Identification & Traceability of Medicinal Products – A tool towards strengthening health systems

The global R&D based pharmaceutical industry is committed to ensure patient safety and is actively engaged in helping to secure the legal supply chain, namely through the use of traceability tools worldwide. Identification & traceability technologies are a set of tools that can effectively help in securing the supply chain, by enabling tracking forward the movement of medicinal products (in this case) through specified stage(s) of the extended supply chain and also trace backward the product's history, application or location[1]. In this paper, we will be focusing on medicinal products (medicines, including biologics and vaccines), though many of these principles can be applied to medical devices. This document was developed by IFPMA with the support of other industry associations (AIFD, EFPIA, KRPIA and PSI).

Substandard and falsified medicinal products pose a major challenge to patients and health systems all around the globe. Pharmaceutical crime, falsified, diverted or stolen pharmaceuticals has impacted 150 countries according to Pharmaceutical Security Institute (PSI). Falsified medicine has been found in every therapeutic category, the number of counterfeit injectables reached 19% which means that nearly one in every five counterfeit medicine detected in 2019 was an injectable formulation. Figures from the World Health Organization (WHO) reveal that around 1 in 10 medicinal products circulating in low- and middle-income countries is either substandard or falsified[2]. Many factors are at play here, but globalization and the tendency for increasingly complex pharmaceutical supply chains is one of the main challenges that Industry and National Regulatory Authorities (NRAs) must tackle by constantly adapting its practices and policies. Substandard and falsified medicinal products represent an equally serious threat to patient safety, when discussing traceability and product identification technologies, the issue of substandard medicinal products is only of concern in contexts where the product is supplied outside of a controlled environment, negatively affecting product quality. Fighting this issue has become even more important in the context of the COVID-19 pandemic, which led to the expansion in the trafficking of substandard and falsified products[3].

Many different models available for implementing a serialization/track & trace system and even though an ideal model is not available, some basic models and characteristics have proven to be more efficient and more effective compared to others. Different systems and implementation plans may also be chosen according to the most pressing issues faced at local level (e.g. Turkey's system was implemented with the initial aim of preventing packaging and barcoding scams).

5 PRINCIPLES FOR SUCCESSFUL IMPLEMENTATION OF TRACEABILITY SYSTEMS:

1. Harmonized Standards
2. Strategic Planning
3. Stepwise Approach
4. Framework for Implementation
5. Early Stakeholder Engagement

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[1] As defined by GS1: https://www.gs1.org/public-policy/priorities/traceability
[2] WHO, WHO Global Surveillance and Monitoring System for substandard and falsified medical products (2017)
[3] UNODC, Research Brief - COVID-19-related Trafficking of Medical Products as a Threat to Public Health (2020)

5 Principles for successful implementation of traceability systems:

The R&D-based industry has built serialization/traceability capabilities and expertise which can prove to be helpful if leveraged in certain contexts. Below we make a few considerations on key areas that are important when planning to implement a product identification or traceability system for medicinal products.

1) Harmonized standards: This will be key in ensuring interoperability, in line with the ICMRA recommendations on this issue[4]. "Manual" changes to existing GS1 standard systems and approaches are also not recommended. Registration systems and fees applied should also be standardized as much as possible to facilitate timely product launch and effective application of safety features. at the same time, be sufficiently flexible to accommodate differences in product packaging, market size, technical infrastructure, and supply chain complexity. National specific traceability requirements should also be avoided, as this can lead to a wider product portfolio and supply chain complexity. Only essential elements should be encoded in the Data Matrix Code following an established standard.

2) Strategic planning: It is paramount that countries looking at these solutions have in place a long-term strategic plan where each stakeholder's roles and responsibilities are clearly defined for each stage of implementation. A five-year implementation period could be seen as the minimum necessary for implementing a lean traceability system. Poorly planned implementation timelines, on the other hand, may lead to an immature IT-system landscape as well as to ineffective processes missing the overall goal of protection against falsifications or even generating drug shortages.

3) Stepwise approach: Attainable timelines, that take into consideration time for testing and validation should be discussed with all stakeholders. For instance, batch-level coding (product code, batch ID and expiry date) can be an appropriate first step before gradually developing the code and the underlying system/database. Identifying priority products or conducting pilot phases before full implementation are useful strategies for a stepwise implementation. Challenges regarding costs for implementation can be diminished with a phased approach, lessening a potential burden for local health authorities, other government institutions and patients.

