Study supporting 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

Final report

Written by EY France / Ramboll
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Directorate D — Medical products and innovation
Unit D.2 – Medical products: Quality, Safety Innovation

Contact: [optional]
E-mail: [...]@ec.europa.eu

European Commission
B-1049 Brussel

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Acronyms

AIFA	Italian Medicines Agency
AME	Affordable Medicine Europe
API	Active Pharmaceutical Ingredient
ATD	Anti-tampering device
BEUC	Bureau Européen des Unions de Consommateurs (European Consumer Organisation)
BDA	Bulgarian Drug Agency
DR	Delegated Regulation
EAHP	European Association of Hospital Pharmacists
EC	European Commission
EEA	European Economic Area
EDQM	European Directorate for the Quality of Medicines
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EMVO	European Medicines Verification Organisation
EMVS	European Medicines Verification System
EU	European Union
EUIPO	European Union Intellectual Property Office
FDA	Food and Drug Administration
FMD	Falsified Medicines Directive (Directive 2011/62/EU)
GIRP	European Healthcare Distribution Association
HOPE	European Hospital and Healthcare Federation
IMT	Inter-Market Transactions
IPR	Intellectual Property Rights
MAH	Market Authorization Holder
MS	Member State
NCA	National Competent Authority
NMVO	National Medicines Verification Organisation
NMVS	National Medicines Verification System
OLAF	Office européen de lutte antifraude (European Anti-Fraud Office)
OBP	On-boarding Partner
OECD	Organisation for Economic Co-operation and Development
PGEU	Pharmaceutical Group of the European Union
ToRs	Terms of Reference (of the Study)
UI	Unique Identifier
UNODC	United Nation Office on Drugs and Crime UNODC
WHO	World Health Organization

1 Introduction

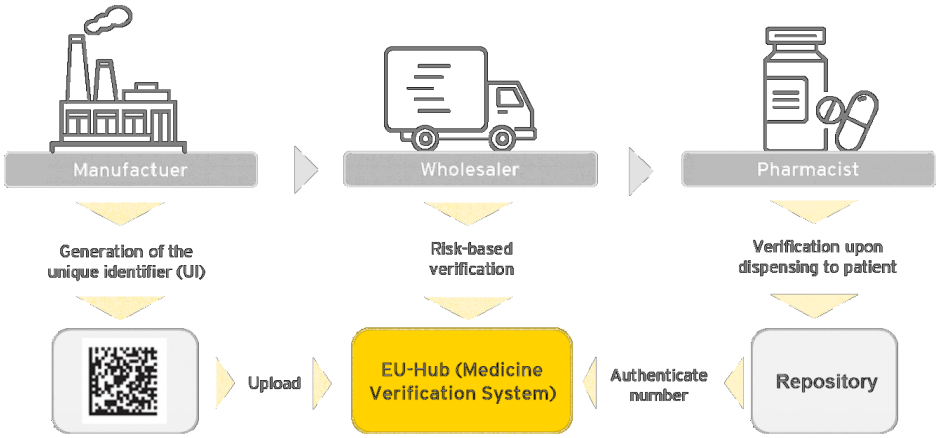
1.1 Presentation of the Context: FMD and DR

The European Parliament and the Council adopted the **Directive 2011/62/EU or "Falsified Medicines Directive"** (FMD)[1] in June 2011 to strengthen the fight against falsified medicinal products through rules and measures to secure their manufacturing, packaging, and ensure that the distribution channels are rigorously controlled. It also reinforces the efforts to harmonise legal frameworks at the level of the European Union (EU).

Article 54 of Directive No 2001/83/CE, as modified by the FMD, provides that medicinal products for human use subject to prescription[2] shall bear **safety features** appearing on their packaging. Detailed rules for these safety features have been laid down by **Delegated Regulation (DR) (EU) 2016/161**[3] of 2 October 2015, which introduces **verification mechanisms and obligatory safety features of medicinal products,** as part of the outer packaging of medicinal products subject to prescription, namely: (i) an **unique identifier** (a 2-dimension barcode), whose authenticity testifies the legitimacy of an individual pack of a medicinal product, and (ii) an **anti-tampering device**, whose integrity demonstrates the authenticity of the medicinal product in its packaging.

The system established according to Article 54 of Directive 2001/83/EC and through DR (EU) 2016/161 aims to **guarantee the authenticity and integrity** of medicinal products by an end-to-end verification for the benefit of patients and businesses, and to **strengthen the security of the medicine supply chain**, from manufacturers to distributors, pharmacies and hospitals. Manufacturers are indeed obliged to upload the information contained in the unique identifier for each individual medicinal products to national/ supra-national repository systems connected with an EU Hub. Depending on their source, wholesalers may also need to scan medicinal products at different points in the supply chain to verify their authenticity (and check their integrity). Pharmacies and hospitals then have to scan each medicinal product at the end of the supply chain to verify their authenticity and "decommission" them from the repository before dispensing them to patients.

Figure 1 Process of verification of authenticity of medicinal products [4]



According to Article 2 of the 2016 DR, the measures applies to: (i) Medicinal products for human use subject to prescription which shall bear safety features, with the exception of the 14 categories of products presented in Annex I of the DR; (ii) the medicinal products for human use not subject to prescription presented in Annex II of the DR (such as the omeprazole); and (iii) the medicinal products to which MS have extended the scope of the safety features, in accordance with Article 54a (5) of Directive 2001/83/EC (i.e., MS may extend the application of the safety features to medicinal products subjected to prescription or to reimbursement for the purposes of pharmacovigilance or reimbursement, as well as, for the purpose of patient safety, any medicinal product).

The DR has applied since 9 February 2019 in the EU and the European Economic Area (EEA), with the exception of Italy and Greece, which have been granted the option of deferring application of the rules of an additional

1 Directive 2011/62/EU amending Directive No 2001/83/CE on 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

2 Other than radiopharmaceuticals referred to in Article 54a(1) of the FMD and unless, by way of exception, they have been listed in accordance with the procedure pursuant to point (b) of paragraph 2 of Article 11 of the FMD

3 Commission Delegated Regulation (EU) 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

4 Source: European Medicines Verification Organisation (EMVO). EMVO (emvo-medicines.eu)

period of up to 6 years, as these countries already had national systems in place for verifying the authenticity of medicinal products and the identification of individual packs. The exception would also have applied to Belgium which did however not make use of it.

Article 3 of Directive 2011/62/EU sets out that "at the latest 5 years after the date of application of the delegated acts referred to in Article 54a(2) of Directive 2001/83/EC6, as inserted by this Directive, the Commission shall submit **a report to the European Parliament and to the Council containing the following**:

- a) a description, where possible including quantitative data, of the trends in the falsification of medicinal products in terms of: categories of medicinal products affected, distribution channels including sale at a distance to the public by means of information society services, the Member States concerned, the nature of the falsifications, and the regions of provenance of these products; and
- (b) an evaluation of the contribution of the measures provided for in this Directive regarding the prevention of the entry of falsified medicinal products in the legal supply chain. That evaluation shall in particular assess point (o) of Article 54 and Article 54a of Directive 2001/83/EC as inserted by this Directive".

1.2 Aims and objectives of the Study

Considering above-mentioned elements, this Study provides necessary inputs for the Commission to prepare the report required according to Article 3 of Directive 2011/62/EU. The study aims to assess the implementation of Directive 2011/62/EU (FMD) and the measures laid down in DR (EU) 2016/161 and their effects (measures on safety features), focusing on two areas:

- **Area 1:** (i) Identifying the trends in the falsification of medicinal products, by pointing out their categories, the supply-chain and the nature of falsifications, (ii) analysing the specificities in the application of the DR, and (iii) defining existing challenges with regards to falsified medicinal products in EU/EEA.
- **Area 2**: Evaluating the adequacy and functioning of the system in place against the objectives and targets set out in the DR (EU) 2016/161, e.g. assessing the extent to which the adoption and the implementation of the measures set in the DR have delivered against its initial objectives and targets.

Ultimately, the Study aims to bring evidence to conclude whether the entire system works from a technical and functional perspective, to explain existing barriers and constraints with the implementation of measures (if any), to identify remaining risks and check whether the current system can effectively address current and future needs.

1.3 Scope of the Study

The **thematic scope** of the Study covers the FMD with a particular focus on the DR as referred to in its Article 54a(2), i.e. on DR (EU) 2016/161 laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use. The evaluative component mainly focuses on the relevance/ adequacy on the functioning, and the effects of the measures set out in the legal texts and of the system as a whole. More specifically, it considers the following five components: (i) The characteristics and technical specifications of the unique identifier (as defined under the chapter 2 of the DR (EU) 2016/161), (ii) The reporting system (Article 37 of Chapter 7 of the same Regulation), (iii) The repositories system (Chapter 7), (iv) The modality for the verification of the safety measures (Chapters 3, 4, 5 and 6), (v) The overall functioning of the stakeholder-driven governance of the system.

In terms of **geographical scope**, the study covers the territory of the European Union and of the European Economic Area (EEA). The analysis of the trends in the falsification of medicinal products (area 1) provides a global perspective on the situation of the falsified medicinal products, occurrence in EU/EEA. Analysis on the adequacy and functioning of the system (area 2) covers all EU and EEA countries where the DR became applicable on 9 February 2019, with 36 more in-depth interviews and desk research focusing on 8 countries: Belgium, Bulgaria, Denmark, Estonia, France, Ireland, Poland and Spain, as well as two comparator countries: Italy and Greece.

In terms of **timeline**, the study covers the period from 2011 until 2022. Specifically, the analysis tries to point out the differences in terms of the effects of the measures laid down by the FMD and its implementing acts before and after 2019.

1.4 Structure and content of the Draft Final Report

This Final Report is the fourth deliverable of this Study; it aims to provide a sound analysis of findings related to Study and Evaluation Questions along with factually based conclusions. This is a revised version that considers the comments made by DG SANTE.

Answers to the study and evaluation questions

The Study aims to answer to both Study and Evaluation questions as follows:

Study questions	
Topic 1: Trends and developments in the market of falsified medicines	• Q1: What are the trends in the trade of falsified medicinal products over time for countries to which the legislation applies in the EU and the EEA and those that currently benefit from the extended transition period (Greece and Italy)? • Q2: What are the categories of medicinal product and their indications that are of particular concerns and what are the reasons of these concerns? • Q3: How has the falsified medicinal products market changed since 2011 and since 2019, also with respect to increased e-commerce? • Q4: What is the state of play of those medicinal products that may be introduced on the territory of EU/EEA and not put on the market (not intended to be released for free circulation)?
Topic 2: Implementation of the safety features and medicine verification system	• Q5: How many notifications of suspected falsified medicinal products were reported to the European Medicines Agency (EMA) and to the national competent authorities in the EU/EEA? How many of these suspects were eventually confirmed? • Q6: How many unique identifiers have been decommissioned and how many of these have seen their status reverted to active? • Q7: What is the impact of intermarket transactions in the creation of real/false alerts?
Topic 3: Risks associated with the introduction of falsified medicines in the supply chain and stakeholders involved	• Q8: Which are the different stakeholders involved in the pharmaceutical supply chain, their roles and responsibilities for delivering the medicinal product from the manufacturing site to the patient? • Q9: What are the challenges and risks posed by the distribution of falsification of medicinal products?
Evaluation questions	
Relevance and functioning	**EQ1:** To what extent do the measures introduced by DR (EU) 2016/161 and the entire system work well from a technical and functional perspective? Do they still respond to current and future needs relating to the prevention of falsified medicinal products? • EQ1.1: Is the **stakeholder-driven governance** of the system adequate and functioning well? • EQ1.2: To what extent are **the measures related to the UI** adequate and implemented across the EU in a way that it allows to verify the authenticity of medicinal products? • EQ1.3: To what extent is **the repositories system** as a whole suitable and functional (including in terms of protecting commercially sensitive information)? • EQ1.4: To what extent are the **modalities for the verification** of the safety features adequate and well implemented? • EQ1.5: To what extent is the reporting system adequate and effective in contributing to secure the legal supply chain of medicinal products?
Effectiveness/ impact	**EQ2**: To what extent have the objectives of DR (EU) 2016/161 been achieved?

Answers to these questions are included in the Final Report as follows:

Chapters of this Report	**Study / Evaluative Questions answered**
3. Findings related to Study Questions Topic 1 & 3	**Study Questions Q1 to Q4 and Q8 (Topics 1 and 3)**

	• Q1: What are the trends in the trade of falsified medicinal products over time for countries to which the legislation applies in the EU and the EEA and those that currently benefit from the extended transition period (Greece and Italy)? • Q2: What are the categories of medicinal product and their indications that are of particular concerns and what are the reasons of these concerns? • Q3: How has the falsified medicinal products market changed since 2011 and since 2019, also with respect to increased e-commerce? • Q4: What is the state of play of those medicinal products that may be introduced on the territory of EU/EEA and not put on the market (not intended to be released for free circulation)? • Q8: Which are the different stakeholders involved in the pharmaceutical supply chain, their roles and responsibilities for delivering the medicinal product from the manufacturing site to the patient?
4. Assessment of the relevance of the measures set out in the DR	**Evaluative Question 1:** • EQ1: To what extent do the measures introduced by DR (EU) 2016/161 and the entire system work well from a technical and functional perspective? Do they still respond to current and future needs relating to the prevention of falsified medicinal products? (Focus on Relevance / Adequacy)
5. Assessment of the functioning of the safety features set out in the DR	**Study Questions Q5 to Q7 (Topic 2)** • Q5: How many notifications of suspected falsified medicinal products were reported to the European Medicines Agency (EMA) and to the national competent authorities in the EU/EEA? How many of these suspects were eventually confirmed? • Q6: How many unique identifiers have been decommissioned and how many of these have seen their status reverted to active? • Q7: What is the impact of intermarket transactions in the creation of real/false alerts? **Evaluative Question 1:** • EQ1: To what extent do the measures introduced by DR (EU) 2016/161 and the entire system work well from a technical and functional perspective? Do they still respond to current and future needs relating to the prevention of falsified medicinal products? (Focus on Functioning)
6. Assessment of the effects of the measures	**Study Question 9 (Topic 3)** • Q9: What are the challenges and risks posed by the distribution of falsification of medicinal products? **Evaluative Question 2:** • EQ2: To what extent have the objectives of DR (EU) 2016/161 been achieved?

2 Methodological Approach

2.1 Data collection tools used

To achieve the objectives, the Study was structured around four key tasks, presented in the table below.

TASKS	ACTIVITIES	DELIVERABLES & MEETINGS
Task 1: Study Design	• Preliminary field research • Desk research • Methodological approach • Consultation strategy	• Kick-off meeting • Inception Report: April 2023 • Progress meeting: April 2023
Task 2: Consultation activities	• Targeted consultations • Case studies	• Interview reports: July 2023 • Survey summary: July 2023 • **Synopsis Report**: July 2023
Task 3: analysis	• Preliminary analysis (Points of comparison, Application / Implementation review)	• Case study summary report: Beginning of October 2023 • Draft Interim Report: Beginning of October 2023 • Progress meeting: Beginning of October 2023 • **Interim Report** (revised): Mid-October 2023

TASKS	ACTIVITIES	DELIVERABLES & MEETINGS
Task 4: final analysis, synthesis, and reporting	• Final triangulation and answers to the Study & Evaluation questions • Production of the final deliverables of the study	• Draft final report: 16 November 2023 • **Final study report**: 14 December 2023, Revised version and Abstract and executive summary in English, French and German: mid-January 2024 • Meeting to discuss the final report: 20 December 2023

A number of tools have been deployed to gather data for this Study. These tools aim to gather both qualitative and quantitative data through primary and secondary data collection.

2.1.1 Interviews

A minimum of 50 interviews needed to be undertaken for this Study. Throughout the consultation activities, a total of 53 interviews were undertaken as follows:

- 17 interviews with key EU and international institutions and stakeholders, including with DG TAXUD, EMVO, EMA and WHO.
- 36 with national actors in the eight case-study Member States (Belgium, Bulgaria, Denmark, Estonia, France, Ireland, Poland and Spain) and two comparator countries (Italy and Greece).

In addition to these interviews, 19 other interviews have been conducted as part of the case studies. A full overview of the interviews undertaken is presented in Annex 8.2 to this Report.

