate, ineffective, or weak regulatory control leading to unregulated importation;

- Limited use of the WHO Certification Scheme on the "Quality of Pharmaceutical Products" moving through International Commerce as a prerequisite for the authorization/import of drugs; and

- Limited oversight by exporting countries on products for exports.

To better understand import and export regulations for medical products and to provide recommendations to industry and regulatory agencies for further improvements, the Good Import and Export Work group (GIEP WG) was established under the Roadmap project. The GIEP WG consists of members from industry who established the following objectives (No regulators from NRMAs volunteered to participate in this workgroup):

- Identify and evaluate current best practices that cover import and export controls of finished medical products; and

- Provide recommendations to industry and APEC economies based on the information collected and the observations made.

The scope of the objective was further refined to include only finished medical products and raw materials for commercial distribution. The GIEP WG conducted a gap assessment of import and export regulations across APEC economies and began to develop a toolkit to educate regulatory authorities and industry on achieving and managing trade compliance at an operational level. At the time of the Roadmap project's completion, this toolkit is still under development.

The gap assessment also demonstrated that in order to promote compliance, regulatory authorities must adequately support import/export activities through measures such as a National Single Window to streamline the process during customs clearance. [3]   A National Single Window allows parties involved in trade and transport to submit standardized information and documents fulfilling all import, export, and transit-related regulatory requirements through one electronic portal, allowing multiple agencies to easily access information. The primary objective for the National Single Window is to enhance the efficiency of

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[3] See UN/CEFACT Recommendation and Guidelines on establishing a Single Window, UNECE, 2005.

information exchange and the coordination between traders, transporters, and governments for regulatory transactions by reducing the number of transactions for data submission.

Toolkit Summary: Based on the gap assessment conducted by the GIEP WG, having an Import/Export Management program increases the likelihood that an individual company will meet compliance obligations. The GIEP Toolkit is being designed to provide guidance to industry by establishing best practices and familiarizing regulators with the workings of the entire supply chain, from sourcing to manufacturing and distribution. Industry members must comply with the obligations outlined by customs and other regulatory authorities of the countries for which they are shipping product to and from.

Organizations engaged in international trade need to understand laws, regulations, and government expectations of all countries involved. Changes in import/export rules are inevitable, as governments need to update the regulations in order to keep pace with industry changes in supply chain design. The nature of the import/export business requires frequent updates and changes in procedures, thus making it necessary for organizations to hire and train staff involved in import/export on a regular basis. To this end, the GIEP Toolkit will also provide guidance on continuing education considerations.

Interdependencies and Gaps: The GIEP Toolkit should be used in collaboration with other organizational processes, including CGMPs and GDPs. The flow of information and documentation needed for import/export is ultimately driven by the processes and documents generated during GDP and CGMP activities. Synergies can also be established throughout the supply chain through electronic system integration for sharing product-specific information and collaborative processes for cold chain distribution.

The GIEP WG did not undertake an analysis of import/export regulations in Free Trade Zones (FTZ), where medical products can be imported and exported without proper authorization.

4.) <u>Clinical and Retail Pharmacy Practices</u>:

Background and Current Status: Quality control measures implemented at dispensing sites, (e.g., retail and hospital pharmacies) serve as the last opportunity to prevent S & F medical products from reaching patients. Such measures should be in place at the time of purchase and receipt, at storage, and until the products are dispensed or administered. The information and materials below provide overviews of clinical and retail pharmacy practices across APEC economies, identifying best practices and resources required to support implementation.

Volunteers from the United States Pharmacopeial Convention (USP) led the Clinical and Retail Pharmacy Practices Work Group (CRPP WG) in identifying best practices across the APEC economies for ensuring the quality of medicines from procurement and receipt to dispensation. Additionally, the CRPP WG created a toolkit incorporating survey findings from representative sample of APEC economies and a gap analysis identifying areas for further development. Given that significant differences exist across and within APEC economies in the availability of resources, the CRPP WG also assessed the level of support required for implementation of best practices. This is an important consideration because it will allow economies to prioritize efforts based on existing resources.

