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Health systems, medical products and innovation
Medical products: quality, safety, innovation

Brussels, 17 October 2023

Minutes of the 38th Expert Group on the delegated act on safety features for medicinal products for human use

25 September 2023, Brussels

Welcome

The chair welcomed the attendees that joined the meeting, and the agenda was adopted.

1. Implementation in healthcare institutions/hospital pharmacies

At the previous Expert Group meeting, it was agreed that the group would explore with the European Medicines Verification Organisation (EMVO) the best way forward to implement the use of "aggregation" or "consolidation". However, for EMVO this is not a priority. The guidance document "*WG IV: Implementation of the Falsified Medicines Directive in the hospital setting*" on the DG SANTE homepage was generally considered helpful. Accordingly, manufacturers can offer consolidated / aggregated codes to hospitals. In some Member States wholesalers produce special aggregated codes on the box. In other Member States manufacturers offer consolidation. It was suggested that in the future the integration of an aggregated bar code can be used to identify a whole shipment in the European Medicines Verification System (EMVS) would be an appropriate solution. Experts concluded that the guidance provides solutions that make full compliance possible.

2. Proposal to redistribute medicines to prevent waste

NL presented a study intended to explore if it is safe and beneficial to redispense oral oncolytics that have been dispensed to patients and returned due to non-use (e.g., discontinued use due to side effects, death of the patient or ineffectiveness of the therapy). This study was limited to a specific set of oral oncologic medicinal products that have to be stored at room temperature. Moreover, packages concerned should be returned to the same hospital that dispensed them in the first place. The idea of redispensing is fostered by sustainability, critical shortages, costs considerations and finds considerable support across the board, the healthcare professionals and the public in the NL. NL already presented its concept in a letter to Commissioner Kyriakides and discussed with some other Member States.

A study was conducted in 4 hospitals for 12 months, it involved more than 1000 patients and oral oncolytic medicines were dispenses for 1 month to the patient by the pharmacy of the four hospitals. In the Dutch system, hospitals comprise a public pharmacy. The study was conducted with these types of pharmacies. Packages dispensed to patients were sealed in plastic bags with

a time/temperature indicator. Patients could bring unused medicines back to the hospital pharmacy that originally dispensed them. Before redispensing the pharmacy had to check integrity, earlier verifications in the EMVS, that the original package was not opened, storage conditions were not compromised, the expiry data was not exceeded, and the original dispensing took place in the same pharmacy. In the study, 228 packages could be redispensed. Mean annual cost-savings were estimated between €576 and €1348 per participating patient. The study will be published in the Journal of the American Medical Association (*JAMA)* Oncology in November 2023. IT reported on a similar system managed according to regional legislation. Hospitals take the responsibility for the integrity of the returned medicinal products. In ES a similar system is managed by specific hospital pharmacies under national legislation. In several Member States hospital pharmacies never dispense medicines directly to patients.

The Expert Group agreed that the NL experts would convene and lead a subgroup to further explore the general feasibility of the procedure pursued in the study.

3. Implementation Commission Delegated Regulation (EU) 2016/161

DG SANTE reported on meetings held with FR, BG and ES on shortcomings in the implementation of the Falsified Medicines Directive and the Delegated Regulation.

BE reported on the measures taken to ensure that all alerts are followed up and packages causing alerts are not dispensed. The prerequisite was that the general alert rate is sufficiently low. False alerts are still caused by double scanning, packages not uploaded into the repository system (EMVS) or due to interface issues with the pharmacy software. Enforcement in BE occurs via circular letter issued by the national competent authority (NCA) Packages that triggering an alert must be put under "quarantine" and the alert must be investigated. Confirmed cases of falsification are escalated to the NCA. false alerts there is a procedure that allows the decommissioning after the cause is identified. It is also possible to ask for an exemption for a product in dire need. The system was introduced in collaboration with the BE National Medicines Verification Organisation (NMVO) and initiated via a number of webinars to train pharmacies. Pharmacies causing too many alerts are inspected.

DG SANTE stressed that "stabilisation period" approach could not be tolerated any more, and NCAs have to ensure full compliance. It is critical for the purpose of the FMD framework that all Member States are connected to the EU system.

4. End of transition for Greece and Italy in February 2025

DG SANTE reported on meetings held with EL and IT. Both have provided documents on their approach.

EL reiterated that in Greece a national system in place since 1987 which also serves for reimbursement, taxes, and expenses. The required change is quite challenging. Agency and Ministry of Health held meetings since 2019 with all stakeholders to create the required NMVO. This critical step still has to be completed. EL also prepared a gap analysis. Experience and guidance of other Member States were welcome.

IT has been running a national system for all medicines for over 20 years. For a fee the states sells stickers "*bollinos*" to manufacturers to proof authenticity. This "*Bollino model*" system is thus managed by the state, so state services have full access to the information contained into the system. It is also used to monitor shortages, to manage reimbursement, oversee distribution of medicinal products.

IT sent to DG SANTE a proposal for transition with identified milestones. The last milestone is scheduled for 2033 because IT considers expiry dates of medicines with the "*bollino*" still on the market. IT presented a reasoning for the request for a further derogation, i.e. a further prolongation of the transition period.

DG SANTE stressed that the EU system has to be applicable in all EU Member States by February 2025. There would be further bilateral exchanges.