2.1.2 Surveys

Two Surveys were also deployed for this Study. They targeted both:

- **(i) National Competent Authorities (NCAs) of the EU/ EEA**: 19 questionnaires were received from following NCAS: Belgium, Bulgaria, Czech Republic, Cyprus, Estonia, Finland, France, Germany, Hungary, Ireland, Lithuania, Malta, Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain and Sweden. The questionnaire was accompanied by a data request aiming at collecting key information on trends and development in the falsification of medicinal products.
- **(ii) all other stakeholders involved in the legal supply-chain of medicinal products in the EU/EEA**. The survey aimed at stakeholders was disseminated to 55 organisations/ networks that shared it to members. 205 answers were recorded:

  The largest stakeholder group was pharmacies/persons authorised to supply medicinal products (n=71), followed by full-line wholesalers (n=38) and NMVOs5 (n=31)6

  In terms of geographical distribution, the survey reached 25 EU Member States, the 3 Member States of the European Economic Areas and 2 third countries (Switzerland and the UK). The largest number of responses was generated in Ireland (n=68, 33% of total responses), followed by Austria (n=22) and Portugal (n=11). Most respondents from Ireland were pharmacists.

2.1.3 Case studies

The final data collection tool for this Study is the deployment of Case Studies. These Case Studies aim to delve deeper into the functioning and the effects of the measures introduced by the Delegated Regulation and hence to respond to the evaluation questions concerning the effectiveness and relevance of such measures and their impact on national systems.

6 Case Studies have been undertaken:

- E-Commerce (Belgium / Spain)
- Decommissioning of large batches in Hospitals (France / Ireland)
- Specific case of falsification - Avastin (Bulgaria / Netherlands)

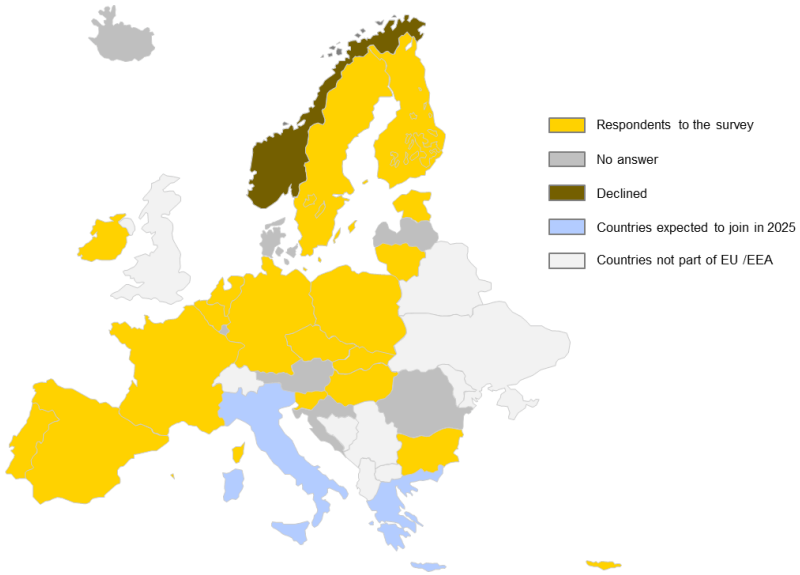
[5] The stakeholder group "NMVO's" contained 30 respondents that are staff that work in a specific national MVO, while one respondent answered as a pharmaceutical association that is on the board of one of the national MVO's.
[6] See section 3.3 for detailed definition of these stakeholder types.

- The use of the EMVS data for investigation purpose (Bulgaria / France)
- Alert Management System (Estonia)
- The delayed deployment of the EMVS in French community pharmacies (France)

The Case Studies consist of both documentary review and interviews. To this end, 19 interviews have been undertaken. Details about the approach adopted for each Case Study, the possible problems encountered, and the solutions found are provided in Annex 8.4.

2.2 Assessment of the data and information gathered

Several challenges have been encountered along the evaluation process.



Delays in obtaining feedback on the NCA Survey questionnaires. These delays can be partly explained by the summer period as well as vacancies encountered at country level. To mitigate these obstacles, the Study team has sent multiple reminder emails over the course of several months to increase the response rates.

Incomplete overview of national contexts and implementation of the DR as 19 NCAs7 (out of 28) responded to the survey. The same applies to data requests, where only 16 sets of data were received from the NCA. Despite this partial view, the Study team considers it has sufficient inputs and evidence to draw robust conclusions, as the respondents allowed for a balanced representation (size of countries, geographical situation, etc.).

Some difficulties reaching certain categories of stakeholders to conduct interviews at national level (e.g., patients' organisations contacted declined participating in the study and other actors and NCA in Denmark did not reply to our invitations, despite multiple reminders being sent from both DG SANTE and the Study Team). The initial scope of interviewees was enlarged to law enforcement authorities, and a range of 2 to 6 interviews per country was undertaken depending on the availability. More information on this topic is given in the interview report, provided with the synopsis report.

The lack of data on falsified medicinal products and the absence of comparable data before 2019 hinder trends analysis: there was no systematic monitoring and reporting of confirmed cases of falsification prior to the entry into force of the DR (EU) 2016/161. No structured and consolidated data on falsified medicinal products was available at EU level before the deployment of the repositories system as from 2019. Data from 2011 and 2017 on the number and characteristics of falsified medicinal products are likely to be based on underestimated figures. Also, we can note an absence in monitoring of the volumes of the confirmed cases of falsification: EMA does not currently track the volumes of confirmed cases identified, nor do NCAs. Thus, the number of "cases" reported do not indicate the actual number of falsified packs that were identified. To mitigate this issue, we asked EMA for an estimate of the "average" volume of a confirmed case, which seems to be about 30 packs. Finally, specific data was not always accessible in a centralized way or even collected at national level, such as the number of UI reverted back to active.

In the end, the qualitative material collected **proved sufficient** to carry analyses desired by the evaluating team. **The quantitative analyses were conducted based on available data and with an awareness of inherent limitations.**

[7] Belgium, Bulgaria, Cyprus, Czech Republic, Estonia, Finland, France, Germany, Hungary, Ireland, Lithuania, Malta, Netherlands, Poland, Portugal, Slovakia, Slovenia, Spain and Sweden. Italy and Greece have been contacted for an interview due to their specific situation.

*Please note that in this Report **the term "stakeholder",** unless otherwise stated, **refers to the private actors that constitute the legal pharmaceutical supply chain**, and notably, manufacturers, importers, parallel traders, wholesalers, hospital and community pharmacists.*

3 Findings related to Study Questions Topic 1 & 3

This chapter aims to respond to

- **Study questions Q1 to Q4 (Topic 1) in *Section 3.1***:
  - Q1: What are the trends in the trade of falsified medicinal products over time for countries to which the legislation applies in the EU and the EEA and those that currently benefit from the extended transition period (Greece and Italy)?
  - Q2: What are the categories of medicinal product and their indications that are of particular concerns and what are the reasons of these concerns?
  - Q3: How has the falsified medicinal products market changed since 2011 and since 2019, also with respect to increased e-commerce?
  - Q4: What is the state of play of those medicinal products that may be introduced on the territory of EU/EEA and not put on the market (not intended to be released for free circulation)?
- **Study question Q8 and Q9 (Topic 3) in *Sections 3.2 and 3.3*:**
  - Q8: Which are the different stakeholders involved in the pharmaceutical supply chain, their roles and responsibilities for delivering the medicinal product from the manufacturing site to the patient?
  - Q9: What are the challenges and risks posed by the distribution of falsification of medicinal products?

Key findings

- **Available data reflect an increase in the number of falsified medicines in the European legal chain towards 2017** (according to the Regulation's 2015 Impact Assessment, whereas only 2 cases of falsified medicinal products were reported in 2012, 12 cases were reported in 2013 and 15 in 2015) **and a decrease thereafter.** According to EMA data, confirmed cases went from 24 in 2017 to 3 cases in 2022. However, collected data on nationally authorised medicinal products, which are based on published studies and questionnaires collected from public authorities during this evaluation, are too partial and inconsistent to draw robust conclusions on falsification trends in the EU/EEA. This is to be linked with a lack of centralised monitoring of falsified medicines at the EU/EEA level as well as diverging tracking and recording processes (as it will be explained further in this Report).
- According to data and qualitative inputs collected, **falsified medicines are mainly traded in the illegal supply chain as confirm the seizures in the last years**. But the permeation into the legal supply chain from criminals and offenders creates a risk of falsified medicines being distributed to patients. In particular, the rise of online sales raises an important risk of distribution of falsified medicines, as these sales offer criminals a relatively accessible gateway into even the most tightly controlled markets. However, it should be noted that legal online sales are quite secure because they are very closely regulated and controlled.
- **Expensive and lifestyle medicines are the most concerned by falsification**. Indeed, the former present the largest economic incentives for falsifiers while the second are widely purchased online by customers concerned about their privacy but less scrupulous about the quality of the product.
- The introduction of falsified medicinal products in the legal supply chain **can cause damages for all the stakeholders involved** in terms of economic loss, reputational damage, less confidence from the public, etc.

3.1 Preamble

3.1.1 Introduction on the EU pharmaceutical market

Europe[8] is the second largest market globally for medicinal products and the first global exporter of medicinal products. In 2022, the world pharmaceutical market was worth an estimated 1 222 billion[9] euros. With approximately 275 billion euros in sales, Europe[10] accounts for 22,4% of the global market, only behind North America which represents 52,3% of global sales. With some major industrial actors, such as Sanofi (38 billion euros revenue in 2021 - France), Astrazaneca (€38 billion - UK) or Glaxosmithkline (47 billion euros - UK), the European pharmaceutical industry plays a major role in pharmaceuticals worldwide. In 2022, the countries of the EU exported approximately 482 billion euros of pharmaceutical products, or 66% of the world's total exports in pharmaceutical product (735 billion euros)[11]. Out of the €482 billion in exports, 59% (286 billion euros) was intended for the Extra-EU market and 41% (196 billion euros) for the EU market.

A large number of stakeholders compose the legal pharmaceutical supply chain in Europe. Estimations vary according to sources:

- **Manufacturers/MAH**: 3 800 manufacturers in the EU (Eurostat) and 2 900 MAH (EMVO).
- **Wholesalers**: 2 020 wholesalers for the EU 25 plus Norway and Switzerland (2015 Impact Assessment) and 4 100 wholesalers in the MS currently participating in the EMVS (EMVO)
- **Community pharmacists**: 154 000 community pharmacies in the EU (2015 Impact Assessment) and 118 000 pharmacies in the MS currently participating in the EMVS (EMVO)
- **Hospital pharmacists**: 21 000 hospital pharmacies in the EU and 7 700 Healthcare institutions in the MS currently participating in the EMVS (EMVO)

While manufacturers usually operate in several MS tough a network of national facilities, the number of wholesalers, community and hospital pharmacies, which essentially serve one local market, **varies greatly between Member States:**

- Wholesalers: Germany (660 out of 4100), Czech Republic (435), Romania (427) and Poland (426) stand out with the largest concentration of recorded wholesalers in the countries participating in the EMVS.
- Community pharmacists: Spain (22 200 out of 118 000), France (20 700) and Germany (18 300) have the largest number of community pharmacies in the EMVS countries according to EMVO.
- Hospital pharmacists: France (2 300 out of 21 000), Poland (1 600), Romania (610) and Spain (600) have the largest concentration of hospital pharmacies in the EMVS countries.

3.1.2 Problem definition: falsified medicinal products

"Falsified medicinal products" have been defined by Directive 2011/62/EU (as these was no previous common definition across EU MS), as follows:

> A falsified medicinal product is a medicinal product that has a false representation of (i) "its identity, including its packaging and labelling, its name and its composition", or (ii) "its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorisation holder", or (iii) "its history, including the records and documents relating to the distribution channels used".

Thus, a falsified medicinal product may contain wrong ingredients, or ingredients - including excipients - of low quality or in the wrong doses, have a fake packaging and be deliberately mislabelled with respect to their identity or source, and have not passed through regular evaluation of quality, safety and efficacy as required for the EU authorisation procedure.

Falsified medicinal products must be distinguished from counterfeit medicinal products, which are products which infringe intellectual property rights (IPR) or trademark law, and thus correspond to a specific category of violation in term of pharmaceutical law. Nonetheless, counterfeit products are often also considered as falsified products in the sense that they involve, most of the time, a false representation of their identity (e.g., incorrect description of their ingredient), history (e.g., product not fulfilling obligations related to safe transport and storage) or

[8] This Study is focusing on EU/EEA countries, but the Context section takes into account Europe countries more globally (e.g. including Belarus, Turkey, Russia and Ukraine), depending on the data available. This is clarified where needed.
[9] EFPIA (2023), The pharmaceutical industry in figures. Key Data, 2023.
[10] Includes Belarus, Turkey, Russia and Ukraine.
[11] UN Comtrade Database.

sources (e.g., product not manufactured in the declared sites). For that reason, **statistics on counterfeit medicinal products are often used as a proxy** to estimate trends in falsified medicinal products.

The WHO established in 2017 its own definition of **"falsified medicinal products"** to ensure a common language between its Member States. These are described as "medicinal products that deliberately/fraudulently misrepresent their identity/composition or source". In this definition, the intention to deceive is required and false representations of the history of the medicinal product are not taken into account.

3.2 Trends and developments in the market of falsified medicinal products

3.2.1 Available data, while reflecting an increase in the number of falsified medicines prior to 2017 and a decrease thereafter, are too partial and inconsistent to draw robust conclusions on falsification trends in the EU/EEA

Data prior to 2016

Past data show a sharp increase in the number of counterfeit medicinal products detected in the EU/EEA in the late 2000s. The 2008 Impact Assessment[12] reported that the seizure of counterfeit medicinal products at EU customs borders went from 560 000 articles to more than 2 500 000 articles in 2007, an almost fivefold increase in three years. While the WHO calculated that counterfeit products could represent 1% of market share in industrialized economies[13], industry studies of 2008 estimated that the volume of counterfeit medicines were increasing by 20-100% per year[14]. In terms of categories of products targeted, a trend towards the counterfeiting of life-saving medicines, such as anti-cancer products, was identified in the same period in the 2008 Impact assessment.

More recent data also show an increase in the number of falsified medicines in the EU/EEA supply chain between 2011 to 2016. The 2015 Impact Assessment accompanying the DR[15] identified 29 cases of falsified medicines found in the EU/EEA legal supply chain between 2012 and 2014 included. When contacted, EMA provided an estimation of **30 potential cases of falsification detected in the EU/EEA** between 2011 and 2016 included. This increase, which implies an intensification of falsification activities, also reflect the motoring obligation of falsified cases made by the FMD since 2017.

	2011	2012	2013	2014	2015	2016
2015 Impact Assessment	*N/A*	2	12	15	*N/A*	*N/A*
EMA	2	1	2	4	6	15

However, these data must be interpreted with caution. The authors of 2015 Impact Assessment warned that the "cases" of falsified medicines identified were not sufficient to provide reliable statistics. Also, prior to the adoption of the DR, the EMA did not keep distinct records for falsified medicines and other issues involving medicines in the supply chain, such as defect or theft. In addition, EMA did not provide the precise number of packs involved in each case, which generally vary between 10 and 100, averaging 30. As such, based on the data available, it is not possible to assess with certainty the exact trends in medicine falsification in the EU/EEA prior to 2016.

Taking into account the limitation on the data reported, a general increase in the number of falsified and counterfeit medicinal products was noticeable after 2010. This situation was exacerbated by a number of factors identified in the 2008 and 2015 Impact Assessment cited above, such as:

- the insufficient or **inefficient medicine protection measures** in the EU (e.g., the lack of effective and harmonized requirement to protect the packaging of medicines in eth EU);
- **the multiplication of points of entry** for falsified products into the legal market with the internationalisation and complexification of supply chains (e.g., intervention of a number of wholesalers, parallel traders, etc.);

[12] Impact Assessment accompanying the Proposal for a Directive of the European Parliament and of the Council amending Directive 2001/83/EC as regards the prevention of the entry into the legal supply chain of medicinal products which are falsified in relation to their identity, history or source (COM(2008) 668 final).
[13] Substandard and falsified medical products (who.int).
[14] Mike Muller, Director of global anti-counterfeiting operations, Eli Lilly, www.scriptnews.com, 27 June 2008.
[15] European Commission (2015), *SWD (2015) 189 final.*

- **the lack of enforcement of "Good manufacturing practices"** for the production of API in the EU and in third countries supplying the EU;
- **the overall lack of enforcement** by Member States and EU authorities of the provision against falsification and counterfeiting.