Toolkit Summary: The CRPP WG's toolkit includes landscape overviews of APEC economies and more detailed profiles of selected individual economies with gap analyses, best practices, and the identification of the resources required for implementation.

Interdependencies with Other Roadmap Working Groups: Good clinical and retail pharmacy practices during procurement, storage, and dispensation cannot ensure the quality of medical products without the same commitment from other supply chain stakeholders. The best practices and tools developed by the other nine working groups participating in this Roadmap project often overlap and must be implemented in collaboration. To assist in identifying where such collaborations are indicated, the CRPP WG cross-references materials advanced by the other work groups throughout its Toolkit.

      5.) <u>Product Security</u>:

Background and Current Status: Given the continued growth of threats to the global medical product supply chain (e.g. S & F medical products, cargo theft, intentional adulteration, product diversion, substandard products, and product tampering), holistic and end-to-end supply chain solutions are necessary to ensure its security and integrity. The Product Security work group was comprised of regulators and a number of experts, many of whom also participate in a global consortium called Rx-360. Rx-360's primary objective is to bring a cross-section of pharmaceutical supply chain stakeholders together in protecting patient safety through standards and technology development.

Toolkit Summary: To develop the Product Security Toolkit (PS Toolkit), the work group used a transparent and collaborative process to create white papers, public presentations, and webinars. The resources contained in the PS Toolkit cover comprehensive supply chain security programs, management of upstream supply chain threats, mitigation of cargo theft risks, audits of logistics service providers, monitoring of marketplace threats to supply chains, response to supply chain security breaches, and measurement of supply chain security system effectiveness.

Ultimately, the PS WG concluded that a holistic, end-to-end system is required to prevent, detect, and respond to security threats in the broad and complex medical product supply chain. While CGMPs are integral to product security, they only protect one aspect of the supply chain. Because all points in the supply chain are vulnerable targets for infiltration by bad actors, countermeasures and controls must be cross-cutting and integrated across the full spectrum of the supply chain to ensure effectiveness. A good management system aimed at establishing standards though corporate policies, quality procedures, employee training, and the thoughtful selection of suppliers and distributors can assist firms in implementing effective product security measures.

Interdependencies, Gaps, and Related Initiatives: This Roadmap project connects all of the work groups and various aspects of the supply chain. As a result, product security processes build on and support most of the other work streams and vice versa. All deliverables from across the work groups should be viewed as complementary and interconnected. Each independent toolkit included as part of this Roadmap project was designed to promote a holistic and integrated system of supply chain management and security.

Supply chain stakeholders should keep in mind that criminals are creative and threats will continue to evolve. It is imperative that all security measures be kept up-to-date, as criminals will adjust to new requirements. Companies and regulators alike must address how to rapidly deploy new tools in case of threats of both an intentional and unintentional nature.

6.) Detection Technology:

Background and Current Status: Various tools are available for stakeholders to use at different points in the supply chain to assure the quality and authenticity of medical products. These tools and technologies, (e.g., handheld portable Raman or near Infrared spectrometers or barcode technologies) are used to assure the quality and authenticity of medical products. Detection of S & F medical products and authentication of drug product and packaging requires the use of numerous complementary features and modes of analysis, such as visual, chemical/forensic, and Track and Trace. As a result, it is imperative that policymakers and end-users alike understand the capabilities and limitations of these technologies. Guidance on the appropriate selection and application of detection technologies is one aspect of ensuring the integrity of medical products along the entire supply chain.

The Detection Technologies Working Group (DT WG) was comprised of regulators from NMRAs and industry stakeholders from across the APEC economies and others, aimed as assisting with the appropriate selection and utilization of detection technologies within their specific settings. To this end, the DT WG developed two resources:

- An overview and guidance document that was initially drafted at a workshop in Beijing in 2011 and has since been updated several times*; and*

- A toolkit that was initially drafted for the August 2015 APEC training program in Cebu, Philippines, and which has since been updated based on feedback received during a 2015 APEC training program in Cebu, Philippines.

Both resources are living documents and will continue to be revised and updated, as appropriate and as resources permit.

