USP-APEC Center of Excellence

Insights to secure medical product quality through the supply chain
Acknowledgments

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APEC is an international organization with the primary goal of facilitating sustainable economic growth and prosperity in the Asia-Pacific Region.

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I. Overview

The global supply chain has become increasingly complex for many different kinds of products, ranging from fast fashion to cars. Since manufacturers can source components from multiple places around the globe and finish products in yet another, supply chains can be non-linear, making quality harder to control.

Figure 1: APEC Supply chain security toolkit for medical products
This phenomenon also applies to medical products, where the stakes can be much higher. Any cracks in the system can pose risks to human health and safety. Today, more than 80 percent of medicines or medicine ingredients intended for the U.S. market come from the outside, primarily from China and India. Ingredients and drug products travel from manufacturing sites to wholesalers and warehouses to distributors and, ultimately, to patients. The more complex the supply chain, the greater the risk that the quality of medicines is compromised. Global health security concerns, such as natural disasters, trade wars, and pandemics like the current COVID-19 crisis, can also expose supply chains to market forces resulting in product failure.

Drawing on learnings from a series of roundtables, workshops, and trainings on the Asia-Pacific Economic Cooperation (APEC) Supply Chain Integrity Toolkit held over the past three years, as part of a collaboration between the U.S. Pharmacopeial Convention (USP) with the APEC Life Sciences Innovation Forum (LSIF), this USP Issue Brief details five key regulatory observations we have gathered, and offers three potential areas of action to secure medical product quality through the supply chain.

The following represents general insights offered by hundreds of regulators, industry, policy makers, and other stakeholders across the Asia-Pacific, with a focus on the upstream quality aspects of the supply chain, including good manufacturing and good distribution practices. Downstream issues, such as good pharmacy practices, internet sales, and screening technology are noted as emerging areas of concern as well, but are not a focus of this issue brief.

II. Defining the problem

The global medicines supply chain enables broader patient access to medicines, but the system also has distinct vulnerabilities. The global supply of quality medicines is increasingly threatened by both chronic supply chain vulnerabilities and acute disruptions. Vulnerabilities refer to underlying weaknesses, which include but are not limited to geographically concentrated manufacturing and sourcing, uneven regulatory environments across the supply chain, and regulatory enforcement or inspection capacity constraints. Disruptions, meanwhile, can be event based and may include climate events, trade wars, and pandemics. The impact of supply chain vulnerabilities and acute disruptions include drug shortages, price spikes, and increased potential for substandard and falsified medicines—all barriers to access to quality medicines. As more patients become more affected by and aware of these challenges, trust in medicines and our healthcare system diminishes over time.

Much of the attention to date has focused on active pharmaceutical ingredients (APIs)—the key ingredients in medicines that produce the intended therapeutic effects—and the final finished products. However, product failure can also be caused by inactive materials, which are known as excipients. Systemic vulnerabilities to the supply chain include poor manufacturing practices and insufficient regulation. The cases of glycerin and heparin (outlined in the Case Studies on page 4), highlight many of these challenges.
Case studies:

Economically motivated adulteration: The cases of glycerin and heparin illustrate instances of economically motivated adulteration driven by opportunity and aided by opacities in the supply chain. Both cases highlight the challenges of assuring medicines quality in a complex global supply chain.

The Case of Glycerin

In 2006, cough syrup distributed in Panama was found to contain diethylene glycol (DEG), an industrial solvent used in antifreeze. Patients suffered from paralysis and other complications that led to 78 identified deaths. It was discovered that a factory in China mislabeled DEG, which is cheaper to make, as glycerin (1). As the product passed through the supply chain, certificates of analysis were repeatedly produced and issued without independent testing. The glycerin case illustrated the confusion over actual substance produced, naming and labeling, licensing or registration of the facility, and responsibility for ingredients upstream in the supply chain. Robust quality assurance programs and a Vendor Qualification Program were lacking.

The situation was hampered by a lack of traceability in the supply chain. The manufacturer of the final product, the cough syrup, in this case did not realize what it had procured and did not adequately test ingredients.

The Case of Heparin

In 2007, the U.S. Food and Drug Administration (FDA) began to receive adverse event reports associated with heparin, a blood thinner widely used to prevent clots. It was discovered that the heparin was contaminated with oversulfated chondroitin sulfate (OSCS), a lower-cost synthetic that mimics the properties of heparin and therefore went undetected initially (2). This substance, which was manufactured in China, was distributed to patients in over 11 countries and resulted in adverse events, including kidney failure and 28 deaths, in the United States. The heparin case illustrated the importance of understanding complexities in how an API is extracted, separated, and purified. The circumstances that led to the adulteration of heparin with OSCS included opaque supply chains, weak analytical controls, and a supply disruption that caused price spikes, incentivizing adulteration.

