Rx-360 Supply Chain Security White Paper

"Taking a Collaborative Approach to Secure Donated Medicines"

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INTRODUCTION

Providing and receiving donated medicines to populations in need through Non-Government Organization "NGO" partners can serve as a tremendous benefit to patients who may not otherwise be able to receive them by way of conventional means.

The risk and challenges that industry and NGOs may face are very similar. Donated medicines can be diverted, expired, not properly stored, stolen or even counterfeited. The problem with donated medicines being compromised within the supply chain can have serious implication to patient health. We need to collaboratively address the challenges and seek solutions to ensure patients receive quality donated product.

SCOPE

This paper will collate the knowledge and expertise from both industry and NGOs to highlight the problems, gaps, challenges, best practices, and the ongoing efforts to strengthen the supply chain for donated product.

Industry, NGO's and Governments have a shared responsibility in getting quality donated medicines to the patients and cannot do it alone.

The authors will provide best practices that industry, regulatory agencies and NGOs can start working on together to provide safe, quality medicines to patients in need.

THE PROBLEM

Patient health can come in jeopardy when there is quality and security related impact on the products being donated and distributed. The pharmaceutical industry and NGO's have presented examples of these challenges as outlined below:

1) NGO's may not have adequate time to distribute product prior to the product expiring due to receiving, registering and delivery requirements.
2) Expired product may not be properly destroyed, and therefore find its way onto the black market.
3) Developing countries may not have the infrastructure to support the storage and transportation requirements for maintaining product stability.
4) Products donated do not necessarily meet the needs of the recipient.
5) Donated products may come labeled in a different language which results in problems with proper administration.
6) NGO's may unknowingly accept counterfeit products due to bad actors taking advantage of the complexity of the supply chain.
7) It becomes a financial burden on the recipient of the medicines or countries to properly store and destroy excess donated products.
8) Lack of standards and requirements relating to donated products being enforced by supply chain

partners, industry, NGO's and health authorities due to lack of resources or political will.

9) No surveillance or monitoring within given countries to detect fake, expired, stolen or improper storage.
10) Lack of due diligence on supply chain partners.

NGO's partners serve as a source for patients in need to receive donated medicines. Pharmaceutical companies provide NGO partners with product for this purpose. The dilemma is that pharmaceutical companies often have more resources to manage the requirements and oversight of their own supply chains than their NGO partners. However, the NGO partners and regulatory agencies may or may not have the resources or sufficient aptitude to manage the necessary compliance.

The WHO set guidelines in 1999 and revised them in 2011. These guidelines were set by a contingency of humanitarian organizations led by the WHO. The principles and guidelines are not mandatory or regulations; but they are best practices that should be adopted by governments and organizations that donate product. Even though these guidelines (in theory) should alleviate the problem if followed, challenges to maintain the integrity of the supply chain for donated products remain a problem.

The biggest potential risk for NGO's is personnel within their supply chain not doing what they are supposed to do with the product. As a result of not distributing the product properly, there are several risks.

- False returns
- Product not getting properly discarded
- Potential for fake or substandard drugs being distributed
- Product diversion into unapproved markets.

At the same time, industry should try to protect against market dilution and set higher standards. Manufacturers should be selective in selecting NGO's and the reverse is true. A solid partnership between the NGO's and Manufacturers is a critical step forward in securing the supply chain.

Importance of the Public-Private Partnership

The importance of public-private partnerships is critical to improve the quality of life for patients who depend on lifesaving drugs. Governments, NGO's, Industry and other sectors need to work together if we are going to improve the infrastructure, processes, and technology to safe guard products from theft, illegal diversion, counterfeiting, as well as, preserve the quality of medicines.

The pharmaceutical industry continues to increase their reach in developed, emerging and developing markets by donating lifesaving medicines to people in need through NGO's. The problem is terrifying when these donated products may be compromised before ever reaching the patient.