Overview and Guidance Document Summary: The DT Toolkit provides guidance for economies on the utilization of detection technologies, their limitations, and the need for global cooperation. There is no single technological solution for the detection of S & F products. This Guidance articulates that the authentication and quality assurance of a drug product and packaging requires the use of numerous complementary features and modes of analysis, such as visual, chemical/forensic, and Track and Trace. The applicable technologies for examining each of these features may require specialized knowledge, experience, and technical expertise.

Toolkit Summary: The DT WG Toolkit identifies current practices and provides recommendations for the deployment of detection technologies to ensure the quality of medical products throughout the global economy. The Toolkit also emphasizes that drug detection technologies must be used in a coordinated

manner by regulators, customs, law enforcement, pharmacopeias, vendors and industry stakeholders in order to successfully safeguard supply chain security.

Interdependencies, Gaps, and Related Initiatives: Successful implementation of the identified practices and recommendations is dependent upon coordination and collaboration with the prescribed best practices and recommendations set forth in the toolkits developed by the other nine working groups. These overlaps and interdependencies are identified throughout the Detection Technologies Toolkit. The DT WG lacked the resources to assess the technical specificity regarding analytical and operational capabilities of detection technologies, particularly with regard to portable tools.

Fortunately, there are other ongoing initiatives that may help fill this gap. For example, the World Health Organization's Member State Mechanism (MSMech) has a detection technologies working group that seeks to survey technologies methodologies and Track and Trace models and to analyze their relative advantages and disadvantages. As a complement to MSMech's work, the United States Pharmacopeial Convention (USP) launched the Technology Review Program in 2016 to objectively evaluate capabilities of existing and emerging detection technologies.

7.) Internet Sales:

Background and Current Status: The growing trend of consumers purchasing their medical products on the Internet is worrisome because of the fraudulent pharmacy websites that offer S & F medical products for sale. The consumer often does not receive the drug they purchased, or the product received may be sub-potent, super-potent, or contain no active ingredient at all. The information and materials below define the scope of the internet sales problem, present recommendations for combatting illegal internet medical product sales, and provide publicly available resource materials. The Internet Toolkit offers key definitions to help national medical regulatory authorities distinguish between legally-operating online medical product sellers and illegal entities.

The Internet Sales Working Group (IS WG) was established to propose activities for reducing illegal online drug sales in APEC and capacity-building to address patient safety concerns. The IS WG consisted of members of NMRAs, industry, and non-profit organizations. The IS WG was tasked with assessing the scope of the internet sales problem, identifying the gaps in internet sales regulation, and developing a toolkit to help economies implement internet pharmacy regulations, enforcement, and educational outreach. As a result, the IS WG developed two resources:

- A survey of how the globalization of the Internet and growth in illegal online drug sellers impacts APEC economies; and

- The Internet Sales toolkit was drafted using survey information and working group members' expertise and refined based on the feedback received during the 2015 training program in Cebu, Philippines.

Toolkit Summary: The Toolkit to Combat Illegal Internet Medical Product Sales (Internet Toolkit) defines the scope of the internet sales problem, presents recommendations for combatting illegal internet

medical product sales, and provides public education resource materials. The Internet Toolkit offers key definitions that pertain to internet sales of medical products globally to help national regulatory authorities distinguish between legally-operating online medical product sellers and illegal entities. The bulk of the Internet Toolkit is the IS WG's recommendations to relevant stakeholders in the internet sale of medical products. These stakeholders include but are not limited to NMRAs, law enforcement, healthcare professionals, and internet commerce companies. The recommendations highlight a few key themes: education and outreach, law and policy development, participation in global activities, and effective enforcement. The resource materials provided are from the World Health Organization (WHO), U.S. Food and Drug Administration (US FDA), and nonprofit groups. These resources aim to inform consumers and healthcare professionals of the risks of buying prescription medicines on the Internet and provide tools to buy online safely.

Interdependencies, Gaps, and Related Initiatives: Internet sales intersect with all areas of the medical product supply chain, and therefore overlap with all of the Roadmap project's work streams. In essence, the Internet is its own medical product supply chain, providing a means for retail pharmacy, distribution, and importation of S & F medical products.

