European Medicines Verification System data

GIRP reflections on potential use of data contained in the EMVS for shortages monitoring

Introduction

GIRP, the European Healthcare Distribution Association, is the umbrella organisation for pharmaceutical full-line wholesalers and distributors of healthcare products and services in Europe. It represents the national associations of over 750 pharmaceutical full-line wholesalers serving 33 European countries, as well as major international and pan-European healthcare distribution companies.

The European Medicines Verification Organisation (EMVO), of which GIRP is a founding member, is a Belgian non-profit organisation representing stakeholders united in securing the legal supply chain from falsified medicines.

EMVO has taken responsibility for advancing the formation of the European Medicines Verification System (EMVS) which has been set-up and managed in accordance with the Falsified Medicines Directive (Directive 2011/62/EU) and its Delegated Regulation 2016/161/EU laying down detailed rules on safety features. It ensures the implementation of a functioning, secure, interoperable and cost-effective system across Europe.

EMVO and the EMVS were established in compliance with the Delegated Regulation which stipulates that the repositories system shall be set up and managed by a non-profit legal entity established in the Union by manufacturers and marketing authorisation holders of medicinal products bearing the safety features and, where they have chosen to participate, wholesalers and persons authorised or entitled to supply medicinal products to the public (e.g. pharmacists and hospitals).[1]

Even prior to the EMVS' inception and during more recent announcements from stakeholders, the idea to use the EMVS for shortages monitoring was and is frequently mooted. Despite our continued efforts to highlight the limitations of the system for shortages monitoring, calls and erroneous and misleading arguments are still developed for use of the EMVS as a means of providing supply chain data for the purposes of monitoring medicines shortages.

FMD and DR provisions

Directive 2011/62/EC of the Parliament and the Council of 8 June 2011 amending Directive 2001/83/EC of the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products, and European Commission Delegated Regulation 2016/161 of 2 October 2015 supplementing Directive 2001/83/EC of the European Parliament and of the Council by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use (Delegated Regulation) are the main legal instruments underpinning the establishment of the EMVS system.

[1] Article 35 (1.b) of Delegated Regulation (EU) 2016/161

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During the process of reflecting on the potential use of data contained in the EMVS for purposes other than those defined in the legal framework, it is important to take full account of a number of important provisions of the Delegated Regulation (DR) - namely DR Art. 35 (h)[2] and Article 38[3] (see below).

The legislation clearly sets out the access rights of National Competent Authorities (NCAs) to data contained in the repository systems for the following purposes: (a) supervising the functioning of the repositories and investigating potential incidents of falsification; (b) reimbursement; (c) pharmacovigilance or pharmacoepidemiology[4]. Our analysis of the suitability of data included in the EMVS for shortages monitoring is based on the assumption of full access to all available data in the EMVS.

Background

The following users are accredited to interact with the different elements of the EMVS (European Hub and National Medicines Verification Systems (NMVSs)):

- On-Boarding Partners (OBPs) for Marketing Authorisation Holders (MAHs) only interact with the European Hub.
- Manufacturers either interact with the system(s) through their MAHs and OBPs connections with the European Hub or in some cases in their capacity as a holder of a wholesale distribution authorisation for their own products - they can interact with the respective NMVS.
- Third Party Logistic Providers (3PLs) or Pre-wholesalers interact either through the credentials of their OBP with the European Hub or in their capacity as holders of a wholesale distribution authorisation. In the latter case they interact with the respective NMVS.
- Wholesale distribution authorisation holders only interact with the NMVS.
- Pharmacies and persons authorised to supply medicinal products to the public only interact with the NMVS.
- National Competent Authorities (NCAs) interact with the EMVS within the context of their right to access data as established in Article 39 of the DR and within the framework of the reports established for this purpose.