Many of the challenges require the harmonization across different sectors and boundaries. Even though the relationship can be complex and frustrating at times, no individual company or NGO can solve the

problem. Both have their strengths and weaknesses that should be carefully accessed and discussed to find common grounds to:

1) improve the infrastructure;
2) develop common processes and standards;
3) obtain financing;
4) solicit discussions and opinions with governments;
5) pilot and launch innovative solutions;
6) waste disposal and destruction;
7) necessary quality requirements.

Recommended Best Practices

Standard diligence

Standard diligence is a simple process to access the compliance and risk before on boarding a supply chain partner. This is a cross functional effort that may be conducted by Compliance, Legal, Quality, Logistics, Security and other business functions to ascertain that the necessary checks, requirements, processes, and risk are addressed in securing the supply chain.

Contracts and Agreements

Requirements and expectations should clearly be stated within contracts and agreements to hold partners accountable. This will also allow for proper supply chain performance and auditing.

Audits

Periodic review of performance against expectations should be undertaken during the period of the contract. Topics such as performance of supply chain processes should be addressed during an audit. This can include security countermeasures, product disposition, proper product disposal and quality to evaluate performance and identify opportunities for improvement. Audit approach should be pragmatic and realistic.

Supply Chain Mapping

Mapping the supply chain is an exercise being conducted more frequently by manufacturers to meet regulations and can be applied to NGOs. Manufacturers should partner with NGOs to include aspects unique to this supply chain. The scope should cover shipments from the manufacturer to the point of administration. Mapping should also include risk and mitigation strategies to address these risks e.g. avoidance of unnecessary domestic shipping to other NGO “partners” which can be a common practice amongst some NGOs, infrastructural challenges with storage and transportation, inventory management, etc...

Establishing a Quality Management System (QMS)

Ensuring product arrives safely to the patient is a key objective of the pharmaceutical supply chain. Due

to the complexities of the supply chain, organizations handling product must establish adequate processes to maintain full accountability of the product and ensure patient safety. Establishing a Quality Management System (QMS) should be a priority.

A QMS is a formalized system that documents processes, procedures, and responsibilities for achieving quality policies and objectives. A QMS allows for the coordination of organization's activities to meet product, customer, and regulatory requirements and improve its effectiveness and efficiency on a continuous basis.

It is encouraged that organizations consider developing QMS processes using the ISO 9001:2015, the international standard specifying requirements for quality management systems.

Implementation of Good Distribution Practice (GDP)

Within the QMS, organizations may choose to incorporate all relevant supply chain activities including processes, procedures, and SOP's pertaining to the storage and distribution of pharmaceutical goods. The concept of Good Distribution Practice (GDP) provides organizations with the appropriate tools to not only have the necessary procedures established but also to prevent falsified medicine from entering the legal supply chain. Ensuring that GDP is in place will allow organizations to control their supply chain and maintain the quality and integrity of the pharmaceutical products.

Pharmaceutical regulatory bodies across the globe do not have a unified approach to GDP, however, many countries have established procedures using existing guidelines established by the World Health Organization (WHO) and the European Union (EU).

Access to the WHO guidelines can be found by visiting www.who.int/medicinedocs

The EU Guidelines can be found by visiting www.ec.europa.eu/health/human-use

GDP is not limited to products that are purchased and sold by distributors and wholesalers. Maintaining GDP for products that are donated by manufacturers and NGO's is an important practice in ensuring medicines that are donated are not stolen, tampered, counterfeited, or diverted. The WHO has established Guidelines for Medicine Donations which can be found by visiting: http://www.who.int/selection_medicines/emergencies/guidelines_medicine_donations/en/

The Use of Technology

Overview

Information and packaging technologies are becoming ever more relevant in the Commercial Supply of Medicines worldwide. The adoption of global standards (e.g.GS1) for technology implementation and best practices (e.g. World Health Organization, Rx-360) for deployment provides a framework for global programs. These existing capabilities and guidelines can improve management of donation and access program products, such as to provide quality metrics for local operations, prove that donations reach the patient, etc.

The use of technology offers the potential to provide data and information about products as well as visibility of product movement along the supply chain. Adoption of suitable technologies can help drive benefits in supply chain efficiencies and enhance supply chain security.