4) Framework for implementation: Without a minimum level of regulatory oversight and enforcement capacity and capability, no system will be successful and protective at the end; A robust data management system must be in place *a priori* for receiving the digital data related to production and make it available to selected actors according to the regulatory body requirement. With no data management and reporting system, serialization by itself has no obvious interest in the frame of anti-counterfeiting activity and securing the official healthcare supply chain. It is also important to note that on the full compliance date, there will exist product in various states of the supply chain including packaged product that is ready to ship, product in transit, and product stored downstream at the distributors and dispensers. There should be a provision for "grandfathering" such products and allow them to continue through the supply chain until those inventories are exhausted.

5) Early stakeholder engagement: A suitable mechanism for consultation with stakeholders should be in place. To ease communications, publicly available databases listing all the registered and imported products can be helpful. This includes coordinating with neighbor-countries and relevant stakeholders even before implementing any regulations, countries can ensure their systems will meet any interoperability criteria deemed necessary, while also taking stock of each other's experiences and lessons learned. Regional initiatives (e.g. EMVO, in Europe) are a good example of how this can be achieved.

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[4] ICMRA, Recommendations on Common Technical Denominations for Track & Trace Systems to allow for Interoperability, WORKING DOCUMENT (2020)

Potential pitfalls in implementing traceability systems and unintended negative consequences

Code structure outside of established standards.
— This may lead to delayed implementation, negative cost impact for all stakeholders.
— It is unnecessary to support the goal of protection against falsifications.

Application of special rules to receive the code, be it from one single source only instead of using open standards, leading to
— Hindrances to quick uptake and usage;
— Hindrances for market entry and competition;
— Extra costs or
— Timewise limited usability (not in compliance with established standards).

Lack of knowledge with respect to established legal, regulatory and quality (GxP) landscape while introducing traceability systems.
— This may lead to conflicts for affected stakeholders not knowing which rule prevails.
— Instead, embedding traceability into the current landscape or even adapting it accordingly to ensure that all aspects fit together is recommended.

Constant change during the implementation phase without detailed impact analysis e.g. of the rules on how a code is to be composed. This can be a source of
— Delays to the "go live date" of traceability systems.
— unnecessary challenges to the capabilities and flexibility of all stakeholders striving for compliant and timely implementation.

Consideration on Detailed Regulations and Specifications

- The number of static and dynamic elements contained in the machine-readable data carrier (e.g. "barcode") should be limited to those elements which can uniquely identify the product. Additional context data can be retrieved from the information systems and provided elsewhere.

- The unique identification of a serialized item consists of the product code (used to identify the product) and the individual serial number (used to identify a single sales pack) together. Using these two elements, additional information about the serialized item can be retrieved from the systems which can provide additional context.

- The lot/batch number and expiration date are customarily added to the barcode and expected in the context of pharmaceutical product-additional elements such as local regulatory codes may be contained in other information systems (which associate product information) are redundant and do not add value to the traceability initiative.

- The recommendation is to allow exemptions to medicinal products which by their production and clinical administration already have a determinate supply chain pedigree such as blood/plasma-derived medicinal products, autologous stem-cell therapies, etc.

- It is also important to allow NRAs and potentially other stakeholders involved in the supply chain the ability to see the history of ownership to help in further identifying potential safety gaps in the supply chain.

Holistic approach to address falsified and substandard medicinal products:

It is important to take a systemic approach to ensure the issue of substandard and falsified medicinal products is tackled effectively. Systems traceability is not a silver bullet. This means that a layered approach encompassing different complementary measures should be preferred, and that adequate communication and coordination between relevant stakeholders are imperative to achieve a successful strategy. A complete strategy to address this issue should encompass:

- Deterrent legislation: People participating in the production and traffic of falsified medicinal products are criminals. They intentionally deceive patients and put lives at risk. IFPMA calls on all governments to strengthen their legislation and enforcement to deter falsified medicinal products. In this regard, the Medicrime Convention is a unique international tool to deter falsified medicines, thereby protecting public health, criminalizing counterfeiting, and ensuring national and international cooperation.

- Regulatory System Strengthening: Product identification and traceability technologies can allow regulators to gradually see and understand better issues like falsified medicinal products. This needs to be complemented with efforts in regulatory systems strengthening which in turn will ensure that NRAs are equipped with the right tools to take action.