Other initiatives related to the mission of the Internet Sales work group include but are not limited to (a) the Alliance for Safe Online Pharmacies' Global (ASOP Global)-sponsored studies of internet sales in select APEC economies, (b) Interpol's Operation Pangea, and (c) the European Union's FakeShare project, led by the Italian Medicines Agency (AIFA). The objectives of ASOP Global's studies are to assess the internet drug sales problem in key APEC economies and to make recommendations for joint government and third-party activities to address the identified problems. Operation Pangea is an annual operation coordinated by Interpol that brings together customs, health regulators, national police, and the private sector from countries around the world to tackle the online sale of counterfeit and illicit medicines and highlight the dangers of buying medicines online. The European Union's FakeShare project incorporates an IT intelligence project, the development of a regulatory proposal, intersectional training sessions (for customs, polices forces, and health authorities), and communication efforts to raise awareness of the risks posed by falsified pharmaceutical products sold online.

8.) <u>Track and Trace Systems</u>:

Background and Current Status: The ability to Track and Trace medical products is critical to curtailing counterfeiting and diversion in the legitimate supply chain. Global standards to identify, capture, and share product information enabling the authentication and traceability of medical products from manufacturer to patient is essential. The Track and Trace Systems Work Group (TT WG) identified and evaluated current traceability best practices across the world with the overall goal of ensuring that pharmaceutical products moving through international commerce are not falsely represented in any way, nor diverted from secure supply chains or distribution channels. The TT WG considers traceability practices critical to the ability to curtail counterfeiting and other illegal activities for improved patient safety. The TT WG also recognized that these solutions can bring added economic value to APEC member states and to all players in the healthcare supply chain, such as increased efficiencies and lower costs. The retail industry provides an example of how the successful use of supply chain standards can

automate data communication to achieve traceability of products as they travel from manufacturer to consumer. In the healthcare arena, the TT WG prioritized traceability measures using electronic systems for finished pharmaceutical products and their supply chain. Medical device products, raw materials, and associated supply chains were not the focus of the TT WG; however, the same global principles may be applied.

The main objectives of the TT WG included: 1) the development of recommendations to achieve regulatory harmonization with regard to traceability requirements and global data standards (GDS), 2) the development of recommendations to enable supply chain security and cost reductions, and 3) the application of expert analyses and the aforementioned recommendations in presenting traceability models that meet GDS and regulatory objectives.

The research and analysis completed by the TT WG resulted in six recommendations that would apply to APEC economies considering or expanding efforts to implement traceability requirements.   The three overarching recommendations include the following: 1) define a clear objective to be achieved for a Track and Trace program, 2) collaborate with all relevant public and private stakeholders through an open dialogue, and 3) use GDS to enable global interoperable product identification, data capture and sharing. The adoption of these three primary recommendations can improve the outcomes and success of any traceability initiatives. Additionally, the TT WG's analysis provides detailed recommendations pertaining to identifying, capturing, and sharing data through the healthcare supply chain.

Toolkit Summary: The TT Toolkit is divided into three parts: an introductory section on how to get started with traceability, an intermediate section on choosing the appropriate traceability system, and an advanced section on implementation of traceability requirements.

The first part of the TT Toolkit is comprised of educational materials relating to terminology, traceability models and technologies, and best practices from APEC regulatory authorities. The Toolkit emphasizes the importance for traceability solutions based on defined regulatory objective(s) (e.g. fighting counterfeiting and/or reimbursement fraud, authentication, verification, traceability, pharmacovigilance, etc.). Once the objective(s) and the relevant traceability system are specified, drug supply chain partners and regulators should work together to set forth an implementation approach (i.e. timing, phasing, governance model including data management and privacy). Collaboration should be ongoing due to the evolving nature of the supply chain.

The second part of the TT Toolkit is the "Traceability Matrix," which is a unique tool developed by the TT WG to assist readers in selecting the appropriate system (i.e. process and model) for traceability to meet the objective(s) defined earlier in the decision making process.

The third part of the TT Toolkit presents real-life examples from manufacturers, distributors, and hospitals, which demonstrate the use of GDS to enable globally interoperable product identification, data capture, and data sharing. In that context, the use of GDS supports global supply chain security and enhances cost effective management. Using GDS also facilitates harmonized implementation of traceability regulatory requirements, which will reduce complexity and cost.