While Global Standards for technology implementation is preferred where they facilitate interoperable systems, allowing data transfer between many parties, in practice, NGOs may find that many technologies available today are stand alone and not interoperable, therefore NGOs may need to deal with many different technologies.

Furthermore, technology alone will never provide a solution by itself and may indeed distract resources from the more basic and needful activities on the ground. The application of technology must therefore be carefully assessed, and if implemented must be accompanied by appropriate processes along the supply chain to deliver desired outcomes.

Consideration should be given to cost/risk/benefit of technology implementation, including identification of the stakeholders along the supply chain who need to be engaged. In addition, practical matters, such as local service provision (internet, cellular network, etc.) device availability (PC, smart phone, etc.), support services (technical, IT, logistics, etc.) and skills and knowledge of those who need to use devices, technologies and processes, needs to be fully understood to assess implementation requirements and risks.

Technology Selection

This section will provide a high level guide to technology options currently in circulation or on the horizon, for consideration by Manufacturers and NGOs.

The number of security and other technologies applicable to medicines is constantly growing. This White Paper will only assess a few common basic approaches to provide some initial guidance and visibility to interested partners, to trigger further exploration.

Table 1 provides a compilation of such basic approaches by listing primary use scenarios, benefits for supply chain partners and typical challenges and pitfalls encountered during implementation.

Table 1. Type of Information and Packaging Technologies			
Technology	**Typical use scenario**	**Typical benefits**	**Some typical challenges**
Shipment tracking provided by carrier - used by donor and recipient to assure proper transportation.	Transportation security, concern about proper product receipt	This is a basic capability widely available. It can provide positive confirmation on goods receipt	None
Use of temperature monitors during transportation	Highly recommended for transportation of cold chain products	Verify that cold chain integrity is maintained during transport	Minor: Cost of monitor and logistics of data capture and monitor management
Scratch-off authentication labels	To provide some level of assurance of authenticity to dispensers and patients. Unique serial number revealed when thin layer of foil is scratched away. The number is sent via an SMS message for verification of number to a portal. A message is received by dispenser/patient to indicate genuine number or suspect item.	Improves patient confidence regarding authenticity and tampering. Can provide dispensation/usage metrics to NGO and MFG including geo-tagging May be possible to leverage local existing infrastructure, such as Nigeria's MAS system	Requires phone access. Implies additional cost for system provider and labels, as well administrative overhead for NGO and MFG. NGO may have to handle multiple different vendors, instructions, apps, etc., which will be a challenge, e.g. NGO responsible for applying the serialized labels, developing processes for utilization and data capture. Multiple providers exist in the market with proprietary solutions
Opportunistic use of serialized information already on packaging	Can be another avenue to authentication	Improves patient confidence regarding authenticity. Interoperability and global systems potential. Can provide dispensation/usage metrics to NGO and MFG	This use scenario is not mature yet. See discussion below*
Tamper Evident Labels with overt marking to differentiate donations from commercial distribution	To help identify, product diversion within the target market or to other markets and mitigate risk of product diversion.	Diversion impacts product integrity, availability of medicines, and provides commercial challenges	Implies additional cost for design and application of labels Challenges with finding the real estate to apply the labels without covering regulatory print May interfere with local regulations for donations
Digital Fingerprinting: Use of graphical hidden effects to authenticate a product	To provide high level of assurance of authenticity to supply chain partners, dispensers and patients	Improves confidence regarding authenticity No extra costs beyond initial artwork implementation	Requires access to technology (proprietary smart phone apps etc) as well as internet access Difficult to guarantee that all donated product will indeed have the Fingerprinting feature (due to Supply Chain complexity)
Closed Loop Track & Trace: Using serialized information, plot a path of the product through the supply chain.	When full visibility in the supply chain is needed	Provides visibility about location and status – typically to the item level.	Requires rigorous processes at all supply chain partners. Data access is not guaranteed everywhere. Requires access to technology (scanners etc), internet access and IT connectivity to Track & Trace system. Multiple providers exist in the market with proprietary solutions

*"*Opportunistic use of serialized information already on packaging*": Companies worldwide are required to apply serialization (unique numbers on each pack) based on regulations in many regions of the world, including US and EU. While these numbers may already be present on product, their value can only be unlocked by comparing them to other data already stored in IT systems, for example via an authentication and validity request. Today, corporate serialization systems are focused on meeting regulatory requirements mentioned above and by themselves are typically not well suited to such authentication activities initiated from outside a controlled environment.