For the authors of the 2008 and 2015 Impact Assessments, the overall upward trends in term of falsification and counterfeiting, coupled with the aggravating factors mentioned above, justified the elaboration of a European medicine verification system.

Data from 2016

The European and National actors contacted **struggled to provide data regarding the number of confirmed cases of falsified medicinal products** for several reasons described below. 16 NCA shared their data and the others simply did not respond to our request.

Data from 2016 show very few confirmed cases of falsified medicines in the legal supply chain of the EU/EEA. Two types of data were collected and need to be distinguished because they have a different scope: data from NCA (treat all products with a marketing authorization) and data from EMA (focusing on medicinal products with a European marketing authorization).

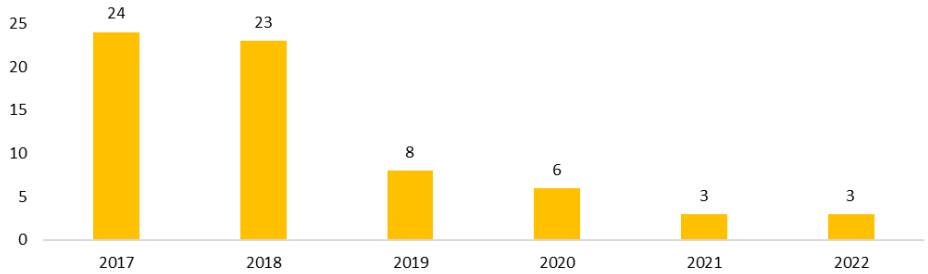
Out of the **16 NCAs** who have shared their data, only two reported one confirmed case of falsification since 2019 (one case in Belgium in 2020 and one case in Finland in 2019).

Data provided by EMA are higher than the data provided by NCA. They show a **net downward trend since 2017** (beginning of data recording). Confirmed cases each year went from 24 in 2017 to 3 cases in 2022 according to EMA[16].

Benchmark focus

The low number of cases reported in the EU/EEA are also reflected in Italy and in Greece. **The Italian NCA reported no confirmed cases of falsified drugs** in the legal chain since the implementation of Italy's own medicine verification system in 2002. The **Greek NCA also reported no case of falsification** in the legal chain since the implementation of a national verification system in 1987.

Figure 2 Number of confirmed cases of falsified medicines for centrally authorized products (2017-2022)

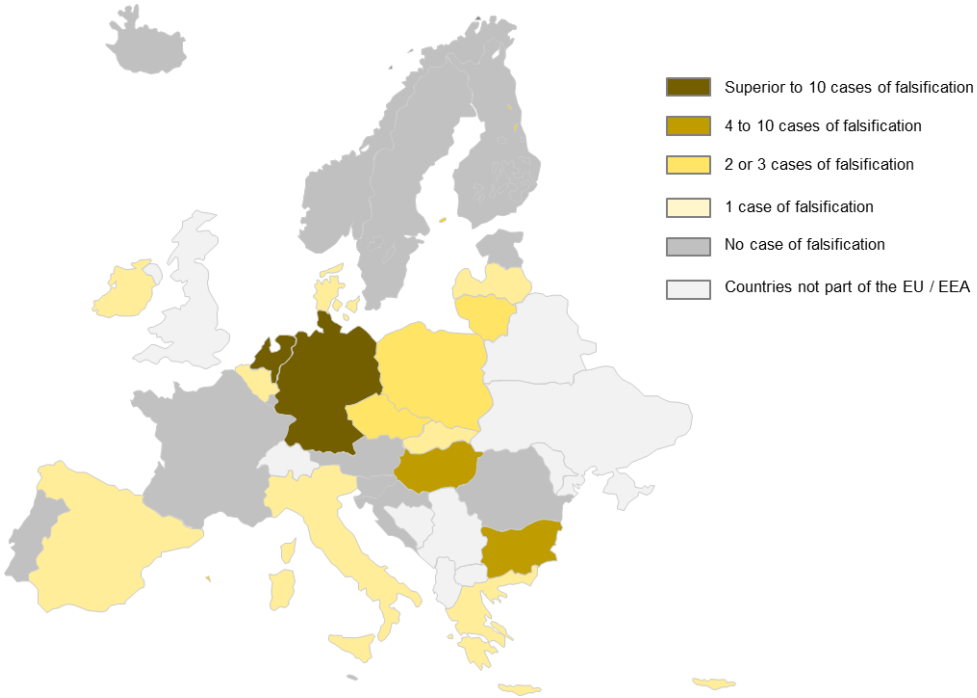


Source: EMA – EY Elaboration

The countries where EMA has recorded the most confirmed cases of falsification between 2017 and 2022 are the Netherlands (21 cases) and Germany (13 cases)17, both with a peak in 2017-2018 (11 cases in the Netherlands in 2018 and 5 cases in Germany in 2017) and few confirmed cases thereafter (1 in the Netherlands and 4 in Germany between 2019 and 2022 included)). Due to the confidentiality of the data on these confirmed cases, no information on the nature of the falsified medicines or the volume and categories involved were shared with the Study Team. The map below shows the distribution of confirmed cases recorded by EMA since 2017, as reported in September 2023.

Figure 3 Breakdown of the confirmed cases of falsification registered by EMA between 2017 to 2022

[16] Please note that these figures are not similar to the ones provided in the Inception Report because EMA updated them since
[17] According to EMA, cases are normally attributed to the country where it was identified. Both NCA and MAH can report cases of falsification to EMA. However, still according to EMA, number reported are not always consistent and one case can be detected in several countries.



Source: EMA data – EY Elaboration

These low numbers reported by EMA and NCAs are aligned with the inputs collected from the stakeholders of the pharmaceutical supply chain. Out of the 152 respondents from the survey to stakeholders of the pharmaceutical supply chain, seven noted they had identified cases of falsification since the implementation of the EU verification system. These were reported by stakeholders based in Czech Republic, Belgium, Slovakia, Germany, Portugal, Germany and one EU level organisation. The perception of trends in medicinal falsification by the stakeholders is also aligned with the decreasing numbers of confirmed cases reported. Out of the 205 respondents, 43[18] (21%) perceived a decrease in the number of falsified medicines since the FMD was introduced in 2011, 121 (59%) did not perceive a change, 13[19] (6%) perceived an increase, and 28 had no opinion (14%).

These rare cases of falsification must nevertheless be interpreted with caution in view of the numerous limits on the data reported.

- Firstly, **the reporting of suspected and confirmed cases of falsification is often partial and inconstancies were detected between reports across European and National authorities**. For examples, Hungary reported to the evaluation team 0 confirmed cases in 2019, but EMA 3. Lithuania also reported 0 confirmed cases in 2020, but EMA 2. More generally, due to a "lack of awareness of the phenomenon", there seems to be a lack of willingness to consistently record data and to share information on medicine falsification and diversion, as reported by Marco Dugato, a researcher at Transcrime and the Università Cattolica del Sacro Cuore[20]. The topic of reporting is further developed in Section 5.5.
- Secondly, whilst NMVOs have no authority to qualify a case as a confirmed case of falsification (which is usually the responsibility of the NCA) and do not keep any records, some NCAs rely on other authorities to monitor the number of confirmed cases (such as the customs or the judicial authorities, which deal with medicines thefts and trade of illegal drugs altogether).
- Thirdly, **records do not always differentiate between falsification cases and other incidents involving medicines.** NCAs pointed out that the same database was used to record cases of falsification in the legal supply chain, cases of falsifications in the illegal supply chain and cases of stolen medicinal packs, as these situations were often difficult to distinguish.

[18] Stakeholders from Belgium (n=7), Portugal (n=5), Austria (n=5), Germany (n=5), Ireland (n=4), Denmark (n=3), Poland (n=3), Romania (n=2), Bulgaria (n=2), Hungary, Luxembourg, Czech Republic, Netherlands, Spain, Greece and Malta (n=1, respectively).
[19] Stakeholders from Austria (n=5), Ireland (n=4) and Cyprus, Denmark, Greece (n=1, respectively).
[20] Contrasto al traffico illecito di farmaci: appello alla condivisione dei dati - AboutPharma.

- Finally, **the incomplete implementation of the verification system makes it difficult to reliably assess the trends in terms falsification** (still 12,7% of the pharmacy hospitals and 0,8% of the community pharmacies were not connected to the system in September 2023 according to EMVO, and the decommission rate averaged 75,4% in 2023 Q2). In that context, it is difficult to assess the real proportion of medicinal products being falsified in the EU/ EEA, as the authenticity of many these products is not consistently verified. In turn, this caveat can contribute to the very low number of confirmed cases of falsification detected by the EMVS.

Besides, reports indicate that falsified medicines are mainly found in the illegal supply chain, as explained in the paragraph below.

3.2.2 Falsified medicines are mainly traded in the illegal supply chain, which can impact the legal supply chain

The NCAs surveyed confirmed that almost all falsified medicinal products were found in the illegal market. In 2021 for example, the European Medicine Agency reported 3 confirmed cases of falsified medicines found in the legal supply chain in EU/EEA. The same year, during operation Shield II[21], 25 million units of counterfeit and misused medicines and doping substances worth 63 million euros were seized[22]. Between 2016 and 2019, 123 million units of medicines worth 500 million euros were seized in Europe under the MISMED operation, the predecessor of SHIELD[23].

The permeation into the legal supply chain from criminals and offenders creates a risk of falsified medicines being distributed to patients. As reported by the Bulgarian Drug Agency (BDA), a number of cases of medicine falsification involved the diversion of medicines in an out of the legal supply chain, with the intervention of criminals. For example, the BDA reported that a pack of Enbrel (etanercept), an anti-inflammatory medicine, was sold in 2022 by a pharmacist to a criminal without decommissioning it. The criminal then falsified the pack of medicine by replacing its content with crayons and selling the syringes in the black market. Having not noticeably altered the ATD, he was able to resell the falsified pack of Enbrel to a local wholesaler, who reintroduced it in the legal supply chain by supplying the Dutch wholesaler. More recently, in October 2023, falsified packs of Ozempic were found at wholesalers in Germany and in the UK after a surge the number of illegal websites selling the packs in question[24] (*the case is described in more details at the end of section 3.1*). Spanish authorities have also raised concerns regarding recent incidents of theft or loss of medicinal products within the wholesale supply chain, indicating that such occurrences may potentially lead to an upsurge in the circulation of pharmaceuticals through the illegal supply chain.

These cases illustrates that the falsification of medicines often involves both the legal and the illegal supply chains, stressing the importance to better protect the legal supply chain from offenders. This is typically the case for medicines traded online, where the distinction between legal and illegal transactions is often difficult to make.

Benchmark Focus

The situation described above is also reflected in Italy. The Italian NCA reported that falsified medicines were exclusively found in the illegal market in Italy. As an example, Operation "Vulcano", coordinated by AIFA, revealed that up to 3 cases of theft from Italian hospitals per week were occurring up to May 2014. The stolen medicines were then, for the most part, falsified and reintroduced in other European markets, such as in Germany and Finland, through unauthorized wholesalers. The operation has led to 80 arrests[25].

3.2.3 The rise of online sales raises an important risk of distribution of falsified medicines to the public

The online pharmacy market is undergoing a significant expansion. Between 2019 and 2023, online revenues in Europe surged from 3,31 billion euros to 5,48 billion euros for pharmaceutical products. Projections indicate a

[21] Operation SHIELD II is a European effort targeting the traffic of counterfeit and misused medicines and doping substances. Coordinated by Europol and led by by the French Gendarmerie (Gendarmerie Nationale/OCLAESP), the Finnish Customs (Tulli), the Hellenic Police/Financial Police Division (Ελληνική Αστυνομία / Διεύθυνση Οικονομικής Αστυνομίας) and the Italian Carabinieri Corps (NAS Carabinieri), Operation SHIELD II took place between April and October 2021.

[22] Europol (2021), *544 arrests and €63 million of fake pharmaceuticals and illegal doping substances seized.*

[23] French Ministry of Home Affairs (2020), *Drug trafficking: an ever-intensifying battle* (Trafic de médicaments : une lutte toujours plus intense).

[24] Intercept fake Ozempic, German drug regulator tells pharmacies, distributors | Reuters.

[25] Giorgio, Domenico & Russo, Diana. (2020). *MEDICRIME VS VOLCANO A practical case study on how the Council of Europe Convention could improve the fight against pharmaceutical crime.*

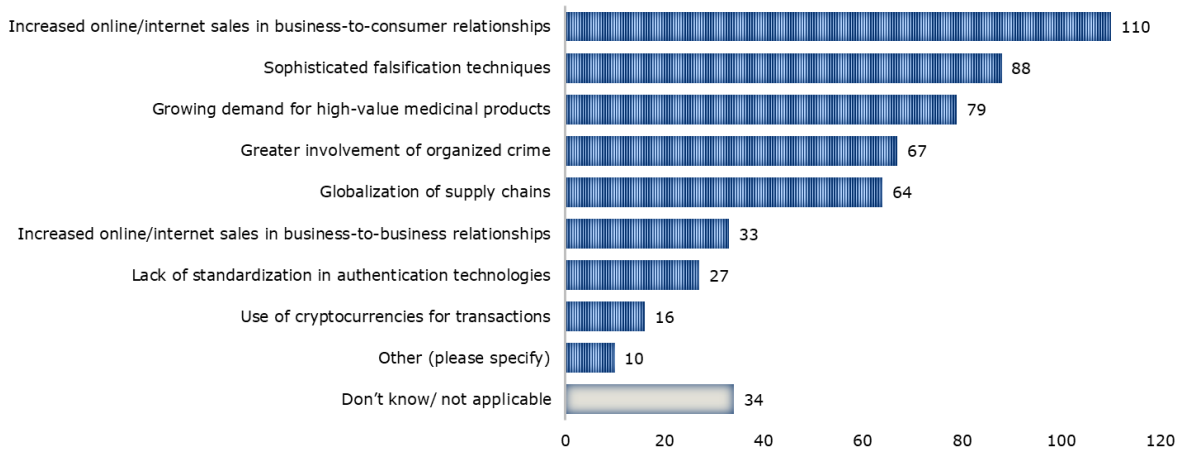
further increase to 7,91 billion euros by 2027, an almost threefold increase within a decade[26]. The COVID-19 crisis has accelerated the use of digital technology in general and online sales of medicines in particular.

However, **the rise of online sales also offers criminals a relatively accessible gateway into controlled markets**. As indicated by the WHO[27], medicinal products purchased online often do not meet established quality standards. These substandard products encompass critical, life-saving medications as well as medications associated with lifestyle choices, such as sexual enhancers and weight-loss medicines. As the e-commerce markets for both types of medications continue to expand, and online pharmacies gain popularity especially in high-income countries, the risk of encountering falsified medicinal products becomes more pronounced.

In 2022 alone, Belgium Customs seized 2 951 packs containing falsified medicines ordered online. More recently, as described at the end of this section, the recent surge in demand for Ozempic has been met with the rapid increase in the number of illegal websites selling falsified version of the antidiabetic. Overall, the issue of illegal online sales of falsified medicines is amplified by the ease of ordering online, the challenge for customs to control the large volume of small parcels exchanged each year, and the low public awareness regarding the health risks involved with falsified medicinal products.

The challenges posed by online sales is also reflected in the perception of the risks by the actors of the pharmaceutical supply chain. Indeed, more than 50% (110 out of 205) of the respondents to the survey to stakeholders identified the increase in online sales as an emerging risk in terms of medicinal falsification. This is one of the most cited risks, in addition to the development of falsification techniques (88 out of 205) and the growing demand for high value medicinal products (79 out of 205), as shown in the figure below.

Figure 4 What are the new challenges or trends in the falsified medicinal products market that have emerged in recent years? (205 respondents)



Source: Survey to stakeholders of the pharmaceutical supply chain – EY/Ramboll elaboration

However, even if the bulk of stakeholders identified online sales as challenging, **some divergences emerged among stakeholders on this topic**. For example, several stakeholders expressed concerns about its potential to increase the risk of introducing falsified medicinal products into the market, especially through illegal online platforms. Others[28], however, saw e-commerce as an opportunity for safe and legitimate sales when properly regulated and tied to licensed pharmacies. Collaboration with physical pharmacies (i.e., implying for example that online pharmacies must operate physical points of dispense or enter a partnership with community pharmacies) was thus deemed essential by some respondents to reduce risks. Others emphasised the importance of effective regulations and information dissemination to prevent e-commerce from becoming a gateway for falsified medicinal products.