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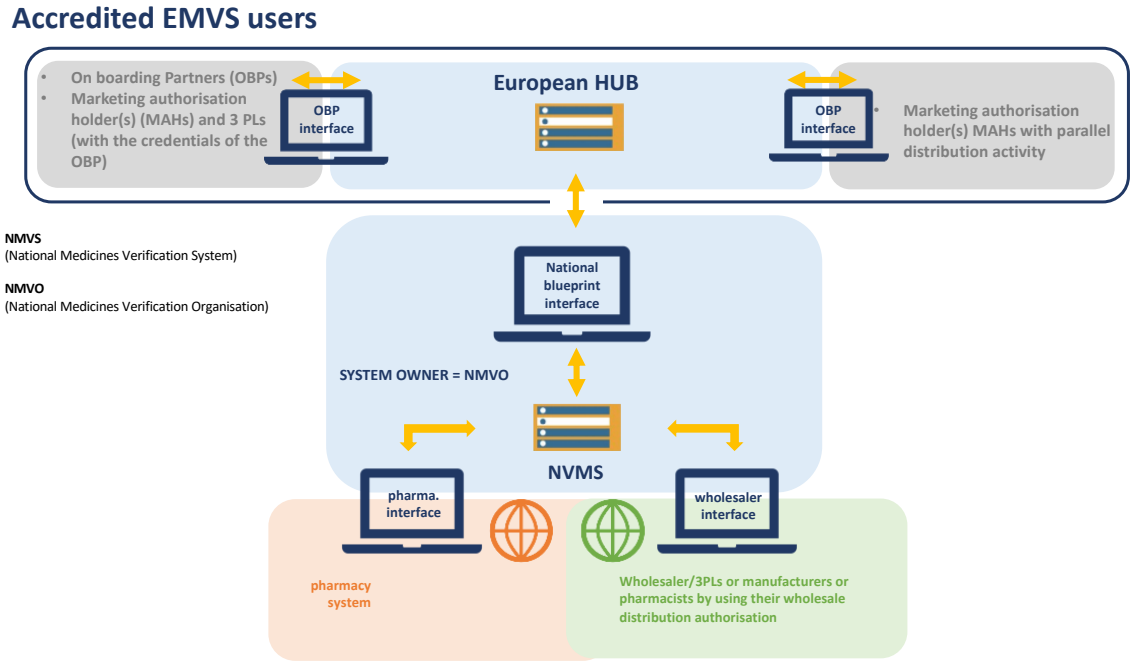
[2] Characteristics of the repository system:
"In accordance with Article 38, its structure shall be such as to guarantee the protection of personal data and information of a commercially confidential nature and the ownership and confidentiality of the data generated when manufacturers, marketing authorisation holders, wholesalers and persons authorised or entitled to supply medicinal products to the public interact with it;"

[3] Data protection and data ownership:
"1.Manufacturers, marketing authorisation holders, wholesalers and persons authorised to supply medicinal products to the public shall be responsible for any data generated when they interact with the repositories system and stored in the audit trail. They shall only have ownership of and access to those data, with the exception of the information referred to in Article 33(2) and the information on the status of a unique identifier.
2. The legal entity managing the repository where the audit trail is stored shall not access the audit trail and the data contained therein without the written agreement of the legitimate data owners except for the purpose of investigating potential incidents of falsification flagged in the system in accordance with Article 36(b)."

[4] *Article 39(a) of the Delegated Regulation establishes that the legal entity establishing and managing a repository used to verify the authenticity of or to decommission the unique identifiers of medicinal products placed on the market in a Member State shall grant access to that repository and to the information contained therein, to competent authorities of that Member State for the purpose of supervising the functioning of the repositories and investigating potential incidents of falsification, reimbursement, pharmacovigilance, and pharmacoepidemiology.*



Source: European Medicines Verification Organisation

The interactions of the above-mentioned operators generate the following data:

- OBPs upload Master Data, a combination of product data and pack data (i.e. serial numbers, product identification numbers, batch numbers, expiry dates, etc…), for their packs which also include an indication of whether it is a single or multi-market pack, with an indication of the potential destinations for multi-market packs. In case of multi-market packs, all countries in which the product can be marketed have to be included in order to root the data down to all the national repositories where the pack can potentially be dispensed.
- MAHs check upon batch release whether the safety features are operational (i.e. by checking one pack per batch).
- 3PLs or pre-wholesalers are required by MAHs to check one pack per batch upon receipt.
- Wholesale distributors will verify within the limits of their obligations packs upon receipt and may perform an additional verification on a voluntary basis (as recommended by EMVO) of one pack per batch as a preventative measure to ensure that products delivered to pharmacies do not raise alerts at the point of dispense. Furthermore, wholesale distributors fulfil their obligation to verify packs, which are returned to them from their customers.
- Pharmacies, hospitals and other persons authorised to supply medicines to the public will verify and decommission the products at the point of dispense (unless exempted in accordance with DR Article 23);
- Member States can exempt a list of entities (Article 23 actors) from verifying and decommissioning the safety features and oblige wholesalers to do this on their behalf;
- The various reason for decommissioning (sub-states) will be visible in the system if either the pack is in hand or the serial number known (EMVO and NMVO stakeholders can only access this information for verification purposes – so the pack must be "in hand").
- National Competent Authorities (NCAs) have access to the system according to the pre-defined reports and will leave a trace in the system when running them, unless investigating a potential case of falsification.

System interactions of different stakeholders

Use Case	Initiator				
	Manufacturer	*Par. Distributor*	*Pharmacist*	*Wholesaler*	*Administrator*
Upload product master data	X	X			
Upload product pack data	X	X			
Recall batch	X	X			
Verify pack	X	X	X	X	
Dispense pack	X	X	X	X	
Decommission pack		X			
Export pack from EU	X	X		X	
Request report	X	X	X	X	X
Withdraw Product	X	X			
Mark pack as Stolen	X	X		X	
Mark pack as Destroyed	X	X	X	X	
Mark pack as Free Sample	X	X		X	
Mark pack as Sample	X	X	X	X	
Mark pack as Locked	X	X		X	

Source: European Medicines Verification Organisation

Assessment

There are several noteworthy limitations / obstacles to the ambition to use the EMVS for shortages monitoring:

In relation to OBPs/MAHs:

- Multi-market packs are uploaded in all potential destination markets and therefore counted multiple times without being available on these markets. Currently 12.5 % of the uploaded packs are multi-market packs and they, on average, target 3 different countries, where they could potentially be sold, but are only physically available in one of the 3 countries. This would mean that medicines available on the European market would be over-estimated by about 2.5[5] billion packs. In some regions, where products can be used in the same packaging in several countries (Baltics, Nordics), the difference between the actual packs in the country and the uploaded packs is even much higher. The systems in the Baltic countries show 5-times the volume than products are physically on the market.
- OBPs upload Master Data upon batch-release, regardless of whether the products have arrived in the destination market(s). OBPs may centrally stock serialized packs with uploaded batch numbers and decide at a later stage to send them to the destination market (for example based on assumptions on local markets' demand and quotas) or eventually decommission the packs and repackage them for another market.
- Some products are removed from supply for testing purposes – serial numbers are uploaded but the actual product will not or was never destined to reach the market. If we assume this is the case for only 1% of all packs, product availability in the market would be overestimated by 150[4] million packs.

[5] based on 10 bio packs of RX medicines included in the EMVS

- Presently, not all packs are authenticated. Assuming that 97% of all packs are authenticated (at present, we are still very far from this scenario), and that products have a 3-year shelf life, this would mean that after 3 years we will have a volume representing 9% of a year's consumption in the system implied as an inventory. For 5-year shelf life products, this would even correspond to 15% of the volume and around 1,5[4] bio packs on the EU/EEA market. This will remain as such for several years until we achieve "100% level" of authentication.

In summary, the EMVS cannot provide a clear overview of national stock levels as the data contained on supply will always be significantly higher than the number of packs actually shipped to the national markets by MAHs. The only reliable information can be obtained from "real world data" of available stock levels of the MAH in the respective national market. MAHs should be required to provide in real time the necessary evidence about the volume of products they have made available for the national market, bearing in mind that the volume of products available at a given time can only mirror the supply situation at this very specific point of time. Further information would be required on the time-span this volume should last until further supplies arrive in the country.

In relation to wholesale distributors:

- Wholesale distributors only verify products when purchased from sources other than the MAHs, manufacturers, or designated wholesalers or when returned to them. They also decommission products on behalf of Article 23 entities, when they either send medicines to destruction, or export them to third countries.
- The EMVS has not been set-up as a track-and-trace system and therefore no stock level data are available as a result of scanning. Introducing a track-and-trace system would have, as shown during the impact assessment prior to the remittal of the Delegated Regulation, a huge and largely disrupting impact on the business processes of wholesale distributors and is therefore practically unfeasible.

In relation to pharmacies/hospitals/persons authorised to supply medicinal products to the public:

- While the number of dispensed packs as well as the number of products decommissioned in total in their territory are available to the relevant NCA, the amounts are not representative of the national demand, especially in situations where the product is short in supply, as only available products can be decommissioned.
- Patient demand is not static over time and is only known after patients need a product. Patent-driven demand is subject to many factors such as season, health crisis, disease outbreaks, etc. As seen during the COVID-19 pandemic, there was a sudden drastic upsurge in patient demand for specific products, which had to be covered.
- Certain products have little or no patient need over long periods, however a sudden localised outbreak of a specific disease (e.g., meningitis) may lead to a sharp increase in patient demand. Due to the stock-keeping function of wholesale distributors, the product is always available although there is generally no patient need.
- National demand could only be evaluated ex-post through the number of prescriptions.

The current EMVS has not been built for the collection of such information and therefore does not allow for the identification of the genuine reasons of supply difficulties that have a negative impact to patient care due to the fact that the system would always show higher than actual supply and lower than actual demand.

Recommendations:

- "Real-world data" of available stock levels of the MAH in the respective national market is the only reliable source for the supplied quantities of critical medicines in the Member State. However, as this information only provides a snap-shot about the stock-level at a specific point of time, further information on the time-span foreseen for this stock to last should be provided by the MAH.

- National early warning systems about shortages, collecting signals about the current supply situation from all stakeholders involved in the distribution of medicinal products (wholesalers, pharmacies and hospital pharmacies) are taken into account as integral part of any shortages monitoring system for critical medicines on national and subsequently at EU level. These market signals (service-level from pharmaceutical manufacturers to wholesalers and from wholesalers to pharmacies) provide an early warning if the continuous supply is at risk for any reason (i.e. unforeseen demand)
- In countries where there is no current institutionalised monitoring of the supply situation, GIRP proposes the introduction of an early warning system that collects market signals from all supply chain stakeholders.
- Interoperability between the national systems should be ensured and a method to aggregate data at European level found.
- Demand forecast models should be developed, based on e-prescription data connected with AI solutions in order to analyse if supply meets demand.

Full data intelligence, while an interesting tool, will not in itself resolve shortages when MAHs continue to exert their dominating influence on the actual production and release of products to national markets. If the product is not produced or as often the case, released in insuffient quantities (quotas), then any supply intelligence data does not result in practical and workable solutions for patients.

GIRP

European Healthcare Distribution Association
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