The TT Toolkit was used to conduct training during SOM III, held from August 27 – 28, 2015, in Cebu, Philippines. Training objectives using the Toolkit included the following themes: understanding traceability, the key drivers for developing traceability regulations, the benefits of working with healthcare stakeholders globally for regulatory harmonization, existing best practices for traceability systems around the world, the challenges in implementing existing traceability requirements, and the benefits of using global data standards to ensure international harmonization.

Interdependencies, Gaps and Related Initiatives: The work of the TT WG correlates to the objectives of all of the APEC work groups, but intersects most directly with the Single Point of Contact (SPOC), GDP, Import/Export, S & F Surveillance and Monitoring, and Internet Sales work groups.

        9.) <u>Substandard and Falsified (S & F) Surveillance and Monitoring</u>:

Background and Current Status: The existence of S & F medical products is an unacceptable and, to a significant extent, avoidable risk to patients and consumers which undermines confidence in medical products, healthcare providers, and health systems. Reducing the harm caused to public health from these products, including socioeconomic consequences and increases in anti-microbial resistance, is high on the international health agenda. As such, global communication and cooperation is essential to identify and monitor for S & F medical products. With the globalization of trade in active pharmaceutical ingredients (APIs) and finished medicines, the World Health Organization (WHO) recognized the need to establish a Global Surveillance and Monitoring System (GSMS) for S & F medical products. Rather than establish a new approach or system, the Roadmap project identified the WHO GSMS as an important mechanism to achieve the desired global communication and cooperation for addressing S & F medical products.

The objectives of the WHO GSMS for S & F medical products are two-fold: 1) provide technical support to Member States when faced with an emergency and, where necessary, issue global medical product alerts; and 2) accumulate a body of validated evidence for policy and decision makers on the scope and scale of harm caused, vulnerabilities in systems, weaknesses in supply chains, and medical products most at risk. [4]

Since the GSMS's rollout in 2013, WHO has conducted 17 regional workshops, trained about 400 regulatory personnel, and established focal points in 125 Member States and 18 of the largest international procurement agencies have been sensitized. About 1,300 S & F products from all therapeutic categories have been reported to the system, and incidents have occurred in over 90 countries. In response, WHO has provided technical assistance in over 100 urgent cases and issued 17 global medical product alerts, in addition to numerous local and regional warnings. [5] WHO continues to work towards reaching full global implementation of the unique monitoring system.

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[4] WHO S & F Medical Products Website: http://www.who.int/medicines/regulation/S & F/en/
[5] WHO Medical Product Alerts: http://www.who.int/medicines/regulation/S & F/medical-products/en/

As part of the Supply Chain Security Workshop held in February 2016, the Surveillance and Monitoring Work Group (SM WG) was tasked with proposing practical strategies and tools for stakeholders for greater participation in surveillance and monitoring, with the goal of preventing, detecting, and responding to S & F medical products.

Toolkit Summary: The SM WG's toolkit includes two resources:

- Visual "Dartboard" of the Prevention, Detection and Response Framework for S & F Medical Products; and

- WHO S & F Medical Products Website at: http://www.who.int/medicines/regulation/S & F/en/.

The Visual Dartboard is a simple tool that identifies twelve core indicators under the Prevention, Detection, and Response framework. This tool may be used to benchmark a minimum set of core functions needed to prevent, detect, and respond to S & F medical products.

The WHO S & F Medical Products Website is a reliable, comprehensive, and up-to-date resource on this topic.

Interdependencies with Other Roadmap Working Groups: S & F surveillance and monitoring is a root driver for the promotion of patient safety though the medical product supply chain, ensuring access to safe, effective, and quality medical products. The WHO GSMS has made important progress, but its continued success relies on global support and implementation.

As such, WHO encourages NMRAs within the APEC economies to be trained in the use of the WHO GSMS as a cost-effective and practical tool to prevent, detect, and respond to S & F medical products. WHO also encourages the pharmaceutical industry to report cases of falsified medical products to NMRAs in a timely manner. In 2016, all trained national regulatory focal points will be able to search the database through a secure link to check if a suspected or confirmed S & F medical product has already been reported to WHO, report products through a secure web portal, and access photograph libraries of confirmed S & F medical products. More training workshops are planned for further global rollout of the system.

