Medicine Shortages: From Assumption to Evidence to Action

A Proposal for Using the FMD Data Repositories for Shortages Monitoring

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Executive Summary

- **The EU Falsified Medicines Directive and its Delegated Regulation[1] provides for the establishment of interoperable repositories or database systems (also called EMVS) containing unique identifiers (i.e., product code, serial number, batch number, expiry date, and where applicable, national reimbursement number) for all prescription medicines sold in the EU/EEA.**
- **This data could provide useful intelligence regarding the number of packs for all prescription products being supplied by manufacturers on the various EU markets, number of packs dispensed in national pharmacies, number of packs exported (and/or imported), as well as on the level of stocks present in the supply chain at country level.**
- **Such a wealth of data would supplement information already provided by Marketing Authorisation Holders on manufacturing and quality related supply disruption to National Competent Authorities, and in providing information on causes and extent of shortages beyond manufacturing related issues, would greatly facilitate the detection and mitigation of genuine shortages.**
- **Considering that EMVS contains all data required to correctly measure the supply of each medicine presentation on all EU markets (see proposed Directive Articles 67§6 and 82§1), and knowing that end users connected to the system (i.e. pharmacists, hospitals, dispensing doctors) must check the authenticity of each pack before dispensing it (therefore producing 'demand' data into the system), industry stakeholders legitimately question whether there are legal barriers to prevent the use of the EMVS by National Competent Authorities for monitoring shortages.**

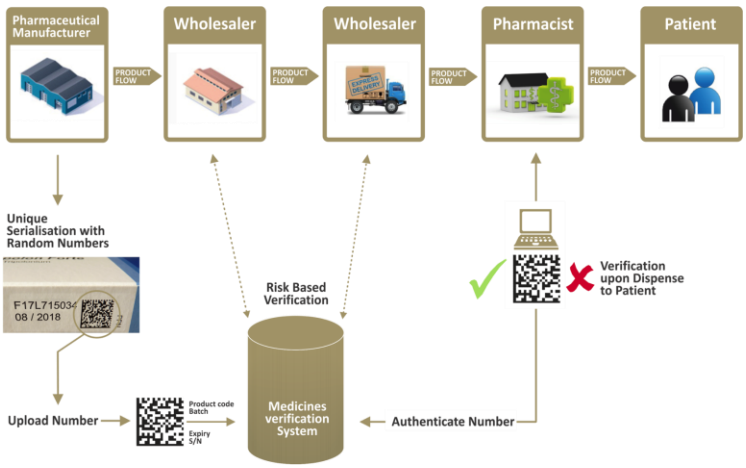
Introduction

In the interest of patient safety, the European Union (EU) adopted the Falsified Medicines Directive[2] (FMD) in 2011 to protect the legal medicines supply chain from the entry of falsified medicines. The FMD 2011/62/EU mandates the supply chain stakeholders to develop, implement and run a medicines verification system, to allow the verification of the authenticity of medicinal products.

How the medicines verification system work in practice

1. Manufacturers place a *unique* identifier on each individual prescription medicinal pack.
2. Manufacturers, prior to release of product into the market, upload the information contained in the Unique Identifier into the European Medicines Verification System (EMVS), the repository database (see further below).
3. Pharmacist are legally required to systematically verify – via the repository system – the authenticity of the unique identifier for each pack, before dispensation to the patient. Pharmacies will therefore only dispense a product if this product is verified (i.e. information is included in EMVS and all

Figure 1: The verification flow along the supply chain



1 https://eur-lex.europa.eu/eli/reg_del/2016/161/oj

2 https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf

data elements of the unique identifier correspond to the correct information uploaded by the legitimate manufacturer).

4. With a risk-based approach, additional verification will be carried by wholesalers along the supply chain. For example, returns or products received from other wholesalers historically represented a higher risk of falsification, therefore the legislation mandates wholesalers to systematically verify these two product categories.

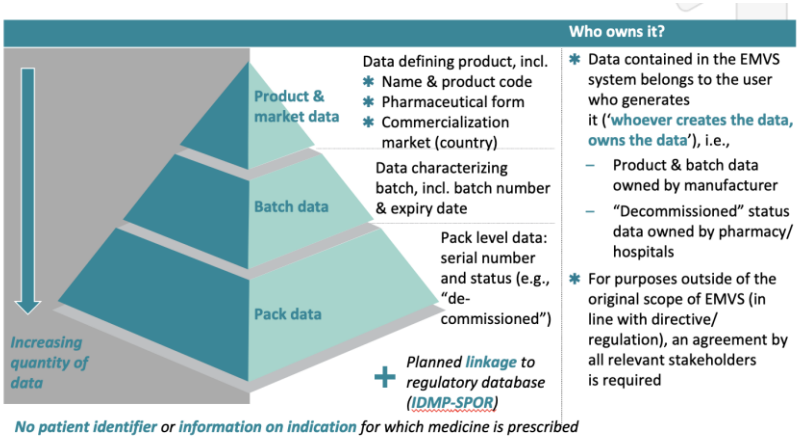
Data availability in the European Medicines Verification System