Mitigating these instances could have involved verification of supply chain and testing using compendial standards and other methods, which are recommended for high-risk ingredients. Good manufacturing practice certification as part of supply chain verification is needed. Regulators need legal authority, clear regulations, sufficient resources for enforcement, and cooperation from industry and other stakeholders.

III. Standards Are Benchmarks of Medicine Quality

Public quality standards, which guide what goes into a medicine, apply across the entire supply chain. Pharmacopeial standards, also known as compendial standards, can be of two types: (1) documentary standards, which can be specifications for particular ingredients, finished dosages, or guidelines for their production and supply, and (2) reference standards, which consist of actual vials of substance or ingredient against which manufacturers can test their product to ensure it meets published specifications. Standards for medicine quality should reflect the “state of the industry” for drug identity, purity, and potency and thus help ensure medicine safety and effectiveness for patients. The focus on medicines quality encompasses all aspects of a medicine’s life cycle, including chemistry, manufacturing, supply chain, storage, and distribution. Gaps in supply chain security can lead to substandard or falsified medicines, which can then have potentially devastating impacts on patients. Pharmacopeial standards provide tools for compliance with regulatory requirements and help regulators and industry ensure continued access to quality medicines. In the United States, requiring manufacturers to comply with pharmacopeial standards, which are used across the supply chain, helps protect patient safety.

Figure 2: Public quality standards
IV. Five Key Regulatory Observations

This section outlines five key regulatory observations or learnings on upstream ingredient quality considerations. These are drawn from a series of roundtables, workshops, and trainings held as part of a collaboration between USP and APEC.

The USP–APEC Center of Excellence (CoE) was established to disseminate best practices, standards, and guidance that improve the quality and security of global pharmaceutical supply chains.

1. Good manufacturing practices (GMP) are relevant to all incoming materials when making a drug. GMP goes beyond manufacturing of the finished product and also includes the need to regulate and control the upstream supply chain of incoming materials. Notable gaps exist between different current GMP guidelines, GMP tools, and implementation schemes. At present, many economies’ medicines regulators cannot oversee GMP for all ingredients. Though specific quality expectations for excipients may differ from APIs depending on the economy, appropriate GMP should be followed. This would entail requiring manufacturers to know material origin, source clearly named ingredients, ensure proper licensing/registration of vendors, and have traceable documents such as a verifiable certificate of analysis (CoA), which documents testing results for composition, identity, impurities, and other types of quality assurance.

2. GMP should be considered together with good distribution practices (GDP) and apply to all stakeholders in the supply chain. GDP has been described as a passing of trust through the supply chain that should be integrated with GMP. Potential solutions to achieve this include training on GDP inspection and making GDP a quality requirement at the economy level. GDP should apply to all stakeholders in the supply chain, not just manufacturers. Further, guidance on writing clear GDP policies on product return and recalls is needed.

3. Verification of incoming materials and vendor qualification is part of overall quality assurance. Manufacturers and distributors should have a standard protocol to check incoming goods, ensure traceability of ingredients, review CoAs, and have the ability to conduct identification and quality testing using...
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appropriate standards. Supply chain mapping would enable manufacturers to identify vulnerabilities and act accordingly. Manufacturers should apply a risk-based approach to quality to assess and evaluate suppliers in their supply chain. Risks include multiple manufacturers, multiple suppliers, thefts and diversions, and returns and recalls.

4. Procedures for product release, including quality assurance and quality control, are a core component of quality and safety. Where product quality is at higher risk, manufacturers of ingredients and finished doses should have capacity, as part of a comprehensive quality assurance system, to test products against applicable pharmacopeial standards. A CoA by itself is not enough to verify quality, as it may be vulnerable to compromises in data integrity and results may not reflect downstream changes to the ingredient or finished product due to transport- and storage-related issues. Considerations for additional testing should account for historical risks, such as adulteration of glycerin with DEG. If regulators choose to accept third party testing, their methods and approaches need to be validated and acceptable.

5. Product quality is a shared responsibility of all players. The leadership of a drug or ingredient manufacturing company needs to provide resources to ensure quality, including audit resources for outsourced activities, and take steps to ensure the quality of incoming materials and quality of products. In the United States, for example, all parties that manufacture, process, pack, or hold an ingredient for use in drug products are responsible for meeting GMP.