In that context, it is indeed important to **recall the distinction between the legal and illegal online channels**:

- **The legal sale of medicinal products**: this market is highly regulated, both at national and European level. At the latter level, for instance, an EU Common Logo for online medicine retailers

[26] "Online Pharmacy – Europe", accessed on 12 September 2023.
[27] World Health Organization, "Global Surveillance and Monitoring System for Substandard and Falsified Medical Products", p 15.
[28] Primarily business associations, designated wholesalers, distributors, and pharmacies/persons authorized to supply medicinal products.

has been introduced and must be displayed on the websites of online retailers, who first must be approved and registered with the competent authorities of their country. This channel benefits from rather positive opinions from the actors consulted, given the important level of supervision from the authorities. Specific studies and interviews conducted in Spain and Belgium, for example, revealed that the two legal national e-commerce channels did not present any particular risks in terms of falsification. No cases of falsification have been recorded in the two legal e-commerce circuits. Safeguards are also always present: in Belgium, for example, medicines have to be picked up in a physical pharmacy even if the purchase was made online.

- **The illegal sale of medicinal products**: this category corresponds to sales from illegal or unauthorized online dealers. It is this category that concentrates the most cases of falsification.

Also, an issue to keep in mind is **the evolution of current medicine falsification trends compared to the time the DR was written**, especially given the growing importance of the internet in shaping demand and supply of falsified medicines. Notably, the role of social media and "online influencers" has taken an unforeseen importance in shaping demand for medicinal products and, in turn, supply from falsifiers. The recent case of Ozempic (semaglutide) falsification, developed in the next paragraph, provides an example on how the advertisement of the weight loss properties of this medicine by online influencers has boosted demand, incentivising falsifiers to enter the market given the relative shortage of production from authorized manufacturers. Overall, the growing importance of the internet in shaping demand and supply of falsified medicines makes trends in falsification **more volatile, reactive, and difficult to monitor and regulate.**

3.2.4 Expensive and lifestyle medicines are the most concerned by falsification

Based on the products seized from the illegal market reported by NCAs, **the falsification of medicinal products mainly concerns expansive medicines and lifestyle medicines[29].** Information shared by NCAs on medicines found in the illegal market show that expensive medicines, such as anti-cancer injections, and lifestyle medicines, such as muscle and sexual enhancers, are the most commonly falsified medicines. Indeed, the former presents the largest economic incentives for falsifiers while the latter is widely purchased online by customers concerned about their privacy but less scrupulous about the quality of the product. As an example, the three confirmed cases of medicine falsification detected by the Finnish NCA (in 2014, 2018 and 2019) involved "Herceptin", "Velcade" and "Alinta" (anti-cancer products), which typically retail at around 1,000 euros a vial in EU/EEA. On the other hand, Estonia, Poland and Spain reported that "Cialis" and "Viagra" (used to treat erectile dysfunction) are amongst the most falsified products found on the illegal supply chain. In the case developed in the box below, demand for Ozempic surged in Europe and globally after the medicine was advertised on internet as a weight-loss medicine, leading to an increase in supply from falsifiers.

Benchmark Focus

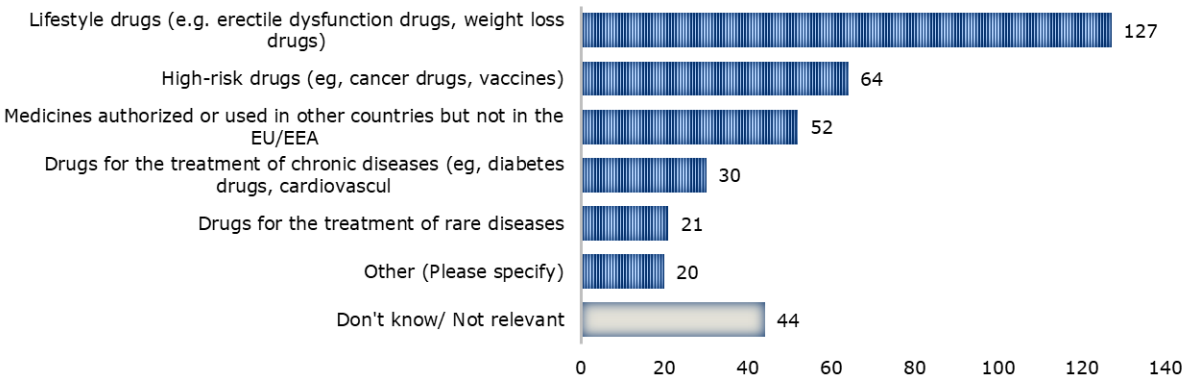
In comparison, the Italian NCA reported similar trends in Italy for sexual and muscular enhancers, and anti-hepatitis being the most commonly falsified medicines found in the illegal market. The Greek NCA also reported anabolic and lifestyle products as the main medicines currently subject to falsification in Greece.

A couple of NCAs reported that **these types of products were often ordered though illegal online platforms**. As such, among the 2 951 parcels of falsified medicines seized by the Belgium Customs in 2022, mentioned above, 62,28% contained lifestyle medicines, 51,52% of which being sexual enhancers.

The stakeholders of the pharmaceutical supply chain consulted reported the same observations as the NCAs. When asked if there were any specific categories of medicinal products subject to the EU safety features that are of particular concern in terms of falsification, most respondents to the survey (61%, or 127/205) answered lifestyle drugs (e.g., pharmaceuticals to treat erectile dysfunction and to foster weight loss), followed by high-risk drugs (e.g., cancer medicines, vaccines) (31%).

[29] To a lesser extent, the falsification of other categories of medicines has also been reported by the authorities consulted. They concern a wide category of products, such as vaccines, dermatological medicines, antiparasitic/ insecticides or anti-infective products.

Figure 5 Are they any specific categories of medicinal products subject to the EU safety features that are of particular concern in term of falsification? (205 respondents)



Source: Survey to stakeholders of the pharmaceutical supply chain – EY/Ramboll elaboration

Due to the confidentiality of the data on these confirmed cases, the study team did not get access to specific data on the categorization of the most falsified medicines in the legal supply chain. However, EMA has confirmed orally that **the categories described above (based on the products seized from the illegal market) are also valid for products in the legal pharmaceutical supply chain**.

The 2023 surge of falsified Ozempic (semaglutide)

Several people were hospitalized in Austria in October 2023 after taking falsified dozes of Ozempic[30]. This incident happened while demand for Ozempic surged, as the medicine advertised on social media for its weight-loss properties had become relatively difficult to obtain, creating incentives for falsifiers to enter the market. Ozempic, a medicine produced by the Danish company Novo Nordisk, was developed in 2012 to treat type 2 diabetes. As a side effect, its active principal ingredient, semaglutide, can also cause rapid weight loss.

Falsifiers' interest for Ozempic increased as the relative availability and accessibility of the medicine decreased in the course of 2022-2023. One the one hand, the interest of the public for Ozempic surged in late 2022 and earlier this year as online "influencers" started to praise the drug for its weight loss effects[31]. In March 2023, the hashtag #Ozempic had 600 million views on the ex-Twitter. This has caused a number of shortages, such as in Canada[32] or in Australia[33]. On the other hand, public authorities, such as in France, began to demand doctors not to prescribe Ozempic for "off-label" usage (i.e., different purposes than those intended) or to new patients with light diabetes. In turn, the surge in demand and the restriction on the offer encouraged falsifiers to enter the market. For example, in October 2023, the Health Products Regulatory Authority of Ireland reported 254 seizures of falsified medicines claiming to contain semaglutide, against 32 in 2022[34].

While these falsified medicines were **mostly found on illegal websites**, as the manufacturers warned[35], some falsified were also **found within the legal supply chain,** and notably in wholesale batches in the UK and in Germany[36]. Some reports indicated that packs were identified by the EMVS during scanning[37].

Overall, this case illustrates the main drivers of medicine falsification and the risks involved. Demand for Ozempic surged as its consumption as a lifestyle medicine (here, for weight loss purpose) soared. As authorities began to limit the access to Ozempic, falsifiers began to offer increasing quantities of falsified packs, and notably online. In turn, some packs ended in the legal supply chain and were eventually identified by the EMVS.

[30] Suspected fake Ozempic puts several in hospital in Austria | Reuters
[31] Ozempic: How a TikTok weight loss trend caused a global diabetes drug shortage - and health concerns | Euronews
[32] Ozempic supply - English (pharmacists.ca)
[33] About the Ozempic (semaglutide) shortage 2022 and 2023 | Therapeutic Goods Administration (TGA)
[34] Irish Examiner (26/10/2023), "Seizures rise of claimed weight-loss ingredient"
[35] Novo Nordisk warns online offers of fake Ozempic, Wegovy are rising | Reuters
[36] Intercept fake Ozempic, German drug regulator tells pharmacies, distributors | Reuters
[37] La Stampa (25/10/2023), "Austria, some people end up in hospital after taking counterfeit version of the antidiabetic Ozempic"

3.3 Role of the stakeholders in the pharmaceutical supply chain and public / regulatory authorities and risks associated with the introduction of falsified medicines

Methodological note: Please note that this section only presents the role of the stakeholders in the pharmaceutical supply chain. It does not describe the responsibilities that they are facing under the DR, that is presented in next Section 5.3.2..

Apart from large companies, the "pharmaceutical sector" in a broad sense includes a variety of other actors, ranging from suppliers of medicinal product ingredients (in particular active pharmaceutical ingredient or API), parallel traders, wholesalers, parallel traders, retailers/pharmacies, and other traders (brokers, etc.). **The increasing complexity of production, manufacturing and distribution systems for medicinal products in EU/EEA provides opportunities to falsifiers and counterfeiters** to permeate the legal supply chain and put falsified medicinal products on the market. The fact that possibilities for falsification exist throughout the legal distribution chain makes the threat of falsification more diffuse, complex to target and more difficult to tackle consistently across MS. This also leads to a wide diversity of systems across EU/EEA as well as a corresponding diversity of national authorities in charge of addressing these risks.

Manufacturers and parallel traders

Manufacturers at EU and national levels are **responsible for producing medicinal products**, ensuring that they adhere to Good Manufacturing Practice (GMP) guidelines and other quality assurance checks for both the active ingredients and excipients. They must be distinguished between originator companies, who sell brand medicines, and generic manufacturers, who sell generic medicine after the expiration of the originator product's patent. **Parallel trade refers to the process where a pharmaceutical company distributes a centrally authorised medicinal product from one EU Member State to another**; this often requires the repackaging of the products. Available data outlines that over half of all parallel imports in EU/EEA (in terms of value in euro) were found to originate from high-income countries (e.g., Germany, France, Belgium etc.). In particular, the German market accounts for more than half of the total sales of parallel imported medicines in Europe. particular, the German market accounts for more than half of the total sales of parallel imported medicines in Europe. As for wholesalers, parallel traders must adhere to Good Distribution Practices (GDP) guidelines.

While parallel distributors in applying good manufacturing and good distribution practices have detected incidences of falsified medicines, in theory, although there is no evidence that this has ever happened, the introduction of falsified medicines in the legal supply chain at the level of parallel traders could also happen and cause reputational damages to the companies concerned and affect the overall trust of the public into the legal distribution by parallel traders of pharmaceutical products.

Full line/ designated/ generic wholesalers, distributors and brokers

Wholesale distributors are responsible for **purchasing, storing and selling medicinal products**. They must adhere to Good Distribution Practices (GDP) guidelines, verify the authenticity of the products they receive, maintain records of all transactions, and ensure that they only supply medicinal products to authorised entities. They also need to register with the competent authority in the Member State where they are established. Distribution falls in different actors' responsibilities. Depending on the country, manufacturers either sell their products via a few pre-selected wholesalers, or wholesalers can act as independent intermediaries between manufacturers and buyers. 'Full line' wholesalers, who distribute all the medicines in demand in a specific market, must also be distinguished from 'short-line' wholesalers, who specialize in a limited range of products. Brokers on the other hand negotiate the sale or purchase of medicinal products on behalf of other parties without physically handling the products.

In addition to the reputational cost incurred by wholesalers, should falsified medicines be introduced into their stock and later be distributed, they are also exposed to economic losses. Most specifically, if a wholesaler purchases a falsified medicine that reveals to be falsified, the wholesaler has the obligation to replace it with a genuine product and to bear the full cost involved.

Besides, the distribution of falsified medicines through illegal channels, and especially online, enters directly in competition with products legally distributed.

Pharmacies and other entities authorized to dispense medicines to patients

Pharmacies and other authorised entities, such as those within prisons, universities, hospice care centers, and other specialised institutions, **supply medicinal products to the public**, either directly or through distance

selling (e.g., online pharmacies). There are about 170 000 pharmacies in the EU, with 154 000 community pharmacies and 21 000 hospital pharmacies, dispensing 18 billion prescription medicines annually[38].

As for the other stakeholders of the supply chain, pharmacies and other point of dispense are firstly exposed to a reputational cost in case of dispensing of a falsified medicine. Most specifically, such an incident can break the link of confidence between the pharmacists and the patient. Points of dispense are also exposed to an economic loss should they identify a falsified medicine in their stock and should the supplier be unwilling or contractually not required to recover the product.

Public / regulatory authorities (EU / national level)

Public and regulatory authorities play a critical role in ensuring the safety, efficacy, and quality of pharmaceutical products in both the EU and national levels. These authorities oversee the implementation of directives, regulations, and guidelines that govern the manufacture, distribution, approval, and monitoring of medicines. Indeed, the main responsibilities lie in ensuring compliance with the applicable regulations and guidelines, conducting inspections and controls, maintaining registration databases, and providing information on authorized entities and the common logo used to identify legal online pharmacies.

At EU level:

- **The European Commission** is responsible for initiating legislation, such as the FMD, and monitoring compliance to both protect public health and ensure the smooth functioning of the single market. Additionally, the Commission closely collaborates with the European Medicines Agency (EMA) and national competent authorities (NCAs) to monitor and enforce these regulations and guidelines, as well as facilitating communication and cooperation between the relevant actors.
- **The EMA** is the primary authority responsible for the scientific evaluation, supervision, and safety monitoring of medicinal products. EMA's scope includes both human and veterinary medicines. Its main tasks include evaluating marketing authorization applications, monitoring the safety of authorized medicines through pharmacovigilance activities, and providing scientific advice to companies and other stakeholders.
- **The European Medicines Verification Organisation (EMVO)** also plays an important role in the implementation of the FMD across the EU. It serves as the operational arm responsible for establishing and managing the European Medicines Verification System (EMVS), which connects various stakeholders, including pharmaceutical manufacturers, wholesalers, and pharmacies, to ensure the authenticity of medicines.

At national level:

- **NCAs** ensure the implementation of the FMD in their respective jurisdictions. This includes the responsibility for granting marketing authorisations for medicinal products, supervising compliance with good manufacturing practices, good clinical practices, and good distribution practices, conducting inspections, and monitoring the safety and efficacy of medicines throughout their lifecycle. They also collaborate with the EMA on different initiatives and take part in the decision-making process for EU-wide regulations and guidelines.
- In cooperation with the EMVO, **National Medicines Verification Organizations (NMVOs)** also play a key role in implementing and managing the verification systems at the national level. NMVOs are responsible for interfacing with the EMVS and ensuring the efficient and secure operation of the NMVS in their respective countries.

Overall, **the introduction of falsified medicines into the legal supply chain undermines the entire European and national regulatory frameworks** regarding the authorisation, manufacture and distribution of medicinal products in the EU. It also affects the trust of the citizens in the authorities' abilities to effectively protect public health.

[38] 2015 Impact Assessment

4 Assessment of the relevance of the measures set out in the Delegated Regulation (EU) 2016/161

This chapter aims to assess the **relevance of the system** established by DR (EU) 2016/161 in the context of combating falsified medicines. As a reminder, the safety features consist in both a Unique Identifier (UI) and an Anti-Tampering device (ATD), which are required to be placed by the manufacturer on the packaging of certain medicinal products for human use for the purposes of allowing their identification and authentication. This chapter therefore **seeks to answer all the evaluative questions from the point of view of adequacy: regardless of the actual functioning of the system, is it relevant in theory?** Has it been well thought out? Assuming that the implementation is going perfectly well, what is its real relevance?