- Awareness raising: Public awareness and education are vital to addressing the impact of falsified medicinal products. Effective awareness campaigns equip patients with the knowledge to help avoid this threat and safeguard their own health. Therefore, awareness is identified as one of the nine components of the work plan of the WHO mechanism. For this reason, IFPMA is a founding member of Fight the Fakes Alliance, a global, multi-stakeholder initiative that raises awareness about the dangerous impacts of falsified medicinal products on communities and healthcare systems.

- Data collection: Accurate data and research on falsified medicinal products is critical for designing effective responses. However, it is difficult to collect, analyze and distribute data on this criminal activity, as counterfeiters conceal their operations. For example, the UN Office of Drugs and Crime (UNODC) has recognized that quantitative information on falsified crime and criminal justice is very limited. In this regard, the Pharmaceutical Security Institute (PSI) is a pioneering organization that is directly addressing the need for data on falsified medicinal products. In 2002, the Security Directors of innovative pharmaceutical manufacturers established PSI to collect, analyze and disseminate information about falsified, illegally diverted and stolen medicinal products.

- The use of additional technology features (packaging overt/covert): Authentication solutions implemented by manufacturers can be used as an extra layer of protection, in addition to other solutions. Because traceability should be visible before use of the product, it is positioned on the secondary packaging. Therefore, it is critical that this secondary packaging has a tamper evident feature following established standards (ISO 21976:2018) so that the content of the packaging cannot be easily changed. Technologies visible to the naked eye (overt features), for instance, require end-users and healthcare providers to be familiarized with them. Strategies and implementation plans are required on how to ensure this. Covert features (not directly visible to the naked eye) can only be authenticated by those who know about them, have the details at hand for manual or an instrument for automatic authentication.

Opportunities in the implementation of traceability systems:

In order to take advantage of the full potential that implementing traceability systems can bring, it is important to consider some of the additional benefits in can bring to all the actors involved in the supply chain of medicinal products. This is a way of ensuring resources put forward for such initiatives are leveraged the best way possible. Some of these other benefits include:

- Inventory management simplification;

- Improved pharmacovigilance;

- Reduced medication dispensing errors;

- Allowing for the automated checking of expiry dates;

- Higher effectiveness in preventing recalled products from being supplied to the patient;

- Efficient handling of product returns and reduced data error between MAH and customer;

- Improved logistics such as stock management processes for pharmacies;

- Increased and better data collection;

- Overall improvement of cold chain management.

Conclusion

The expansion and growing sophistication of the methods used by criminals who manufacture, distribute, and sell substandard and falsified medicinal products poses a global risk to patients and to public health as well as a long-term threat to the research-based biopharmaceutical industry. Verifying the authenticity of medicinal products via product identification and the implementation of traceability systems can be useful in minimizing these dangers.

Implementation of product identification and traceability features must be seen as a long-term goal, requiring complete planning and definition of a multi-year strategy in consultation with all the relevant stakeholders. The series of considerations listed above reflects some of the lessons learned in the past few years and can be useful for partners all around the globe that are working on this topic. To effectively tackle the issue of substandard and falsified medicinal products, a complete systemic approach is necessary, encompassing legislative, regulatory, data collection, technological and public awareness components.

IFPMA supports the use of product identification and traceability features globally as an effective strategy to fight substandard and falsified medicinal products, optimize supply chain management and ultimately ensure the delivery of quality safe medicinal products. We stand ready to work in partnership with NRAs across the world and the WHO in establishing the most effective system in the interests of patient safety.

ANNEX: GLOBAL LANDSCAPE - EXAMPLES AND LESSONS LEARNED

The European example shows that even with a central repository and coverage of all supply chain actors, the importance of using global standards for data encoding, scanning and printing equipment is extremely clear. Vendors of end-user scanner systems need to be included in testing or would require a certification before connecting to the system. A transition period is required for all actors to get used to the system.

- The lack of mandate to scan/verify a serial number throughout the supply chain (at all nodes of the supply chain) prevents internal brand protection organizations from being able to determine the provenance of a product.

- Establishing the EMVO (Non-profit organization) to administer the Falsified Medicines Directive and to maintain the central database has proven to be beneficial to all stakeholders in both the implementation and maintenance of the central database.

- The introduction of track and trace requirements requiring specific national codes (like national reimbursement codes) has proven onerous for both service providers and manufacturing organizations (MAH's & CMO's)

- The combination of anti-tampering device application together with serialization requirement is relevant. It is imposed by regulation.