For more information, please contact the WHO S & F Surveillance and Monitoring Team at rapidalert@who.int.

10.) Single Points of Contact (SPOC):

Background and Current Status: The primary objective of the Single Point of Contact Work Group (SPOC WG) work group was to produce a toolkit with recommendations on implementing a SPOC System for 1) proactively identifying officials at the national and international level to coordinate regulatory, law-enforcement, and judicial actions; and 2) reactively addressing incidents with S & F medical products. A well-maintained SPOC network allows authorities to build intelligence on best practices and to coordinate their actions domestically and internationally, as most of the incidents involve

more than one country. The SPOC WG was led by the European Directorate for the Quality of Medicines (EDQM)/Council of Europe and included members from industry and regulatory authorities from across the APEC economies.

The SPOC WG has held training sessions on Toolkit recommendations during the APEC Senior Officials Meetings that took place in Qingdao, China in May of 2014 and Clark, Philippines in January of 2015. Both sessions included health and law enforcement authorities from across the APEC economies and focused on the establishment of SPOC systems at the national, regional and global levels. The general format of the trainings consisted of: informing trainees of the risks associated with S & F medical products, describing the benefits and role of SPOC in securing the supply chain, and breaking out into sessions for further development of strategies to establish SPOC systems tailored to the needs of particular economies.

Toolkit Summary: The SPOC WG produced a Toolkit modelled after EDQM's adopted approach that was developed by the Council of Europe for Single Points of Contact. This model approach has been part of EDQM's work on the MEDICRIME Convention, aimed at promoting cooperation and information exchange for health authorities, customs, police and other competent authorities at the national level; cooperation between authorities and the commercial and industrial sectors; and international cooperation in the risk management of S & F medical products (see MEDICRIME Convention, Articles 17 and 22, Single Points of Contact).

The SPOC Toolkit describes the structure and function of a SPOC, as well as the requisite skillset for the officials responsible for operating and maintaining the SPOC within an individual economy and between economies. To account for the significant differences in resources, environment, and governmental structure, the SPOC Toolkit also provides for flexibility with regard to implementation by APEC economies. To illustrate alternative approaches to implementation, the appendices attached to the SPOC Toolkit include the shared experiences of economies that have implemented SPOC systems.

Interdependencies, Gaps, and Related Initiatives: The SPOC WG envisions that implementation will include: the identification of National SPOCs across the APEC economies, establishment of an APEC SPOC database, and translation of the SPOC toolkit into as many languages as possible. These implementation efforts should be aligned with related regional and global initiatives, such as the Post-alert System administered by the Association of Southeast Asian Nations, the online Rapid Alert and Exchange of Information System for Falsified and Fraudulent Medicines in place in South America, and the World Health Organization's Global Surveillance and Monitoring System for Substandard and Falsified (S & F) Medical Products.

V. THE TOOLKIT'S ROLE IN PREVENTION, DETECTION, AND RESPONSE

Comprehensive product quality and supply chain security requires a multilayer approach that includes prevention, detection, and response strategies and actions. The Supply Chain Security Toolkit is a comprehensive resource that addresses areas of vulnerability in the medical product supply chain. It contains recommended best practices and tools to detect S & F medical products, prevent them from

reaching the consumer, and respond to incidents involving S & F medical products. This section highlights the utility of the toolkit in in the prevention, detection, and response of S & F medical products.

PREVENTION

Preventing Substandard and Falsified (S & F) products from entering the supply chain requires, among other things:

- Improving transparency, accountability, and integrity of the supply chain by ensuring compliance with robust current good manufacturing, distribution, and pharmacy practices.
- Implementing Track and Trace systems and end-to-end product security and supply chain solutions to help ensure medical products are legitimate and enhance detection of illegitimate drugs.
- Ensuring robust import and export regulations to protect the legitimate medical product supply chain from entry of S & F products.
- Strengthening oversight of the sale of medical products on the Internet, including who may sell and what may be sold, in order to prevent the entry of S & F medical products into the supply chain.