However, in the coming years serialization may also become more valuable for donations, e.g. if one or more of the following scenarios were to develop:

- Corporate serialization system ('EPCIS') vendors offer widely available smart-phone apps for authentication.

- A standardized industry-wide app is developed that can create a verification query against the relevant manufacturer system – for example by decoding the relevant manufacturer from the GTIN.
- A donation organization develops a serialization data cloud to be used exclusively by donors and donation users to capture and recall donated product serialization info.

Best practice and challenges around track and trace & serialization

All shipments should be individually agreed between donors and recipients, to assure product is received and no illegitimate activity is missed regarding shipping and receipt. There must be agreed reporting methods for receipt confirmation and issue resolution.

Well established logistics providers should be used that can provide tracking services for shipments. Tracking information shall be received and used by donor and recipient to assure proper transportation.

Existing serialization on commercial packs can be utilized. Note that most serialization is only on smallest saleable unit, i.e. carton – may not be present anymore at point of use for donations. Existing serial numbers (SNs) could be used for investigative purposes – e.g. a serialized donated product was found in the commercial supply chain. This information can be used to determine last known ownership of a diverted product. To get any real value from this approach, the serialization info would have to be used and tracked in the NGO supply chain, ideally to the point of dispense. This is generally difficult and cumbersome. There are only limited methods for using the legislated serialization information (US, EU etc) due to system limitations of the corporate serialization systems and the system provider offerings. For example, most manufacturers' system doesn't allow this type of tracking and smartphone authentication by themselves, because typically a national data system (such as the Eurohub cloud) manages these activities.

Field Examination Technologies

In order to detect falsified medicines and screen for poor quality, substandard medicines, a process for monitoring products as they enter a territory/country or along the product's supply chain is necessary. Once that is established, detection and screening technologies are selected based on key factors such as applicability and benefit, level of training necessary to operate and interpret results, and cost of ownership. At border crossings, points of entry, customs inspections and along a product's transit, storage and distribution routes, field examination and testing may be more expedient than sending to a laboratory, although does not replace confirmatory analysis.

The first step in a field examination process is visual inspection of the product packaging and finished drug product. Key signals of falsification can be found on packaging. For example, expiry dates may be passed or mismatched between inner and outer labels. Other common and easily observed indications that a product is not genuine are spelling mistakes and absence of critical product information such as manufacturer information, lot or batch information, active ingredient name and dosage strength, and medicinal product's country registry number. It may also be possible to verify the authenticity of the suspect product's lot information and pedigree, in coordination with the purported manufacturer.

If, after examination of packaging, the authenticity or quality of a product is still questionable, then it may be warranted to break any present tamper-evidence seals and extract the product's dosage form (i.e., tablets, capsules, solution, etc). Examination of the dosage form may reveal inconsistencies in shape, color, size, and/or clarity indicative of a falsified or substandard drug.

When prior observations and investigation of a medicinal product does not support passing authenticity or quality, then further screening of the drug product using the more advanced technologies described below is warranted. It is desirable to use more than one technology in addition to visual inspection for field screening to provide a more thorough understanding of a suspected falsified or substandard medicinal product's quality.

Results obtained from screening technologies cannot replace comprehensive quality testing, but rather an assessment of authenticity based on differences in composition and presence of the correct active ingredient. Typically, field screening technologies are not able to determine the quantity of active ingredient, the presence or quantity of impurities, or sterility. Therefore, screening results are used to inform the decision to investigate further, for example by a qualified chemist using laboratory analyses.