- The first section is a **preamble** and reminds why the fight against falsification in the legal and illegal chain are to be dissociated.
- Section 2 questions **the relevance of the scope of the FMD and DR**: is the restriction to medicinal products under prescription adequate or are there remaining risks?
- Section 3 questions **the relevance of the safety features in their design**: have they been designed in a relevant way as set out in the DR? (EQ1.2)
- Section 4 questions **the relevance of end-to-end verification modalities**: is this choice relevant and sufficient in theory to fight against the introduction of falsified medicines? (EQ1.4)
- Section 5 questions **the choice of establishment and management of the system** and therefore the stakeholder-led governance: was this choice adequate? (EQ1.1)
- Finally, the last section addresses **the relevance of the design of the systems repositories**, with its two-tier architecture and the scope of data contained (EQ1.3)

This section also presents, in relation with the answer to EQ1.4 (Verification modalities) the **responsibilities of the stakeholders involved in the supply chains regarding verifications** (Study Question Q8: Which are the different stakeholders involved in the pharmaceutical supply chain, their roles and responsibilities for delivering the medicinal product from the manufacturing site to the patient?). It also outlines answer to Q7: What is the impact of intermarket transactions in the creation of real/false alerts?

Key findings

- **The fight against falsified medicines in the legal and the illegal pharmaceutical supply chains constitute two complementary approaches**. As such, the claim that the DR is not targeting the heart of the issue of falsified medicines (given the high stakes in the illegal supply chain) cannot be accepted.
- **Restricting the scope of the DR to prescription medicines is intended to provide an optimal response to the risk of medicine falsification, while reducing the verification burden for stakeholders.** The legislation also allows for national adaptations of the scope of the DR depending on Members States preference, an opportunity that is unequally used across the EU/EEA and that can generate logistical challenges for the stakeholders.
- **Technical specifications of the UI (full harmonization) prove to be fully relevant.** In addition of protecting patients against falsified medicines, the integration of both UI composition and carrier also harmonizes national product coding systems and allows for the use of one software and scanner type, therefore facilitating systematic verifications. While the **ATD** is a necessary feature, the **lack of specification of physical standard** in the DR prevents it from acting as a reliable safety feature.
- Assuming that the system was fully and well implemented in all MS**, end-to-end verification procedures with risk-based verifications by wholesalers are proportionate and relevant** towards those risks and sufficient to avoid the distribution of falsified medicines to patients. Nevertheless, end-to-end verification procedures **do not consistently prevent the diversion of authentic medicines into the illegal market** (even if that is not an objective of the DR). Aggregation offers a welcome flexibility and may need reinforcement in the texts to mitigate the risks that it may bring. **The desire to move towards a track and trace system is not relevant with the objective of combating falsified medicines,** but it may be relevant with other purposes (ex: monitoring shortages) that are outside of the scope of the DR.
- **The stakeholder-led governance constitutes a unique and unusual approach to ensuring coordination of actors with respect to the EMVS implementation**. Seeking to involve the most concerned stakeholders of the supply chain in order to engage them, this model appeared to be the most relevant option to foster the implementation of the FMD.
- **The relevance of the design of the repositories system is proved** as it allows for national data to be stored and managed nationally and permits transfer of information when needed without increasing the risk of the introduction of falsified medicines. However, in case of investigation the process can be

complicated by this two-tier architecture as full audit trail are not immediately available to competent authority, even though this was laid down in the DR (Article 35(1)(g)).

- Regarding the reporting system, it is fully relevant that the IT system backed by an obligation to carry out compulsory investigations in the event of alerts by the NMVO should be supplemented by an obligation to provide spontaneous information in case of suspicion. This double mechanism (IT and spontaneous alerts) is **aligned with the objective of fighting falsified medicinal products as it creates extra security in the verification system.** End-users can perform simple verifications of the medical packs all long the supply chain and automated alert mechanism should identify suspected falsification at the time of decommissioning. However, **the DR is unclear about the actual details of the spontaneous alert mechanism** (about the identity of the person that the end-user has to inform and the timing).

4.1 Preamble: Targeting the legal chain is justified even given the high stakes in the illegal supply chain

The scope of FMD and DR is restricted to the **legal pharmaceutical supply chain**. It thus, by definition, **excludes all distribution channels considered illegal** (e.g., unauthorized retail in beauty salons, fitness centers, or on illegal internet sales). However, as discussed in the previous sections, the vast majority of cases of falsification are detected in the illegal chain, leading many of the actors consulted to claim that the DR is not targeting the heart of the issue.

Nonetheless, it is important to **recall that the focus of the DR on the legal supply chain is relevant**:

- The fights against falsified medicines in the legal and the illegal pharmaceutical supply chains do not operate in the same way and constitutes two complementary approaches. On the one hand, the fight against illegal channels relies primarily on criminal law enforcement and police investigations. One the other hand, the prevention of falsified medicines entering the legal market, as envisioned by the DR, relies primarily on self-regulation by the stakeholders conducting regular verifications and reporting suspected case of falsifications.
- Another fundamental difference is that patients, when purchasing medicines via illegal or unauthorised channels, are often themselves aware of the illegality of the process. When patients obtain medicines from the legal supply chain, however, they often trust that the distribution chain is secure from falsification attempts. To uphold this trust, the legal supply chain must ensure some guarantees of authenticity.

In that context, the following paragraphs will elaborate on the relevance of the scope of the DR without questioning its focus on the legal supply chain.

4.2 Relevance of the scope of the DR

As a reminder, according to Article 2 of DR 2016/161/EU, this Regulation applies to:

- *(a) medicinal products subject to prescription which shall bear safety features on their packaging pursuant to Article 54a(1) of Directive 2001/83/EC, unless included in the list set out in Annex I to this Regulation;*
- *(b) medicinal products not subject to prescription included in the list set out in Annex II to this Regulation;*
- *(c) medicinal products to which Member States have extended the scope of application of the unique identifier or of the anti-tampering device in accordance with Article 54a(5) of Directive 2001/83/EC.*

On this last point (Article 2 (1c) of the DR), **Member States can extend the scope of application of the UI and the ATD** to some products not initially covered by the legislation. This extension must be decided in accordance with Article 54a(5) of Directive 2001/83/EC, which states that that:

"Member States may, for the purposes of reimbursement or pharmacovigilance, extend the scope of application of the unique identifier referred to in point (o) of Article 54 to any medicinal product subject to prescription or subject to reimbursement. […] Member States may, for the purposes of patient safety, extend the scope of application of the anti-tampering device referred to in point (o) of Article 54 to any medicinal product."

The DR also states that NCAs shall conduct a **risks assessment** and notify the Commission when they judge a non-prescription medicinal product to be at risk of falsification (Article 46). This risk assessment must be based on the criteria listed in Article 54a(2)(b) of the Directive 2001/83/EC: the price and sales volume of the medicinal product; the number and frequency of previous cases of falsified medicinal and frequency of such cases to date; the specific characteristics of the medicinal products concerned; the severity of the conditions intended to be treated; and other potential risks to public health.

Benchmark Focus

In Italy and Greece, the authenticity sticker, which is the only safety feature used, **applies to all medicinal products for human use**, prescription medicines and OTC products included. A few categories of medicines are exempted from bearing the sticker, such as radiopharmaceuticals products in Greece and medicinal gases in both Italy and Greece.

4.2.1 Restricting the scope of the DR to prescription medicines is intended to provide an optimal response to the risk of medicine of falsification, while reducing the verification burden for stakeholders

As reported by the actors consulted, **medicinal products present different risks of being falsified, depending on their nature, and most of all their price.** On the one hand, innovative medical products, such as anti-cancer or anti-hepatitis products, are the most expensive and thus present the most economic incentives for falsifiers. Generic medicinal products and OTC (over the counter) products, on the other hand, are relatively less expensive in average and consequently less falsified. Congruently, no evidence of falsification of OTC products has been presented in the 2015 Impact Assessment.

In that context, three options were available when determining the most relevant scope for the DR:

- **Option 1: scope applicable for all medicinal products**. This would have allowed for a far-reaching product-related protection covering all products but would also have resulted in considerable costs for the pharmaceutical industry (one-off costs of 11,55 billion euros for product serialisation according to the 2015 Impact assessment) and would have impacted in particular the generic and over-the-counter industry.
- **Option 2: scope applicable for products determined on a risk-basis assessment**. While allowing for a wide flexibility, this option would have created confusion as to the products addressed and would have shifted falsification activities from products covered by the DR to those not covered, depending on the choices made in countries.
- **Option 3: scope applicable for prescription medicines only**, with the possibility given to Member State to adapt the scope of application of the safety features.

Eventually, t**he latter option was retained for the DR as it was the most cost-effective and risk-proportionate one:** by covering prescription medicines only, the legislation has targeted the medicinal products most at risk of being falsified, and therefore fully contributes to objective of protecting the supply chain from falsified products. This option also limits criminals' ability to shift from one category of prescribed medicines to another.

As such, **all the 19 NCAs respondent to the survey answered that the scope of the DR was either "fully relevant" (9 NCAs) or "rather relevant" (10) to achieve the objectives of the FMD and the DR**. The scope allows to cover all risk while leaving flexibility for Members Sates to accommodate their national specificities. Nevertheless, if this possibility for adaptation is overall welcomed by the Member States, it can also create some confusion, as described in the following sections.

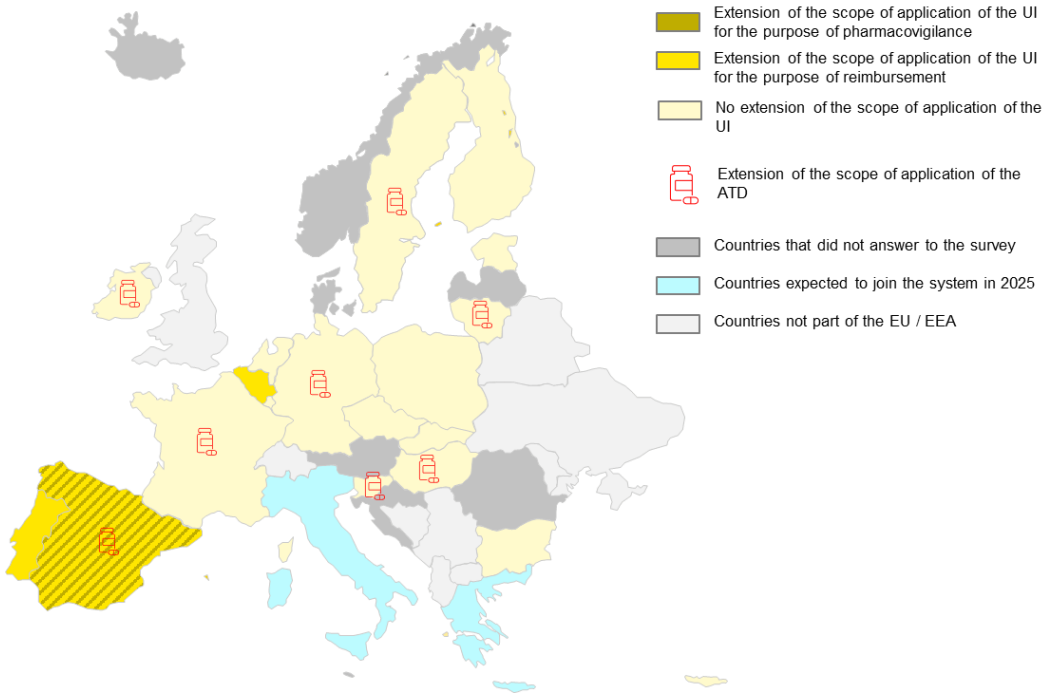
4.2.2 The legislation allows for national adaptations of the scope of the DR depending on Members States preference, an opportunity unequally used across the EU/EEA

As stated in Article 2 (1c) of the DR, the legislation gives the possibility to MS to extend the scope of the DR depending on the national preferences. In practice, out of the 19 NCAs respondent to the survey, **10 countries have extended the scope of application of the safety features**:

- Spain has extended the scope of application of the UI for the purpose of pharmacovigilance
- Belgium, Portugal and Spain have extended the scope of application of the UI for the purposes of reimbursement
- France, Germany, Hungary, Ireland, Lithuania, Slovenia, Spain and Sweden have extended the scope of application of the ATD for the purpose of patient safety. France, for example, has extended the ATD to all medicinal packs, including over-the-counter (Decree n°2012-1562, 31 December 2012), to increase patient safety. This measure has notably received the support of the professional

pharmacists. In the other Member States, Marketing Authorization Holder (MAH) can generally extend the ATD on a voluntary basis, also for the purpose of patient safety.

Figure 6 Mapping of MS depending on the extension of the scope of application of UI and ATD according to the survey distributed to NCAs (n=19)



Source: Survey to NCAs – EY elaboration

In addition, **the legislation proposes measures to take into account additional risks on the basis of a risk assessment of Member States**. In practice, out of the 19 NCAs respondents to the survey, **only Ireland has performed such a risk-based assessment** and notified the European Commission afterwards. On that note, the Irish NCA declared not being satisfied by the way the Commission handled the notification, since there was "no explanation provided on why certain products were included" on the Commission list.

4.2.3 The different national adaptations of the scope of the DR generate logistical challenges for the stakeholders, although mitigation measures exist

While overall agreeing on the relevance of the scope of the DR, **5[39] NCAs have raised that the difference in the scope of application of the safety features between Member States can cause challenges and confusion for the distribution of "multi-country packs"** (i.e., packs distributed in several Members States). Most of the argument raised pertain to logistic and administrative challenges for MAH, and notably for parallel traders, who must add or remove safety features to the same product according to the country where they supply it.

Nonetheless, France and Germany also noted that **it is normal for MS to decide which medicinal products should, for example, be subject to prescriptions and should bear safety features in their country**. Besides, no critical arguments or inputs were submitted by the wholesalers justifying their incapacity to adapt to these national specificities. At a last, to alleviate this challenge, the Belgium NCA recommended to align the safety feature requirements on multi-country packs across the markets where they are distributed. Allowing and encouraging voluntary application of the safety features by the MAH can help in that sense.

[39] Belgium, Germany, Lithuania, Malta and Slovakia

4.3 Relevance of the safety features set out in the DR

4.3.1 A fully harmonized Unique Identifier that is totally relevant in the fight against falsified medicines

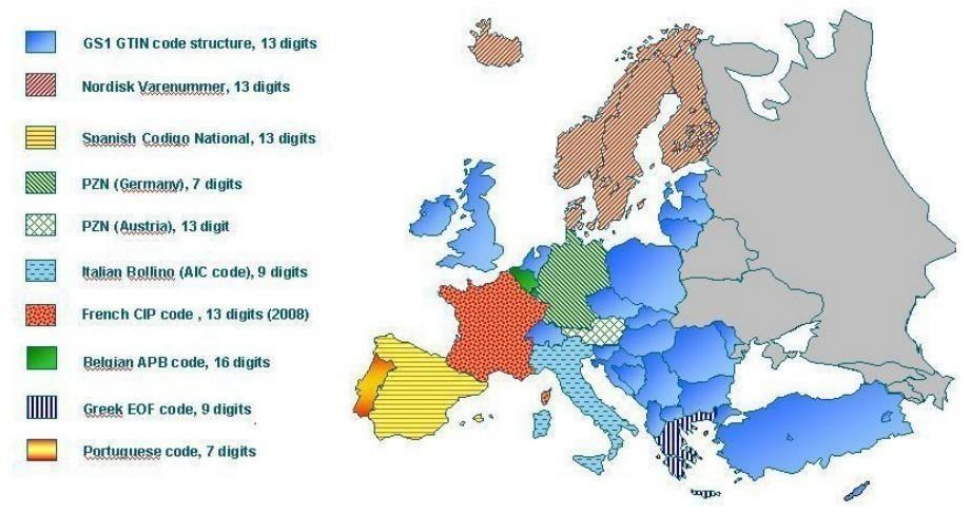
CONTEXT BEFORE DR

As stated in the 2015 Impact Assessment accompanying the DR[40], **no effective technology was in place prior to the implementation of the EMVS to reliably protect EU/EEA citizens from falsified medicines.**

Firstly, only a few Member States had implemented a "specific national labelling" requirements to ascertain the authenticity and identify of medicines in 2015, as allowed by the EU legislation. Even when such provisions were in placed, they were often too limited to be effective. For example, a number of Member States were relying on paper trails to ascertain the origin of medicines, a costly and easily forgeable process. Besides, the pack identification system was sometimes implemented on a voluntary basis only. In Belgium for example, it was not mandatory for manufacturers to use the coding system to identify single packs.