DETECTION

Detecting Preventing Substandard and Falsified (S & F) products in the supply chain requires, among other things:

- Incorporating detection technologies in order to improve surveillance and monitoring and identify products that are S & F.
- Improving surveillance, investigation, and actions against suspect S & F medical products.

RESPONSE

Responding to incidents of Preventing Substandard and Falsified (S & F) products in the supply chain requires, among other things:

- Establishing a single point of contact (SPOC) program among the national medical regulatory agency, law enforcement, and others in order to facilitate coordination, communication, and information-sharing regarding incidents with medical products.
- Improving communication about incidents by reporting to the global surveillance and monitoring system for S & F medical products.

VI. CONCLUSION

Over the past few years, the Roadmap for Supply Chain Security project has provided an international forum for experts in medical product quality and supply chain security to come together in an unprecedented and meaningful way. The results of the Roadmap project include not just our final comprehensive Supply Chain Security Toolkit, but the development of a well-connected community of experts that are poised to address the continuing challenges of an increasingly globalized and complex supply chain of medical products.

To sustain this forum and continue these efforts, the Roadmap project work will continue to be implemented, and training provided, through APEC Center of Excellence (CoE) programs. To date, the APEC RHSC has endorsed two pilot programs on supply chain security, one sponsored by the United States Pharmacopeial Convention (USP) and the other by the University of Tennessee Health Science Center (UTHSC). The CoEs are developing pilot programs for training on various aspects of the Roadmap project and the comprehensive Supply Chain Security Toolkit. Moving forward, CoEs will be well-aligned and complementary such that economies world-wide can find a program the best meets their needs.

To ensure sustainability and relevancy of the information and training in this comprehensive Supply Chain Toolkit, the CoEs will assess the content, as appropriate, and recommend where the information or individual toolkits could benefit from updating. Updates will be done on a case-by-case basis as resources allow. Each Roadmap project working group has affirmed their continued availability to assist in such efforts.

In addition to attending CoE programs for training, economies may continue to consult the Supply Chain Security Toolkit, which will be maintained on APEC AHC's website at http://www.nifds.go.kr/apec/SupplyChain/APEC_SupplyChainToolkit_170317.pdf. In an effort to achieve a secure global supply chain, those involved in this project hope these resources will be of assistance to regulators and industry members within any economy interested in developing its supply chain infrastructure.

VII.   CORE CURRICULUM

Please double click anywhere on the last page of this document to view the core curriculum in its entirety.

APEC Roadmap to Promote Global Medical Product Quality and Supply Chain Security

Centers of Excellence Training Curriculum

Part I: Introduction to the Roadmap and Toolkit

What is the Roadmap to Promote Global Medical Product Quality and Supply Chain Security?

    A. Roadmap project work groups

What is the Supply Chain Security Toolkit?

    A. How the Toolkit was developed
    B. Contents of the Toolkit
    C. Interactive PDF

Part II: The Toolkit's Role in Prevention, Detection, and Response

Discuss the Toolkit's resources in the context of prevention, detection, and response

Regulators and industry will discuss case studies of supply chain threats and how each entity reacted to prevent, detect, mitigate, or respond to the threat

Part III: Core Competencies

Objectives:

    A. Trainers will share best practice recommendations and resources
    B. Trainers will meet the expectations established for each work stream to provide consistent and quality training
    C. Students will participate in tabletop exercises, case studies, and site visits to learn how to apply the toolkit materials to prevent, detect, and respond to supply chain threats
    D. Students should be able to apply lessons learned and use resources from the toolkit to strengthen the medical product supply chain in their respective economy or company

Performance Indicators for each Work Stream:

Each work stream is paired with performance indicators/metrics as a way to measure success of the training and to standardize training among all CoEs. To assess adherence to performance indicators, the CoE will develop a survey for participants to complete at the end of the training program. In addition, the CoE or the Supply Chain Steering Committee is encouraged to reach out to regulatory authorities that participated in a CoE training to assess their success with implementing Toolkit materials/recommendations.