Table 2 summarizes several techniques for field testing suspected falsified and/or substandard products that are commercially available, and a selection of devices that, due to the fast pace of electronics miniaturization and prevalence of smart phone and cloud connectivity, are on the horizon. Techniques for which devices are commercially available at the time of writing this whitepaper are noted as such. An evaluation of relative portability is shown based on the size of the device, which may range from *Small* - hand held devices with sizes comparable to an adult shoe (commercially available) or even smaller than a smartphone (on the horizon), to *Medium* - approximately the size of carry-on luggage, to *Large/transportable* - larger instruments which are designed to be transported as part of a mobile lab. Relative cost of ownership is subjective, but as a general guide a rank of high, medium, or low has been provided. The ease of operating and maintaining the device and interpreting the results has been estimated as shown in the "Training Needed" column. It is assumed that devices are supported by experts available within the organization or from the device manufacturer for method development and updated data sets to support continued use in the field. General comments are provided to capture aspects that are pertinent to the technique, such as limitations or other considerations not described in other columns.

Table 2. Portable Detection Technologies for Screening Suspected Falsified Medicines

Technique	Relative Portability	Applications	Commercially Available	Relative Cost of Ownership	Training Needed	Sample Preparation	Comments
Minilab (colorimetry + disintegration + Thin Layer Chromatography (TLC))	Medium	Multi-faceted testing of typical tablets, capsules, and other types of solid oral dosage forms	Yes	Low	Low	No sample preparation, but the sample is consumed	Widely in use New methods/products added routinely Multiple techniques in one unit
Multiple wavelength light sources, e.g. Counterfeit Detection Device n°3 (CD3)	Small	Aids visual authentication of tablets, capsules, and other types of solid oral dosage forms. Feasible to use for visual examination of packaging components and other dosage forms, although this use has not yet been reported	Yes	Low	Low	No sample preparation necessary, but dosages must be removed from packaging	Available to government agencies, possibly NGOs, but not for industry currently
Hand Held Raman	Small	Spectroscopic test which provides a fast pass/fail result	Yes	Medium	Low	None Tablets and capsules may remain in clear blister packaging Applicable to some liquids	Widely in use in regulatory and industry API must be somewhat high concentration to be identified Not applicable to all medicines, due to fluorescence interference from some excipients
Ion Mobility Spectrometry (IMS)	Small/Medium	Authentication of solid or liquid medicinal products. Identification of API or adulterants possible	Yes	High	High	None Surface analysis - may damage a small portion of the surface of a tablet, for example	For coated tablets, only the tablet coating is analyzed unless further sample prep to remove the coating is performed. Not currently in wide use. Identification of API or adulterants in drug products or dietary supplements.
Portable NIR (Near Infrared) Analyzers	Small	Spectroscopic test which provides a fast pass/fail result. Typical samples are tablets or capsules, but may be applied to non-water liquids	Yes	High	Low	None Tablets and capsules may remain in clear blister packaging, potentially	Not widely in use, although it is based on a common laboratory technique and so prior education/training could be utilized. Not applicable for medicines with high water content
Fourier-Transform Infrared Spectroscopy (FTIR) portable device	Medium	Spectroscopic test which provides a fast pass/fail result Typical samples are tablets or capsules, but may be applied to non-water liquids	Yes	High	Medium		Not widely in use, although it is based on a common laboratory technique and so prior education/training could be utilized. Not applicable for medicines containing significant moisture
X-ray Fluorescence (XRF)		For surface and material elemental analysis	Yes	High	High	None Surface analyses technique, non-destructive'	Not widely in use, although it is based on a common laboratory technique and so prior education/training could be utilized
Portable Gas Chromatography (GC)	Medium to Large/ transportable	Based on the chemical separation technique, this instrument is capable of analyzing gaseous samples such as the 'empty' headspace in a container or a liquid that has been turned to gas in the instrument. Provides authentication by detection, identification, and perhaps quantization of individual components.	Yes, but smaller instruments are not marketed for pharma	High	High	Varies depending on instrument	Not widely used for pharmaceutical samples; marketed for environmental testing (e.g., water quality) Headspace analysis can be useful for detection of volatile organic compounds (VOCs) but not a direct analysis of the medicine
Nuclear Quadrupole Resonance	Medium	Uses a form of radio-frequency spectroscopy related to Magnetic Resonance Imaging (MRI) or Nuclear Magnetic Resonance (NMR) for the non-invasive and non-destructive screening of packaged pharmaceutical products	No	High	Low	None Reportedly can analyze medicine while within carton	Developed for counterfeit drug detection Suitable for compounds containing nitrogen, chlorine or bromine, sodium and potassium, which includes over 80% of all drugs