Secondly, the lack of harmonization between the medicine identification rules across the Members States generated further loopholes and inefficiencies. Different coding standards were used to identify medicine packs (see figure below). Product number could contain between 7 and 13 digits, attached to a variety of information and purposes (national reimbursement code, expiry dates, etc.). For example, France was using a 2D barcode to track batches of products for recalls, while Belgium or Italy introduced a 1D barcode for reimbursement rumpuses. In that context, it proved necessary that in the European medicine verification system in preparation, coding standard had to be harmonised to avoid systems errors, obligation for pharmacists to scan multiple times, and the cost of maintaining multiple identification systems. As such, the 2008 Impact Assessment[41] estimated at 1bn euros per year the cost of maintaining non-harmonised coding systems.

Figure 7 Fragmentation of coding requirements for medicinal products in the EU/EEA



Source: 2015 Impact Assessment

As a result, with regards to these lacks the DR provides full harmonisation of both UI composition and carrier while leaving the possibility for manufacturer to include additional information.

A Unique identifier (UI) is defined by the DR as "*the safety feature enabling the verification of the authenticity and the identification of an individual pack of a medicinal product*". In practice, the UI consists in a two-dimensional data matrix code, which complies with specific technical specifications regarding composition (Article 4 of DR) and packaging and printing (Article 5 and 6).

A pack containing a UI with a product code, serial number, batch and expiry date

Regarding **composition of the UI**, according to Article 4 of the DR:

[40] Impact Assessment Accompanying the document Commission Delegated Regulation (EU) No 2016/161 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 (SWD (2015) 189 final).

[41] Impact Assessment report of the Commission services accompanying the proposal for Directive 2011/62/EU (2008).

(a) The unique identifier shall be a sequence of numeric or alphanumeric characters that is unique to a given pack of a medicinal product.

(b) The unique identifier shall consist of the following data elements: (i) a code allowing the identification of at least the name, the common name, the pharmaceutical form, the strength, the pack size and the pack type of the medicinal product bearing the unique identifier ('product code'); (ii) a numeric or alphanumeric sequence of maximum 20 characters, generated by a deterministic or a non-deterministic randomisation algorithm ('serial number'); (iii) a national reimbursement number or other national number identifying the medicinal product, if required by the Member State where the product is intended to be placed on the market; (iv) the batch number; (v) the expiry date.

(c) The probability that the serial number can be guessed shall be negligible and in any case lower than one in ten thousand.

(d) The character sequence resulting from the combination of the product code and the serial number shall be unique to a given pack of a medicinal product until at least one year after the expiry date of the pack or five years after the pack has been released for sale or distribution in accordance with Article 51(3) of Directive 2001/83/EC, whichever is the longer period.

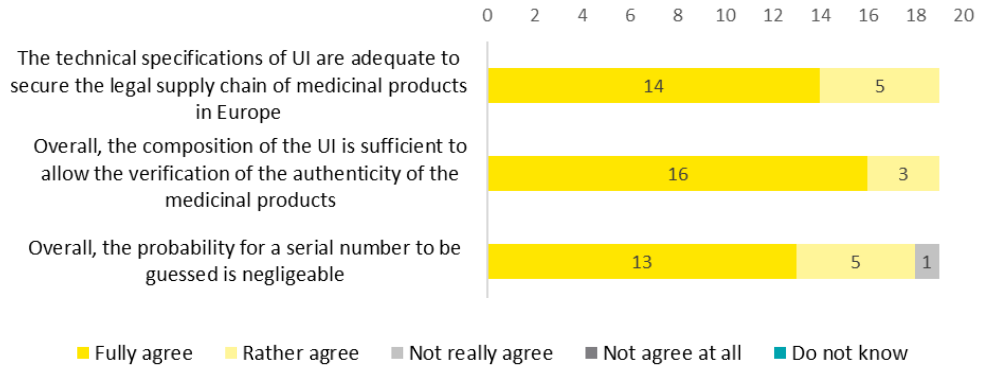
(e) Where the national reimbursement number or other national number identifying the medicinal product is contained in the product code, it is not required to be repeated within the unique identifier."

Also, manufacturers may include additional information in the two-dimensional barcode according to Article 9 of the DR.

Regarding **the carrier of the UI**, Articles 5 and 6 of DR specify the format of the UI (two-dimensional barcode), as well as the **modalities of encoding** and printing. In particular, a minimum level of print quality is expected from manufacturers based on 7 parameters: contrast between the light and dark parts, uniformity of the reflectance of the light and dark parts, axial non-uniformity, grid non-uniformity, unused error correction, fixed pattern damage, and capacity of the reference decode algorithm to decode the Data Matrix.

This full harmonisation is praised by all the stakeholders and NCA met with regards to the objective of securing the legal supply chain of medicinal products, both at European and national level and among stakeholders and NCAs. All 19 NCAs surveyed and almost all supply chain actors (92% of the respondents) consider the UI is adequate in terms of technical specification and composition. They also consider that it is highly unlikely that fraudsters guess the correct serial number, except for one NCA (Slovakia) that did not disclose why.

Figure 8 To what extent do you agree with the following assertion related to the safety features? (n=19)



Source: Survey to NCAs – EY elaboration

Only 4 countries have included additional information on the packaging / UI. Bulgaria for instance included the national number of the product, before excluding it in 2020. Germany requires the "Pharmazentralnummer (PZN) to be printed on the outer package. The PZN is an identification key issued by the German information centre for medicinal products (IFA) for all pharmacy products and serves reimbursement purposes. In Portugal and Spain, the National Marketing Authorization Number, and the National Healthcare Reimbursement Number, respectively, must also be included with the UI for reimbursement purposes. No stakeholder ever requested the inclusion of additional information according to the NCA survey.

Based on these observations, **technical specifications of the UI prove to be sufficient and fully relevant**. In addition of protecting patients against falsified medicines, the integration of both UI composition and carrier also:

- **harmonizes national product coding systems** (see Figure 9 on Fragmentation of coding requirements for medicinal products in the EU/EEA) that were deemed inefficient and not secure enough. According to the Impact Assessment 2015, "the national product coding systems are, in most cases, not suited to efficiently preventing fake medicines from entering the legal supply chain because conceived for reimbursement purposes rather than to identify single packs […] and can be easily copied".
- **allows for the use of one software and scanner type**, therefore facilitating systematic verifications.

This option seems the most appropriate among the other policy options considered regarding the UI, which include:

- **Partial harmonization** (the manufacturer would have been free to choose the carrier/barcode and part of the information contained e.g., batch number and expiry date) would have entailed definite risks for the safety of medicinal products against falsification. In comparison, the chosen option eliminates the divergent national packaging requirements.
- **Varying the mandatory/ non mandatory components of the UI** (the harmonization of the carrier but not the composition of the barcode, or vice versa) would have addressed only part of the obstacles linked with the lack of harmonisation.
- **The no action option** would have placed the Commission in contradiction to its obligation to act via a delegated act, as stated in the FMD.

4.3.2 The lack of specification on the ATD standard makes it more fallible than the UI even though it remains a necessary feature

CONTEXT BEFORE DR	Prior to the 2011 FMD, there were no requirements under EU law to place a safety feature on medicinal packs to prevent tempering attempts. The 2008 Impact Assessment indicated that some pharmaceuticals companies voluntarily placed safety features on their packs for added security. However, in the absence of legal requirements protecting their integrity, these features were often removed, covered, or discarded in the subsequent supply chain. This situation not only removed the usefulness of the safety features, but also disincentivised manufacturers to develop additional technique to guarantee the authenticity of their products, as reported in the Impact Assessment.

The anti-tampering device (ATD) is an additional safety measure provided by the legislation which completes the UI requirements. The ATD is defined by the DR as a "*safety feature allowing the verification of whether the packaging of a medicinal has been tampered with"*. **This feature is viewed as necessary by both stakeholders of the supply chain and NCA**, in complementarity with the UI, to ensure the authenticity of medicinal products. In France for instance, the introduction of this safety feature has been supported for years by wholesalers, who recognize the need for an ATD as a way to assess the authenticity of the medicines returned to them by pharmacists.

However, **the DR does not specify physical standards for the ATD**: ATD's design and placement on the medicinal product are left to the manufacturer to decide, and these can be a complete package, a sticker, or glue to seal the openings. As such, NCAs[42] and actors[43] raise concerns from all MS related to a difference in quality of the ATD produced by manufacturers that can damage the fight against falsified medicines.

Summing-up, **the ATD is a necessary and fully relevant measure** in the fight against falsified medicines and is the mandatory counterpart of the UI for this fight to be complete and effective. However, **the fact that there are no technical specifications opens a gap in this fight against falsification and weakens the alignment with the objective of the FMD**. In fact, this lack of specifications has already been used in one case of falsification studied by the Evaluation, as is shown in the next part related to the Functioning of the safety features.

Benchmark Focus

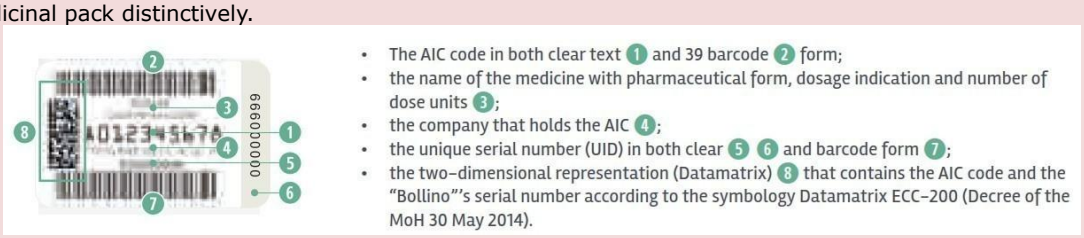
[42] 4 out of 19 NCAs do not agree with the statement "the ATD is adequate to ensure the legal supply chain of medicinal product in Europe" (vs. non negative opinions on the UI) (source: questionnaire to NCAs, question 20).
[43] More than 22% of the stakeholders consider the ATD measures are not adequate considering the risks and proportionality principles, which can be seen as a high rate.

A few countries, namely **Italy and Greece, stood out at the time of adoption DR for their already well-established medicine authentication system.** This situation justified their delayed integration to the EMVS. The following paragraphs elaborate on both systems.

Italy

The Italian medicine verification system was set up in 2002 and later developed into full track and trace system. It relies on **two main components: the authentication of medicine packs with the "bollino"** (or authentication sticker), **and the recording and transmission of authentication information through a central data base.**

The bollino is a three-layer sticker of 40x25 mm produced by the Italian National Printing House (the IPZS) at the request of pharmaceuticals companies, who are required to place it on the pack of all medicinal for human use they distribute in Italy. The bollino contains several elements allowing for the identification of each medicinal pack distinctively.



Source: AIFA (2020), *The Italian Drug Traceability System*

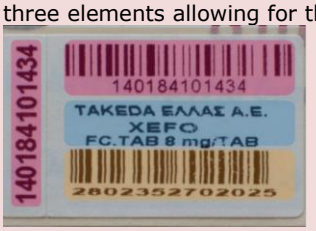
To ensure its authenticity, the bollino is manufactured according to strict antitampering methods. As shown in the graph below, security fibers must appear when exposed to UV light. Besides, watermark shapes must be visible when the bollino is held against light.

Source: AIFA, The Italian Security Label for Pharmaceutical Product

All actors of the pharmaceutical supply chain, from the manufacturer to the pharmacist, are required to transmit the product codes and destination of the packs they supply down the distribution chain in a Central database owned and operated by the public authorities[44]. The information thus collected are used by the public authorities for pharmacovigilance and epidemiology, monitoring shortages and fighting against reimbursement fraud.

Greece

Greece has a similar medicine verification system to Italy, which is operating since 1987. The system relies on an authentication sticker placed on all medicinal products for human use distributed in Greece, under prescription and OTC, with a few exceptions (radiopharmaceuticals and medicinal gases). The sticker displays three elements allowing for the identification of each induvial medicinal pack:



Sticker barcode:
Unique Serial Number in barcode format.

MAH brand name
Product name, pharmaceutical form, dosage.

Product barcode
Package code in barcode format.

Similarly, to the Italian bollino, the Greek sticker presents a **set of characteristics designed to deterring falsification**. The sticker is printed on a special watermarked paper and shows the national coat of arms and the letters "EOF" (the name of the Greek NCA) when exposed to UV light. The pattern and the color of the design change each year to add a level of protection and to recognize the year of manufacturing of a sticker.

The Sticker is manufactured under the supervision of the EOF and distributed to Marketing Authorization Holders when their reserves of stickers fall below the equivalent of one and a half month of production. Before release to market, the MAH is responsible for uploading into a central data base operated by public authorities, GRELIS, the information attached to the medicinal packs (serial numbers and the medicinal products barcode, etc.). At the end of the supply chain, the medicinal product must be decommissioned (e.g., by the pharmacist upon dispensing to patient or by the wholesaler before export).

[44] article 40 of Law 1st March 2002 no. 39.

Overall, the system is used by public authorities to protect the legal supply chain from falsified medicines, to trace medicinal packs, and to monitor fraud and reimbursement issues.

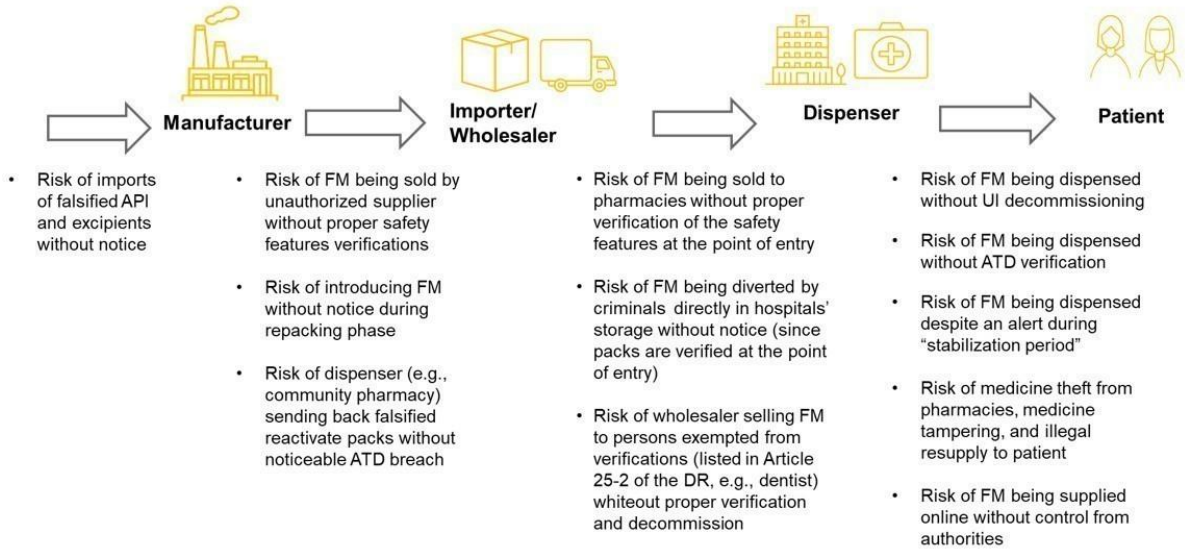
4.4 Relevance of the verification modalities of the system

Methodological note: to assess the relevance of the verification modalities, we assume in this section that the system is fully and well implemented in all MS, notably verifications are made by wholesalers on a risk-based assessment.

4.4.1 Risks of the introduction of falsified medicines exist at several levels in the chain of actors

As synthetised in the figure below, a number of theoretical risks of introduction of falsified medicines exist at each step of the legal supply chain.

Figure 9 Risks of introduction of falsified medicines in the legal supply chain



Source: Desk review – EY Elaboration

Producers of API and excipients and manufacturers of medicinal products

At the top of the pharmaceutical supply chain, APIs (the ingredients responsible for the effects of the medicine) and excipients (the substances helping to deliver the medication) are produced from raw materials and then supplied to manufacturers of finished medicinal products. API and excipients imported from non-EU countries must receive a written confirmation from the regulatory authority of the country of origin (except for exporting countries with an equivalent regulatory framework). In addition, the DR mandates that the suitability of Good Manufacturing Practice (GMP) for excipients must be evaluated by the importer in the context of their usage in the final product. Following the DR, guidelines were issued outlining the formal risk assessment process required for determining the GMP of each excipient.