The **EMVS** was established by manufacturing/ marketing authorization holders in Europe, with the contribution of distributors and pharmacies (i.e. a stakeholder model). It is a single-point of data entry, with strict and robust technical requirements in place to make sure that only legitimate manufacturers (i.e. marketing authorization holders in Europe) can connect and upload data into the system and only pharmacies/persons authorized to dispense medicine to the public can decommission data for each pack. This means the **EMVS is also an end-to-end verification system, recording and reconciling the supply of each prescription medicine placed on the market with its respective dispensation to patients** (or subsequent removal from the supply chain: exported, destroyed, withdrawn etc.)

EU National Competent Authorities (NCAs) supervise the system and have access to all data contained in this repository.
The EMVS holds the following information (see also Figure 2):

- Product Code (plus national reimbursement number if appropriate)
- Batch number
- Expiry date
- Serial number
- Product Master Data
- Marketing Authorisation Holder
- Manufacturer details (the assigned manufacturer of the batch)
- Current status of the unique serial number, i.e., active or de-commissioned—in case of "de-commissioned" also the detail, e.g., dispensed, recalled, stolen, etc.;
- By whom/where a change of status has happened
- Time and date of preceding changes.

Figure 2: Data available in the EMVS



The requirement of recording the status of the unique identifier (when decommissioned by persons authorized to dispense medicines to the public) is equivalent to the generation of sales data on a continued basis (this requirement for decommissioning also applies to parallel traders and to wholesalers under some circumstances).

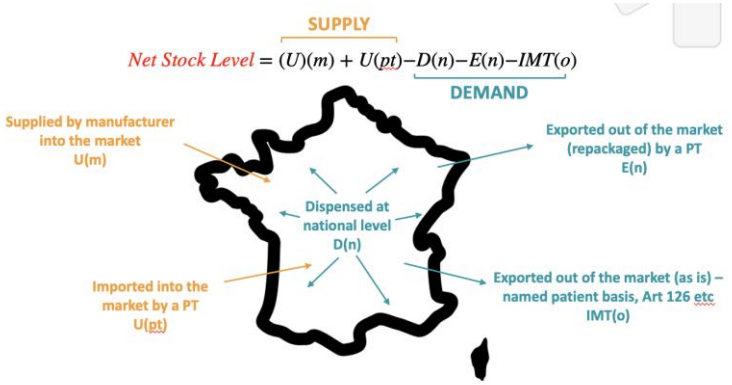
Where EMVS data meets supply chain reality

Considering all of the above, we believe that the data stored in the interoperable network of national repositories being set up in the context of the Falsified Medicines Directive and its Delegated Regulation on safety features can be used to provide additional intelligence to monitoring shortages.

This data could provide useful intelligence regarding the number of packs for all prescription products being supplied by manufacturers on the various EU markets, number of packs dispensed in national pharmacies, number of packs exported (and/or imported), as well as on the level of stocks present in the supply chain at country level. The real time information in the repositories can be analyzed according to very granular time frames (per day, per week, per month etc.) as well as per region (postal codes). That wealth of data would supplement information already provided by Marketing Authorisation Holders on manufacturing and quality related supply disruption to NCAs, and in providing information on causes and extent of shortages beyond manufacturing related issues, would greatly facilitate the detection and mitigation of genuine shortages.

Figure 3 shows how a NCA can identify the Net Stock Level of available medicinal packs in its territory at any given moment.

Figure 3: Net Stock Level calculations



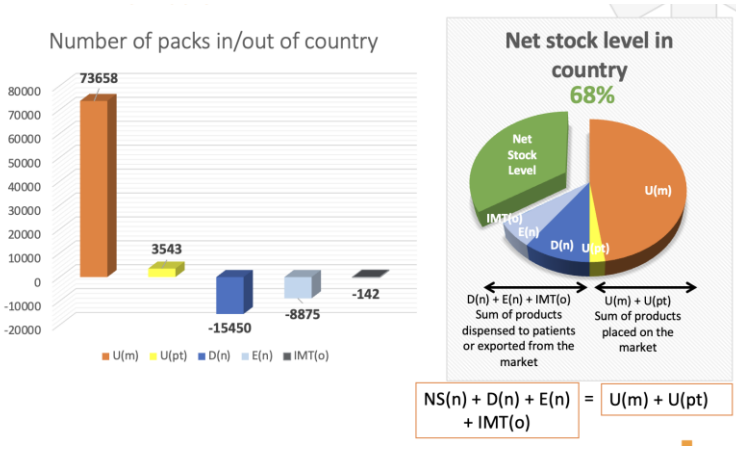
Functionality of the system.