More details about these technologies are available in external references, for example see Asia Pacific Economic Cooperation (APEC) Supply chain Toolkit, Detection Technologies; the WHO Draft Guidance on Testing SSFFC Medicines and other activities in the WHO Member State Mechanism work plan; and a summary of scientific articles reviewed by a team from the University of Washington, Seattle. Furthermore, USP (and others) are currently working on several projects aimed at understanding the capabilities of current technologies from previous publications, as well as evaluating new technologies as they are close to commercialization and practical application

CONCLUSION

Best practices to secure the supply chain at numerous touch points while deploying effective use of technology cannot be the sole responsibility of one organization. It is critical for all involved to keep in mind that patient safety is a shared responsibility between industry, regulatory agencies, and NGOs.

Providing safe quality medicines to patients in need across the globe comes with unique challenges that have serious repercussions if not managed appropriately. The ideas shared in this white paper will not prevent these challenges from impacting the supply chain but instead serve as a guideline of best practices that can be implemented in tandem with other organizational needs.

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KEY TERMS

Technology Section - Glossary of Terms

Authentication: The use of technology applied to packaging or product to help identify suspect product.

Closed Loop Track and Trace: For purposes of this document, a closed-loop track and trace system is a commercially available solution that encompasses all necessary steps for an end-to-end solution. Typically a vendor in this space would generate serial numbers, print labels with these numbers, have methods of tracking the codes at multiple steps in the supply chain, provides the ability to 'use' or decommission the number by an end user, and finally presents all track & trace data. Such solutions are often used independent of any compliance driven serialization requirements and may not be capable of meeting regulatory requirements.

Digital Fingerprinting: A graphical feature converted into a coded string of binary digits, generated by a mathematical algorithm, which provides a unique identifier for the feature.

Diversion: Practice in which goods intended for a specific market are **diverted** to be sold in another market, usually without the knowledge or permission of the primary vendor.

EPCIS: EPC Information Services (EPCIS) is a GS1 EPCglobal standard designed to enable EPC-related data sharing within and across enterprises. EPC means 'electronic product code'. EPCIS data sharing is aimed at enabling participants in the EPCglobal Network to obtain a common view of the disposition of EPC-bearing objects within a business context. More at www.epcglobalinc.org

Geo Tagging: The process of adding geographical identification via metadata.

GS1: Is a not-for- profit organization that develops and maintains global standards for business communication.

GTIN: Is an identifier for trade items developed by GS1. Such identifiers are used to look up product information in a database (often by inputting the number through a barcode scanner pointed at an actual product). The uniqueness and universality of the identifier is useful in establishing which product in one database corresponds to which product in another database, especially across organizational boundaries. Usage granted to organization members of GS1.

MAS: A directive to pharmaceutical manufacturers as well as importers, distributors and marketers of anti-malarial & antibiotic drugs was issued in Nigeria to implement the Mobile Authentication Service (MAS) system. This system works primarily via scratch-off labels that reveal a unique code that can be verified by any end user such as a patient via SMS

Overt Marking: Application of a feature which is visible.

Rx360: A nonprofit consortium led by manufacturers and suppliers from the pharmaceutical and biotech industries who volunteer to enhance the security of pharmaceutical supply chains.

Tamper Evidence: Having one or more indicators or barriers to entry which, if breached or missing, can reasonably be expected to provide visible evidence that tampering has occurred.

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