Producers and importers of APIs and excipients face multiple challenges in ensuring the safety, quality, and efficacy of these materials. These challenges include **increased complexity of global pharmaceutical supply chains, varying quality standards, inadequate regulatory oversight**, counterfeit documentation, limited traceability, and insufficient testing and quality control. These risks are compounded by the fact that it is currently **challenging to distinguish substandard and falsified medicines by analytical methods**. For example, substandard medicines may have genuine packaging but can contain impurities or varying doses of APIs. Falsified medicines can encompass a wide range of products that may have altered packaging, formulation, or APIs. For instance, falsified medicinal products could contain the accurate API and dosage, an entirely different API, no API at all, the API in an incorrect dosage, or any combination of these[45]. With substandard medicines often having

[45] Bakker, I.M., Ohana, D. and Venhuis, B.J., 2021. Current challenges in the detection and analysis of falsified medicines. Journal of Pharmaceutical and Biomedical Analysis, 197, p.113948.

genuine packaging but containing impurities or varying API doses and counterfeit medicines covering an array of product alterations, it becomes complex to accurately identify and eliminate them from the supply chain.

Since no single analytical method can detect all possible falsifications, **this renders the establishment of uniform guidelines on detection methods difficult.** As a result, producers and importers must constantly check the quality and authenticity of the APIs and excipients in the market. This challenge necessitates even more robust quality assurance, risk assessment, and control measures for producers and importers combined with the utilization of comprehensive and diverse analytical methods to detect any potential falsifications.

Parallel traders/ importers and wholesalers

Parallel trade in pharmaceuticals, while lowering the expenditure on pharmaceuticals for high-price countries, carries in theory several risks and challenges when tackling falsification. For example, **the risk of falsified medicines entering the supply chain is theoretically increasing due to additional steps** being taken in the process through parallel imports. Complex supply chains, changes in packaging, transport routes, and relabelling multiply the potential entry point of falsified medicines and can make it more challenging for national authorities to trace the history of pharmaceuticals bought and sold by intermediaries across EU Member States. Added to this are **the (higher) risks of infiltration of the illegal parallel trades**.

Similarly, **the multiplicity of distribution networks** (i.e., multiple channels and pathways through which products, such as pharmaceuticals, are distributed and supplied to the end consumer) increases the risk of permeation at the wholesale level. It was for example the case in 2012 and 2014, when cases of Avastin stolen from Italian hospitals were reintroduced in the legal supply chain through authorised wholesalers[46].This trend is further exacerbated by the development of new micro-distributors, short-line wholesalers, secondary wholesalers, small import/export firms, etc. Besides, the lack of enforcement of verifications and the sophistications of falsification techniques increases the chances of falsified medicines being introduced unnoticed in wholesale facilities. As an illustration, in 2022, the Bulgarian Drug Agency reported that a criminal purchased a pack of Enbrel (etanercept) from a registered pharmacy, replaced the pack's content with pencils without damaging the ATD, and then resold the pack to a local wholesaler, and was able to resupply it to a foreign parallel trader.

The risks of falsification linked with parallel trade and medicinal products imported from outside the EU/ EEA, **generated various opinions among stakeholders surveyed**. Overall, 30% of the respondents (64 out of the 205 respondents to the survey to stakeholders) believe that globalisation of the pharmaceutical supply chain constitutes an emerging risk in terms of medicine falsification. Supporters of parallel trade argued that their operations were subject to extra verifications procedures, in addition to those required by the legislation, guaranteeing the safety of the supply chain. The latter also argued that falsifiers are more incentivised to divert medicinal products outside of the EEA/EU, where prices are high and control is low, rather than reintroducing the products into the legal supply chain in another EEA Member States where controls are significant.

Pharmacists

At the end of the supply chain, patients are also exposed to falsified medicines due to risks at the pharmacy level. Firstly, these risks can arise from a lack of verification from pharmacists. As discussed in the section 4.3.2, the lack of specifications and monitoring of ATD verifications can lead to the deliverance of medicinal packs with a breach of ATD. Secondly, in the countries where the stabilization period is still in place, pharmacists can deliver products despite an alert being triggered. That being said, even during the stabilization period, pharmacists are required to withdraw packs when a serious suspicion of falsification exists, which reduces the probability of distributing falsified packs. Thirdly, the dispensation of medicinal packs ultimately relies on a human intervention, which does not exclude that pharmacists can willingly abstain from verifying a falsified pack and deliver it to a patient. Fourthly, as regard to hospital pharmacies, the large volume of medicinal packs entering and exiting storages increases the likelihood of falsified packs being introduced without notice. Besides, the fact that hospital pharmacies decommission packs when products are delivered to the hospital means that a falsified product introduced after the decommissioning phase could be delivered to patients, still without notice.

The development of online sales, which accelerated during the COVID-19 pandemic, poses a particular source of complexity in the control of medicinal product supplied to the public. Indeed, the delivery of products purchased online relies on mail and courier services, which are the main modes of transport for counterfeit and falsified medicines worldwide (95% of customs seizures of medicinal products between 2014 and 2016 involved postal services)[47], and are particularly difficult to control consistently. On that note, it is important to distinguish illegal online pharmacies from legal one, who must be registered with the competent authorities are submitted to the same control and obligations as physical pharmacies.

[46] European Commission (2015), Impact Assessment accompanying the Delegated Regulation (EU) 2016/161.
[47] OECD, EUIPO (2020), Trade in Counterfeit Pharmaceutical Products, Illicit Trade, OECD Publishing, Paris.

4.4.2 End-to-end verification procedures with risk-based verifications by wholesalers are proportionate and relevant towards those risks and sufficient to avoid the distribution of falsified medicines to patients

CONTEXT BEFORE DR	Prior to the implementation of the EMVS, no effective rules were in placed to reliably protect EU/EEA citizens from falsified medicines. **Even in the presence of a pack identification system, verification requirement along the supply chain were most of the time lacking across the Union**. In fact, out of the 19 NCAs who responded to our survey[48], only Belgium reported having a national system similar to the EMVS allowing for the verification of the authenticity of medicines before the DR. In Belgium, a unique number issued by the reimbursement institute was given to each reimbursable pack to verify against double reimbursements. The manufacturer was required to print the code on the medicine packs and to communicate it to the reimbursement institute. At the end of the supply chain, the pharmacist had to scan the code when dispensing the pack and submit it together with the reimbursement request to the competent authority. Contrary to the EMVS, nonetheless, this system was not compulsory, and the codes only consisted in a series of 6 unrandomized numbers.

The verification process is essential in two ways as it ensures that: (i) the authenticity of the pack originates from the legitimate manufacturer (through the verification of the unique identifier) and (ii) the integrity of the medicinal product has not been altered since it has left production (through the verification of the ATD).

The process of verification laid out in the DR is structured as **an end-to-end system: safety features placed on the medicinal products at the manufacturing stage (Article 14) shall be verified at the end of the supply chain** upon decommissioning of the medicine packs (Article 25-1). Additional verifications are also required along the supply chain when a risk of introduction of a falsified medicine is deemed important (e.g., a wholesaler must verify the safety feature when he receives medicinal products from a wholesaler who is neither the manufacturer nor the wholesaler holding the marketing authorization (Article 20-b)). Moreover, if the manufacturer (Article 18), the wholesaler (Article 24), or the person authorized or entitled to supply medicinal products to the public (Article 30) has reasons to believe that the product may not be authentic or that is has been altered, she/he should not release the product and inform the "relevant competent authorities". Besides the verifications required by the DR, the EMVS offers the possibility for users (typically a pharmacist or a wholesaler) to **perform a simple verification of a "pack at hand",** without changing its status. In practice: (i) the operator first scans the pack; (ii) the data scanned are then compared to the data stored in the national system; (iii) the system finally returns the status of the pack.

Finally, according to (4) of DR, "medicinal products at higher risk of falsification should be additionally verified by wholesalers throughout the supply chain to minimise the risk of falsified medicinal products circulating undetected for lengthy periods of time."

The following table lists the role and responsibilities of the stakeholder in the verification procedures and all the verifications steps required along the legal supply chain by the DR (EU) 2016/161.

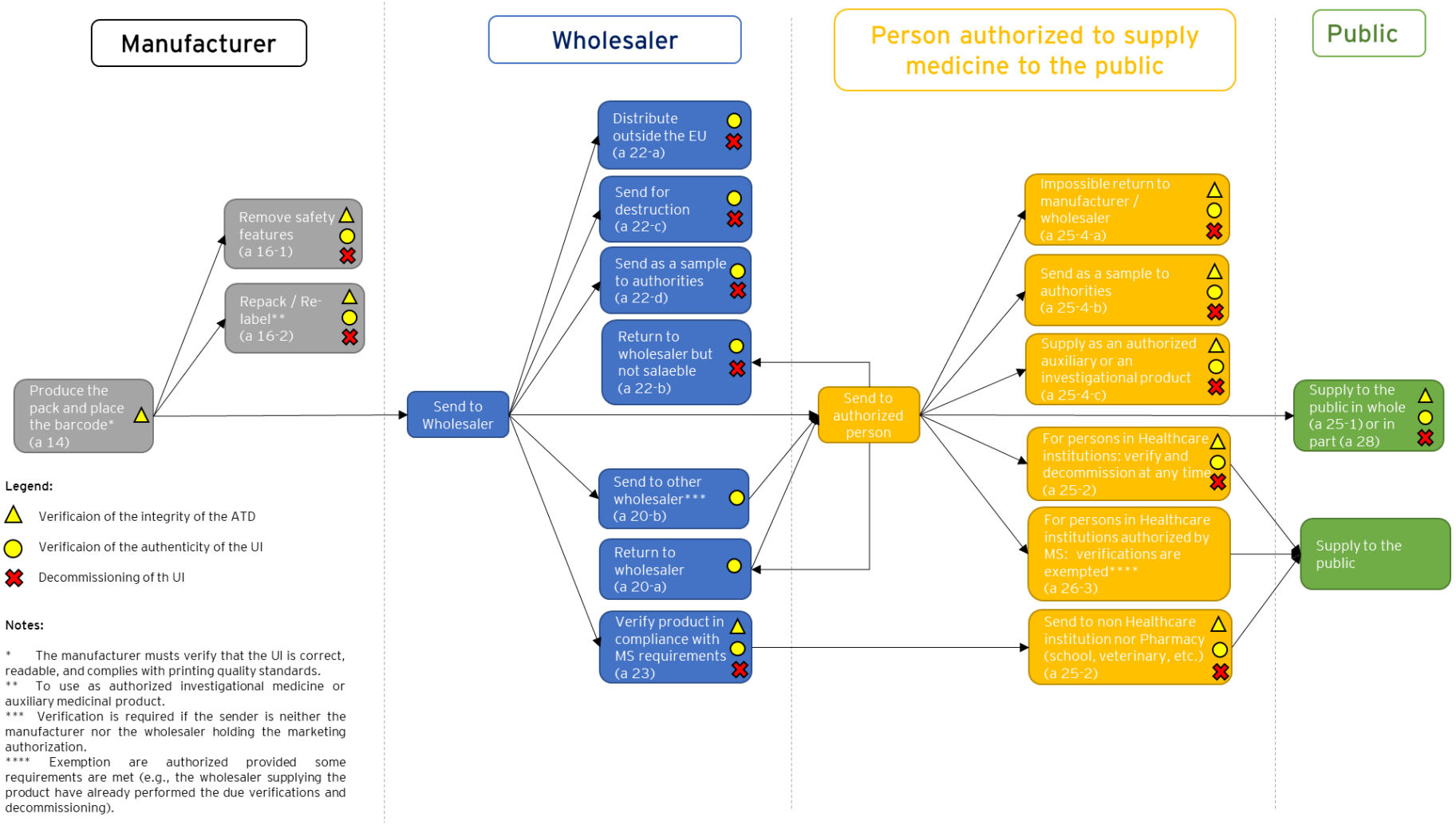
[48] The survey was only summited to the Member States currently participating to the EMVS, which excludes Greece and Italy.

Table 1 Verifications of Medicines Packs Required by DR (EU) 2016/161 and Roles and Responsibilities of the stakeholders involved

Entity	Role and responsibilities in the system	Verification cases	Derogations: cases of exemptions
Manufacturer / MAH	▶ The implementation of the DR has instigated notable changes for pharmaceutical manufacturers. These encompass labelling provisions and the imperative to adapt production lines. It is crucial to underscore that manufacturers are primarily responsible for the application of the unique identifier and anti-tampering device as mandated by the DR, whether acting as the marketing authorization holder or under contract. ▶ **Manufacturers are responsible for uploading this unique identifier to the European hub** (also known as the EU Hub) **as well as placing an Anti-Tampering Device on product package**. This process allows the end-user to authenticate the product through a scanning operation during dispensing. Manufacturers engaged in wholesale activities and directly supplying healthcare institutions are also responsible for verifying and decommissioning medicinal products.	▶ The manufacturer placing the safety features shall verify that the two-dimensional barcode is readable, contains the correct information and complies with the printing quality requirements of Articles 5 and 6 (article 14) ▶ Before removing the safety measures, the manufacturer shall verify the safety features (ATD and UI) and decommission the UI if replaced (article 16-1). ▶ Before repacking or re-labelling the product to use it as authorized investigational medicinal product or auxiliary medicinal product, the manufacturer shall verify the safety features and decommission the UI (article 16-2). ▶ When placing an equivalent UI to comply with Article 47a of Directive 2001/83/EC, the manufacturer shall verify that the UI complies with the requirements of the Member State where the product is intended to be placed (article 17).	
Wholesaler	▶ Under the DR, **wholesalers are required to authenticate medicinal products returned by other parties**, such as community and hospital pharmacies, other wholesalers, and organisations that supply medicines. ▶ The verification and decommissioning processes they need to perform vary depending on their specific operation, such as whether they only supply other wholesalers or receive products exclusively from manufacturers. Verification of authenticity when a medicinal product changes ownership but remains in the physical possession of the same wholesaler is not required, or in circumstances where the distribution occurs between a wholesaler's own warehouses. ▶ Similar to manufacturers, **wholesalers may also have the responsibility to decommission the unique identifier by scanning the 2D matrix barcode**. For example, wholesalers may have to decommission the UI in specific cases, such as when they supply medicines to another wholesaler without a 2D matrix barcode scanner, and then distribute products to countries outside the EU.	The wholesaler shall verify the safety features (no decommissioning): ▶ When the medicinal product is returned to him by persons authorized (article 20-a) ▶ When he receives medicinal products from a wholesaler who is neither the manufacturer nor the wholesaler holding the marketing authorization (article 20-b) The wholesaler shall verify the safety features and decommission the UI: ▶ When the product is requested as a sample by competent authorities (article 22-d) ▶ When the product is intended for destruction (article 22-c) ▶ When the product returned to him by an authorized persons cannot be returned to saleable stock (article 22-b) ▶ When the product is intended for distribution outside of the EU (article 22-a) To accommodate the specificities of the local supply chain, Member State may also require that wholesaler verify the safety features and decommission the UI when they supply the medicinal products to	▶ When the product changes ownership while remaining in the possession of the same wholesaler, he is not required to verify the UI (article 21, in derogation to article 20) ▶ When the production is distributed in a MS between two warehouses owned by the same wholesaler, he is not required to verify the UI (article 21, in derogation to article 20)

		certain institutions, such as veterinarians, dental practitioners, schools, or prisons (article 23)	
Person authorized or entitled to supply medicinal products to the public	▶ **They must verify the authenticity of the products they receive by checking the safety features** on the outer packaging and ensure that the products are not falsified. ▶ In particular, this includes the necessity for authorised entities to decommission the UI at the time of supplying it to the public. The DR also provides the possibility for hospitals to verify or decommission products in their internal supply chain. The dispensing part of a pack also impacts dispensing operations, thus authorised entities are required to decommission the package before opening it.	The authorized person shall verify the safety features and decommission the UI: ▶ When supplying the product to the public (article 25-1). ▶ When the product in the authorized person's possession cannot be returned to the manufacturer or wholesaler (article 25-4a) ▶ When the product in the authorized person's possession is requested as samples by competent authorities (article 25-4b) ▶ When the authorized person supplies a product as an authorized investigational medicinal product or an authorized auxiliary medicinal product of Articles 2 of Regulation 536/2014 (article 25-4c) ▶ When supplying only a part of a pack of a medicinal product to the public, the person authorized shall verify the safety features and decommission the UI when the pack is opened for the first time (article 28). In addition: ▶ When operating within a healthcare institution, the authorized person may, at any time, verify the safety features and decommission the UI of the products in the possession of the institution (article 25-2).	▶ When the authorized person received a product as a free sample ▶ When the authorized person does not operate within a pharmacy or a healthcare institution, provided verification and decommissioning have been placed on the wholesaler by a Member State in accordance with Article 23 (article 26-2) ▶ Notwithstanding Article 25, Member States may exempt the authorized person operating in a healthcare institution to verify the safety features and decommission the UI in order to accommodate the specificities of the local supply chain. To be applicable, these exemptions must meet certain requirements (e.g., the manufacturer supplying the product should have already performed the due verifications) (article 26-3)

Table 2 Verifications and decommissioning along the supply chain required by the DR (EU) 2016/161



Benchmark Focus

Regarding decommissions, similarly to the DR, **the Greek system provides for different requirements depending on the stakeholders and the circumstances involved**. As such, as reported by the EOF, the serial number of the authenticity sticker must be decommissioned by:

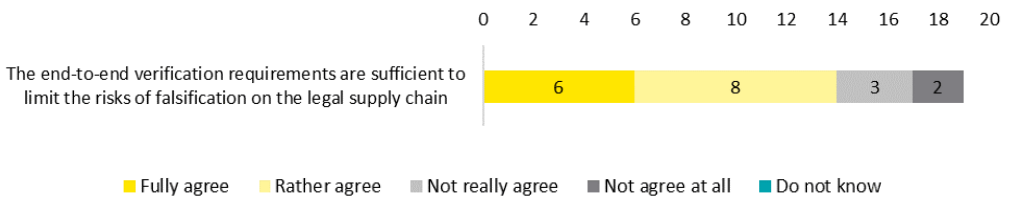
a) the pharmacist, during dispensing of the medicinal product to patients;
b) the MAH, for medicinal products with packaging materials in Greek language for export;
c) the MAH, for medicinal products that are donated;
d) the MAH, for medicinal products for clinical studies;
e) the MAH, for medicinal products that are disposed;
f) the wholesalers, before every export, through the EOF's application "GRELIS" in real time.