NS(n) = net stock level at national level
U(m) = number of unique identifiers uploaded into the national market by the original manufacturer (corresponding to the number of physical packs released on the market)
U(pt) = number of unique identifiers uploaded into the national market by parallel trader(s) (corresponding to the number of physical packs imported in the national market)
D(n) = number of unique identifiers decommissioned at national level by persons authorized or entitled to supply medicinal products to the public, typically community pharmacists, hospital pharmacists or in some cases wholesalers (on behalf of Article 23 actors) (corresponding to the number of physical packs which have been dispensed to patients within the territory)
E(n) = number of unique identifiers decommissioned for export at national level by parallel traders (corresponding to the number of physical packs exported from the national market)
IMT(o) = number of unique identifiers destined for the national market but decommissioned in other markets via the Inter Market

Proposal for Collaboration Between National Competent Authorities and Manufacturers in Order to Proactively Monitor Country Stock Levels

Continuously monitoring the Net Stock Level of a medicinal product in a Member State allows for proactive measures to be taken both by NCAs and by manufacturers to avoid the national Net Stock Level to fall in negative territory. For this purpose, we propose the creation of a "dashboard" type early-warning mechanism (see Figure 4 for an example of such dashboard) whereas a NCA would notify the manufacturers once a certain minimum threshold is reached at national level (for example, Net Stock Level reaches 20%) so that the manufacturer can take actions to pre-emptively re-supply the respective market. As the data access rules within the system are strict, this early warning notification system can only be triggered by NCAs (as they have access to the full data) and be exchanged only at aggregate level. Depending on the type of product different thresholds can be set for different medicines, in collaboration with the original manufacturer (depending on manufacturing lead time, availability of stock in other markets, etc.).

Figure 4: Dashboard for monitoring net stock level



Issue of Multimarket Packs

Some medicinal products are released for sale in multiple markets at the same time (and are packaged according to the packaging requirements—for example the language of the patient information leaflet—of multiple countries). In such cases, a manufacturer will upload the unique identifiers of the batch released for sale into the repository systems of the countries in the multi-market pack cluster. When a medicinal pack is decommissioned for dispense in one market then the unique identifier is automatically decommissioned in all markets. Therefore, there is a need for collaboration and data exchange between the NCAs in the respective markets of the cluster so that the data can be interrogated and aggregated for all markets of the cluster. The formula outlined above still holds but will show the net stock level across the markets in the cluster.

Issue of Multi-Source Products

Currently the data in the system can only be identified according to Product Code (corresponding to a physical Stock Keeping Unit). While this is straightforward for single source products (typically on-patent medicines) the analysis is further complicated in the case of multi-source products (typically off-patent medicines) as NCAs need to analyze the net stock level in parallel for multiple medicinal products which are deemed interchangeable for the treatment of a specific condition in order to identify the risk of shortage. Currently this can be done in a manual way by running and aggregating multiple reports, however, once the connection with the EMA IDMP/SPOR database, NCAs will have the possibility to run reports on an ATC class level. Such reports would automatically assembly the required data for multiple products in a specific class.

The European Commission's approach regarding extended uses of EMVS

In April 2023 the Commission released its legislative proposals (Regulation and Directive) for the revision of the General EU pharmaceutical legislation. In Article 67§6 of the proposed draft Directive, **the Commission** proposes the use of the EMVS for monitoring the implementation of the regulatory data protection prolongation for market launch provision. In so doing, the proposal **indicates that the EMVS includes all data needed to check if medicinal products have been "*released and continuously supplied into the supply chain in a sufficient quantity and in the presentations necessary to cover the needs of the patients in the Member States in which the marketing authorization is valid*"** (Article 82, §1).

Considering that EMVS contains all data required to correctly measure the supply of each medicine presentation on all EU markets, and knowing that end users connected to the system (i.e. pharmacists, hospitals, dispensing doctors) must check the authenticity of each pack before dispensing it (therefore producing 'demand' data into the system), industry stakeholders legitimately question whether there are legal barriers to prevent the use of the EMVS by NCAs for monitoring shortages. Given the clear advantages of using such a 'ready-made' and forward looking digitalised system, and our shared goal of tackling medicines shortages, we commend all parties involved in advancing the legislation to seize this opportunity.