The approach taken in the U.S. is more decentralized. In this case, peer-to-peer connectivity on top or besides existing data exchanges is an added burden and requires large investments from all involved actors. This requires an extremely robust local environment and collaboration amongst trading partners. The lack of a harmonized system in the U.S. and the heterogeneity in the adoption of track & trace systems present barriers for the U.S. supply chain to realize the full value of traceability. Lack of U.S. FDA guidance and engagement with industry efforts to establish standards and governance for interoperability as required under the DSCSA in 2023 likewise presents barriers to fully realizing the benefits of interoperability. Further, lack of standardized methods for resolution of incomplete verification responses received via saleable returns verification poses challenges across trading partners.

Turkey can be seen as a pioneer country: A centralized system built and managed by Turkish Ministry of Health was established in 2010. This structured tracking system for product traceability was originally built mainly to prevent packaging and barcode scams. This system has successfully prevented illegal product reselling and redistribution in Turkey, which in turn provided a significant amount of budget saving within the national health care expenditure in Turkey.

- Turkey started the system implementation process with two phases – starting with adding unique identifiers and only later product aggregation.

- Turkey's centralized system enables the Turkish NRA to take urgent action on issues relating to patient safety (e.g. facilitating recalls, providing detailed information about potential falsified products) and enhances the visibility of the stakeholders who have the product batch in their stocks.

- The ability to track product stock levels with its system has allowed active stock level tracking from manufacturer to pharmacy, leading to increased product availability in the market.

In Korea, the government mandated serialization requirements that cover all pharmaceutical products.

- The labeling system introduced in 2011 attaches a unique serial number to the minimum distribution package, enabling traceability and management at all stages of manufacturing, import, distribution, and use. Aggregation is voluntary but strongly encouraged.

- The Korean Pharmaceutical Information Service (KPIS) was established to standardize relevant product information; collect, manage and review distribution data and monitor compliance reporting. Manufacturers must attach a serial number when manufacturing or importing pharmaceuticals and report the serial number to KPIS at the first step of shipping pharmaceuticals.

In most Africansountries the progress on traceability initiatives has been limited when compared to other parts of the world. This has provided an opportunity for some solution providers to influence in certain markets, resulting in the uptake of non-standardized, global solutions. This in itself is a cause for concern as it threatens medicine supply by adding additional complexity to global supply chains of pharmaceutical companies supplying products to the region.

As explained in this paper, global data standards within traceability of pharmaceuticals is greatly beneficial to patients, regulators and industry stakeholders - African governments and health authorities are aware and keen to explore the existing landscape globally, while recognizing the importance of utilizing established global standards for pharmaceuticals already in use in many markets and regions of the world. This will ensure that with the appropriate infrastructure in place, a "point of dispensing verification" model can be adopted, and full traceability can be seen as a future adoption if required.

A cautious approach should be taken when planning for new type of system set-ups. As previously adopted by Nigeria, few "patient verification" systems have been established globally . Therefore, it is particularly important to refer to the ten principles above and move forward with prudence, as questions will certainly be raised by all stakeholders involved and involving them as co-creators can prove to be beneficial. y.

Ethiopia has taken a very measured approach to their journey of pharmaceutical traceability with the Pharmaceutical Products Traceability Directive, which requires a phased approach across 7 – 8 years, which is to be commended, as it supports patients by helping to ensure continuity of medicine supply.

Additional resources:

1. https://www.rxgpsalliance.org/resources/

2. The *"Global Standards Technical Implementation Guideline for Global Health Companies"*, issued by USAID and formally endorsed by The Global Fund, the Global Drug Facility, UNFPA, UNDP, PEPFAR, aims to be the implementation road map for international procurement agencies. The document is to a large extend based on GS1 Global Standards.

3. The African Healthcare Conferences in Addis Ababa (May 2018) and Lagos (September 2019) hosted by GS1, has been attended by National Regulators as well as Global Public Health organizations (WHO, the Global Fund, The World Bank , USAID, the Global Drug Facility, a majority of African NRAs, MOH, ,GAVI, UNICEF, local manufacturers and distributors, …).

    a. In Lagos a "Call to Action" on Africa Strategy for Pharmaceutical Traceability has been signed by representatives from national and regional economic communities (RECs) from across Africa. It is a strong engagement to intent to explore and move towards implementation of pharmaceutical traceability policies, processes, and systems. Several African countries are now also preparing phased regulatory roadmaps (Nigeria, Ethiopia, Ghana, Kenia, Rwanda,...).