5. Interrelation between FMD regulatory framework and shortages management

A small working group comprised of participants from BE, BG, MT, SE, SI the European Medicines Agency (EMA) and DG SANTE met on 10 July 2023 (virtually) to investigate the link between the EMA European Shortages Monitoring Platform ESMP[1] and European Medicines Verification System (EMVS). Participants expressed the opinion that the EMVO/NMVO database is the most reliable data source currently available to ascertain what is on their market unless a Member State maintains an independent national monitoring system. The latter is not a viable option for many smaller Member States. In this respect, the accumulation of several of the current EMVO reports (e.g. PH 1 and PH 2), available to NCAs who applied for the necessary credentials, could provide some significant input allowing extrapolations on the number of products available on a market. However, there is no distinct legal reference allowing NMVOs to release data for other purposes beyond reimbursement, pharmacovigilance or pharmacoepidemiology purposes. Therefore, legal adaptations are necessary to put such query of the EMVO on a solid basis.

DG SANTE reiterated that the current proposal for a new Directive and a new Regulation, which revise and replace the existing general pharmaceutical legislation[2] does not modify the content of the articles inserted by the Falsified Medicines Proposal. If such changes were desired, it was for the co-regulator (Council and Parliament) to suggest respective amendments.

6. Access by Member States Competent Authorities to the EMVS repositories system (audit trail)

EMVO presented the progress made on the 2-step approach agreed by the group in May 2023 to provide access information located in repositories of another Member State ("audit trail").

[1] For details see here: https://www.ema.europa.eu/en/documents/presentation/presentation-update-european-shortages-monitoring-platform-esmp-development-progress-roadmap-p-pina_en.pdf

[2] See at https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en

EMVO reiterated that the repository system was never created with this purpose in mind. The necessary adaptations cause a lot of complications and require highly complex changes in the system and its interfaces. At the same time the resulting solution would need to be effectively used. Step 1 would be deployed in spring 2024, while Step 2 would further be discussed in the workshop scheduled the day after the Expert Group meeting.

Not all Member States could agree on the approach. EMVO said they would consider comments in the envisaged workshop.

7. EMVO alert management proposal to reduce false alerts via a FMD/Non-FMD list

EMVO reported on progress made. A pilot would be started with EMVO stakeholders soon. Austria, Belgium, Ireland and Spain agreed to participate.

8. EMVO report

EMVO reported on its observations on the latest implementation monitoring. Member States experts had received the full documentation before the meeting. The average alert rate reached 0,14 %. Nineteen markets lowered the alert rate to the target of 0.05 %. During summer 2023 peaks in alerts were observed. Some could be traced back to batches that had not been uploaded into the system. The connection of pharmacies in FR improved a lot. Still a large portion of hospitals in ES and FR are not connected.

EMVO reiterated that the "stabilisation period" was accepted initially to avoid delivering problems and was supposed to be as short as possible. EMVO referred to the workshop on 26 September 2023 where further details would be discussed.

9. EMVO workshop on 26 September 2023

EMVO provided an overview of the workshop and showed a table with the main issues that would be discussed. The table informed of improved co-operation between National Medicines Verification Organisations (NMVO) and National Competent authorities (NCA), enforcement, streamlining alert management, ending the "stabilisation period".

10. Revision of Q&A document

a. ECJ cases C-224/20, C-204/20, C-147/20

The rulings in these joint cases concern predominantly trademark protection and parallel import of medicines. On the request of DK, the Expert Group was invited to discuss if the judgments have any consequences for national practice or legislation regarding parallel import of medicinal products, the legislation on safety features, and on the guidance provided in the questions and answers document (Q&A). Several Member States pointed out that they have national legislation on the subject mirroring the guidance provided in the Q&A. Others thought that changes to the Q&A were needed. One concern was the wording in the judgment on the assessment of the integrity of the anti-tempering device by pharmacists.

It was decided to further discuss this matter in the future .

b. *Request to add a Q&A on best practice for the scenario where EU manufactured medicinal product batch is taken outside EU only for the logistic purposes but is meant to be distributed only in EU*

Member State experts agreed that the logistic had to be arranged according to the legislation. This meant decommissioning for export and issuance of a certificate for re-import.

11. Information on the study being conducted as per statutory request

The consultant commissioned to provide a study to support the 'report to the European Parliament and to the Council on trends in the falsification of medicinal products and measures provided according to Directive 2011/62/EU (Article 3)' presented the methodology and the status of the work conducted so far. Member States that had not yet provided feedback on the questionnaire sent can still send their answers. Initial findings indicate that the system is not fully deployed. This was also due to technical issues and human errors. The system appears to be effective in prevention.

The key challenge mentioned by most national competent authorities are online sales.

12. Any other business

a. *Inspection of EMVO by BE and ES*

The joint inspection of the EMVO with 4 inspectors (3 BE, 1 ES) was carried out in July 2023. An intermedium report was sent to EMVO for comments and the final report will be made available to the Expert Group. The inspectors assessed amongst others the working of the information technology, quality assurance, contract managements, links to onboarding partner, and governance structures.

BE and ES suggested that a template for this type of inspection was agreed. Other Member States may want to participate in future inspections.

b. *Reconciliation of serial numbers*

Several Member States stressed that the EMVS is designed as a verification system and data in the system should be as accurate as possible. Reconciliation should be indeed organised by the manufacturers.

Conclusions

The Expert Group agreed the following actions:

1. NL would convene and lead a subgroup of the expert working group to further explore the general feasibility of the procedure pursued in the study.
2. A pilot project to reduce false alerts via a FMD/Non-FMD list would be started with EMVO stakeholders soon with AT, BE, IE and ES.

3. Continued cooperation on study to support the report to the European Parliament and to the Council on trends in the falsification of medicinal products and measures provided according to Directive 2011/62/EU.
4. DG SANTE would seek input to clarify whether and how the Q&A document needs to be modified in the aftermath of the judgment in joint ECJ cases C-224/20, C-204/20, C-147/20.
5. Next Expert Group meeting is foreseen in January 2024 via videoconference.