Economies have varying levels of regulatory authority over ingredients, particularly excipients that sometimes are not held to the same standard as APIs. Some regulatory authorities of reference, for example the U.S. FDA, treat everything that goes into a drug as a drug, in which case drug-level manufacturing standards and practices apply. In recent years, there has been an increase in the number of FDA-issued warning letters citing manufacturers for excipients or inactive ingredients in violation of current GMP. The letters indicate that (1) pharmaceutical manufacturers must perform at least one test to verify the identity of each drug component and (2) manufacturers must validate and establish the reliability of supplier test analysis, if they are relying on CoAs. In U.S. law, all parties that manufacture, process, pack, or hold an ingredient or drug product are responsible for meeting GMP. Other economies may not have the capacity for similar levels of enforcement, or they may rely on the regulatory systems of others or the WHO prequalification program to provide quality assurance. Developing economies have limited resources for inspection and qualification of raw ingredients and ingredient suppliers. As a result, regulators must be proactive in holding manufacturers responsible. Further, regulators need to align on how ingredients are defined in their systems. Information-sharing between economies with more advanced regulatory systems and those with less advanced systems can help provide more oversight.
V. Three Potential Areas for Action

Based on findings from APEC convenings and additional conversation with experts, USP has identified three potential areas for action and future discussion, structured around the principles of transparency, resilience, and global cooperation.

1. Transparency: Increase line-of-sight over all aspects of the supply chain. Participants in the USP–APEC collaboration collectively recognize limitations in ingredient regulations within their respective regions. Increasing line-of-sight includes obtaining details on manufacturing site, volume, and capacity. Currently treated as proprietary, this information would enable regulators to have a clearer line-of-sight across the entire supply chain. This problem is especially true of excipients. There is a need for a balanced approach based on risk (historical, known, logical) when evaluating excipients. Enhanced traceability includes knowing the source of starting material, registering with regulatory authorities, and requiring manufacturers to prove that incoming materials meet standards for quality.

2. Resilience: Deploy and use existing tools to secure medical product quality. Collaborations such as the USP–APEC CoE have led to the development of tools that have prompted increased dialogue among regulators, industry, and policy makers in different economies, e.g., the APEC Supply Chain Roadmap and Tool Kit. Other economies and regional collaborations can start to look at problems that are specific to their geographical areas. Regulators should look across GMP practices highlighted in the APEC Supply Chain Tool Kit—such as supply chain and supplier verification, incoming material analysis, and product release procedures, for example—for global practices that can better secure ingredient quality, and then work to raise awareness among stakeholders within and among economies. Risk analysis can help economies understand the most critical points in the supply chain. Mitigation strategies include enhanced documentation and quality control procedures, training, and qualification/verification.

3. Global Cooperation: Improve communication and share information among regulators. Roundtable and workshop participants acknowledged there are limits of regulatory reach as they apply to ingredients that are regulated differently across different jurisdictions, but there may be an opportunity to engage the “regulatory sandbox” to identify innovative, harmonized approaches. Economies often are reluctant to share information on supply chain matters but doing so can be critical to ensuring the safety of their own supply chains. Economies can enter into recognition or reliance arrangements, the process by which one agency recognizes or relies upon another’s work as equivalent to its own. Government regulators can work together and share resources to ensure that their citizens have timely access to safe, quality medicines. Regulatory authorities that share information or that rely on each other’s work have expedited the approval of essential vaccines and medicines, prevented the distribution of substandard and falsified medicines, and quickly mobilized resources during drug shortages and public health emergencies.

VI. Conclusion

Regulators, industry, policy makers, and other stakeholders all have roles to play in promoting a quality culture in the supply chain. Additional dialogue, alignment, and communication are needed to achieve more transparency in regulatory processes. Emerging areas of concern include good pharmacy practices, screening technologies, and internet sales, which take place further downstream before the consumer or patient receives a medical product. These past several months have seen the world’s healthcare systems under pressure in response to the COVID-19 pandemic. The medical product supply chain is uniquely stressed, leading to potential shortages of much needed, quality-assured medicines and other health products. There are steps regulators around the world can take now, cooperating with each other, industry, and other partners, to help mitigate these challenges and build a more transparent, resilient—and ultimately stronger—supply chain to secure medical product quality.
The mission of U.S. Pharmacopeia (USP) is to improve global health through public standards and related programs that help ensure the quality, safety, and benefit of medicines and goods. USP applies a multistakeholder approach, including working through its cadre of dedicated volunteers, members, and staff, and working collaboratively with key stakeholders around the globe.