A unique feature of the Greek system is that the serial number of the authenticity sticker can not only be verified by wholesalers, but also by any person wishing to verify the status of a medicinal product, through the web-based application of EOF.

As such, excluding the public's access to the medicine verification functionality in Greece could present a challenge as the DR enters into force in Greece.

For the **NCA**, according to the survey opinions on the adequacy of verification modalities (e.g., adequacy of end-to-end verification, risks in reversing the status of a decommissioned UI, etc.) were generally positive. 5 NCAs nonetheless expressed diverging opinions[49], but related to the effectiveness of this system to react in case of falsification and not based on its relevance: they think that the end-to-end verification system does not provide enough information to properly investigate into suspicious of falsification.

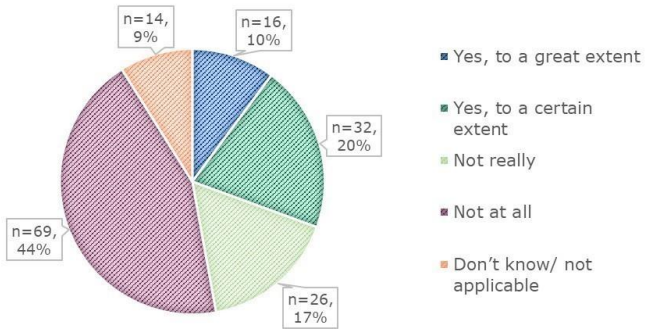
Figure 10 To what extent do you agree with the following assumptions related to the adequacy of the verification modalities? (Q28, n=19)



Source: NCA survey – EY elaboration

For the **stakeholders of the supply chain**, 61% (95/157) of respondents to the survey answered that additional verification was not really required/ not required at all. This view was primarily shared by both pharmacies/ persons authorised to supply medicinal products and wholesalers. The small proportion that was in favour of additional verification were primarily composed of NMVOs (17) across 13 countries[50].

Figure 11 Do you think there is need to require additional verification at other stage(s) of the supply chain and thus to migrate towards a full tracking verification system? (n=157, One option possible)



[49] Bulgaria, Estonia, Germany, Slovakia and Slovenia.
[50] These include Bulgaria, Croatia, Czech Republic, Estonia, Iceland, Latvia, Lithuania, Malta, Netherlands, Norway, Portugal, Slovenia, Sweden.

Source: Survey to other stakeholders – EY/Ramboll elaboration

Summing-up, end-to-end verification procedures are relevant and sufficient to secure the legal supply chain if they are well implemented and if wholesalers are compliant with risk-based verifications. Above all, **they are proportionate** to risks: they are less cumbersome than a "track and trace" system (which would involve systematic checks at each stage of distribution) and allows for almost as high-risk coverage as the latter system thanks to the risk-based verification carried out by wholesalers. Moreover, it is much more secure than the simple "end-to-end verification" option discussed during the drafting of the DR, which did not provide for spontaneous verifications by wholesalers. These verification methods, which include this additional security of verification by wholesalers, are also relevant because they increase patient safety and, above all, **allow for faster detection of falsified medicines**: this prevents a falsified medicine from entering the legal chain remaining there for weeks or even months before being scanned by end-users. The 2015 Impact Assessment provides the example of fake interferons detected at first by a German parallel distributor in September 2013 and two months later in Romanian pharmacies. According to EMVO, no such data related to the time between upload and decommissioning of medicinal packs exist, thus preventing the Evaluation to draw conclusions on that.

Besides, the fact that wholesalers shall verify and decommission medicinal products in specific situations increase the safety of the supply chain as these situations were described by wholesalers themselves during the elaboration of the DR as the riskiest. According to 2015 Impact Assessment, "The European association of wholesalers distributors identified specific situations where fake medicines can enter their premises: (i) when the product is not obtained from either the MAH or the manufacturing authorisation holder and (ii) when the product is returned by another wholesale distributor or a pharmacy". In these specific situations, **the DR has taken the risks into account and indeed requires the wholesaler to perform verifications.**

Table 3 Article 23 of DR: a welcome flexibility granted by the legislation

The DR allows for adaptations of the verification procedures to accommodate for the characteristics of the supply chain of Members States. As such Article 23 of the DR allows MS to require wholesalers to verify the safety features and decommission the UI of the medicinal products they supply to specific categories of persons and institutions (e.g., dental practitioners, paramedics, armed forces, etc.). Almost all countries consulted made use of this possibility: out of **the 19 NCAs that responded to our survey, 18 (all but Malta) took the opportunity of Article 23 to adapt the verification modalities to the characteristic of their national supply chain**. Nevertheless, similarly to the confusion generated by the different national scopes of application of the safety features, discussed in section 4.2.3, varying national approaches create inconsistencies and complications for distributors and wholesalers operating across multiple countries. For instance, some countries might have more stringent measures for handling alerts or decommissioning procedures, while others may streamline the process to facilitate quicker resolution. **In conclusion, if national adaptations on verification procedures can create some confusion for the stakeholders of the supply chain, they nonetheless appear necessary for the accommodation of national specificities and other situation unforeseen by the EU legislation.** For example, while Czech Republic, Hungary, and Slovenia require wholesalers to decommission vaccines before they get supplied to vaccination centres, Spain extended these requirements to medicinal products supplied for disaster control, such as the during the COVID 19 pandemic. At last, wholesalers did not submit elements indicating their inability to adapt to these national specificities, implying that business practices can ultimately accommodate for them. Furthermore, in view of the theoretical risk involved in decommissioning which occurs early in the supply chain, **it might be appropriate for the NCAs to step up process audits to check that all those involved in Article 23 have put in place appropriate risk management process systems.**

4.4.3 Nevertheless, end-to-end verification procedures do not consistently prevent the diversion of authentic medicines into the illegal market

As mentioned in section 3.2.2, t**he legal supply chain is not entirely protected from the attempts of criminals to divert or steal medicine packs**. The OCLAESP (Central Office for Combating Environmental and Public Health Offences), which is the French authority responsible for fighting medicine trafficking, reported that diversion of medicinal products from the legal supply chain are mostly occurring when medicines get transported (e.g., from that manufacturer to the wholesaler or the wholesaler to the pharmacy), stolen from hospital pharmacies' storage, or when medicines get dispensed in community pharmacies based on fake prescriptions. As an illustration, the OCLAESP has estimated that 40% of the packs of Subutex dispensed in the Parisian agglomeration in 2017 were given based on fake prescriptions. In 2021, the OCLAESP has dismantled a trafficking

network worth 4 million euros. The medicines were stolen from two Parisian hospitals and 13% were exported to Egypt.

Other cases of diversion were reported in the EU/EEA. For example, during the 2014 operation "Vulcano" coordinated by the Italian NCA, investigations revealed that packs of Herceptin were regularly stollen from Italian hospitals, falsified, and then reintroduced into the German supply chain through unauthorized wholesalers. More recently, in 2022, the Bulgarian Drug Agency reported that a criminal purchased a pack of Enbrel (etanercept) from a registered pharmacy, replaced the pack's content with pencils, and then resold it to a local wholesaler. This last case happened with the complicity of the pharmacist who purposefully avoided to decommission the pack of Enbrel, according to the BDA, leaving the status of the pack active and thus fit for a later reintroduction into the legal supply chain. But it must be recalled that **medicinal products diverted from the legal supply mostly end up sold in the illegal market, and that the purpose of the DR is first of all to prevent falsified medicines to enter the legal supply chain, not legitimate medicines to be diverted out of the legal supply chain.**

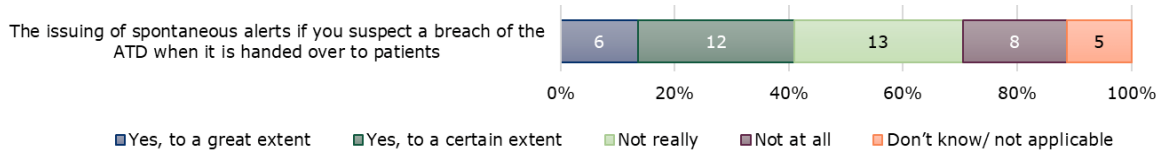
4.4.4 The lack of precision regarding ATD verification procedures can lead to loopholes while aggregation opportunities may need developments

ATD verification procedures

First, **the lack of precision in the DR related to ATD verification process** may lead to loopholes. In addition to the lack of standard mentioned in the DR for the ATD (see section 4.3.2), **actors (both stakeholders and NCA) also raise concerns regarding the lack of specifications related to ATD verification procedure**. Articles 18, 24 of DR states: "*Where a manufacturer/ wholesaler has reason to believe that the packaging of the medicinal product has been tampered with […] the manufacturer shall not release the product for sale or distribution and shall immediately inform the relevant competent authorities*". As such, there are no specific guidelines on how to conduct these verifications and the verifications are only declarative. Indeed, materializing the proof of verification would be impractical for the actors consulted (e.g., taking a picture of all the ATD verified seems not feasible considering the volume of packs involved).

As a result, end-users are not well aware of verification procedures related to ATD: less than half of the end-users who responded to the survey said they had received information/training on how to issue spontaneous alerts in the event of suspected falsified ATD. Thus, most of the actors interviewed admitted that verifying the authenticity of the ATD was a simple formality that never led to a product recall. **Thus, the verification of the ATD can remain a challenge for stakeholders.**

Figure 12 As people authorized / entitled to supply medicinal products to the public and representatives of the "end" of the supply chain, in contact with patients, have you been made aware / received training regarding the following? (n=44, one option possible)



Source: Survey to other stakeholders – EY/Ramboll elaboration

This difficulty has been confirmed during NCA inspections. Thus, the Swedish NCA said in a report relayed in EMVO newsletter[51] in 2022: "*The most common deficiency was pharmacists lacking knowledge of the purpose of the anti-tampering device and what to do when encountering a package with a broken or missing anti-tampering device*". Therefore, **there is a theoretical risk that a product falsified at the ATD level will be distributed** to patients.

Aggregation and "bulk verification"

Hospital pharmacies handle large volumes of packs of medicines daily, causing practical challenges regarding the verification and decommissioning of each individual packs. In France, for example, there are approximately 3 000 hospitals, using 240 million packs of medicines annually, representing 1 540 boxes per week each in average. For the 41 hospitals of the "Assistance publique de Paris", the number of boxes used per week reaches in average 6 230 per hospital[52]. Assuming that verification take in average 3 seconds per pack,

[51] EMVS Community 2022 Holiday Bulletin
[52] Figures transmitted by the "Hospices Civiles de Lyon"

that represents more than 5 hours of scanning per week in the example of the hospital of the "Assistance publique de Paris," or more than 10 hours if verifications and decommissions are done in two steps. According to the hospital pharmacists consulted, verifications and decommissions are particularly difficult to conduct on a pack-by-pack basis for bulky, heavy, and/or refrigerated products. Moreover, these verifications require to dedicate equipment and rooms that are not allocated to other functions of the hospitals.

Thus, standard verification procedures are not adapted and flexible enough to fit the particularities of this type of stakeholder. In this context, bulk verification using "aggregated codes" or "consolidated codes" was developed to facilitate the application of the DR in hospital pharmacies. The focus below includes the main points developed in the case study specific to aggregated code.

Figure 13 Focus on aggregated codes

Aggregated codes are used to verify and decommission the UI of multiple medicine packs simultaneously. In practice, a supplier sends a shipment of products with their UIs and other relevant information (product name, expiry date, etc.) listed in a standardised data file. This data file can be matched to the shipment with an additional barcode, or "aggregated code", that is send along the shipment using a parallel repositories system to the EMVS. Once the hospital pharmacy has received the shipment and matched it with the corresponding data file using the aggregated code, it can decommission all products in the shipment without the need to scan each individual UI. Aggregated codes were discussed by the Member State Expert Group on Safety features, who approved their use by hospital pharmacies in a working paper published in 2018.

Specific consultations and investigations conducted in Ireland and France, two countries who have been experiencing with aggregated codes, has led to several conclusions. Firstly, **aggregation is widely supported by end users** and its promotion could highly improve the connection and participation rate of hospital pharmacies in the EMVS. Secondly, **the information contained in the data filed attached to aggregated codes could be better protected.** Indeed, information exchanged between end users and providers of aggregation services currently transit through a system parallel to the EMVS, and thus do not benefit from the provisions of the FMD or the DR. One recommendation suggested by the actors consulted in that sense is to standardise the process of aggregation in the European legislation. A second recommendation was to integrate the aggregation process within the EMVS to better secure flows of information. This last proposition was also promoted by the MS Expert Group in 2018: "ideally, for security reasons, this aggregation should be fully integrated into the EU repository system (EMVS and NMVSs)".

4.4.5 The desire to move towards a track and trace system is not relevant with the objective of combating falsified medicines, but it may be relevant with other purposes

Making the current system converge towards a full track and trace system **would require extending the verification requirements to all stakeholders of the supply chain**, including wholesalers, in all situations. Such a system would provide an exhaustive monitoring system of the flows of medicines at each stage of the supply chain and could be used, for example, to precisely locate medicines shortages and eventually to anticipate them.

Such an evolution has been largely debated among public authorities and stakeholders of the supply chain, leading to diverging views. Overall, **manufacturers tend to support the convergence of the current verification system into a track and trace system** to better monitor the movement of medicinal products across the EU/EEA. This would allow manufacturers to identify precisely where their products are distributed, and through which channels. **This proposition has also received the support of some NCAs**[53], who believe that such system could be beneficial for public health purpose by allowing the monitoring of shortages. However, **most of the other stakeholders do not share the same opinion**. Indeed, the survey to stakeholders found that 60% of respondents (95 out 157) believed that the system should "not at all" or "not really" evolve from an end-to-end system to a track and tracing system. Wholesalers argue that this system would require them to scan all the medicinal packs they handle, an operation deemed highly impractical and too costly for a low margin industry. The pharmacists interviewed shared mixed opinions on this issue. About half were worried that by extending the scope of the verifications and the purposes of the DR, they would be submitted to further reporting obligations and would have less control over their data. The other half believed that extending the track and trace system to patients (i.e., by reporting which patient was supplied which medicine) could also serve a public

[53] 10 out of the 19 NCAs consulted are explicitly in favour of using the EMVS to monitor shortages: Belgium, Bulgaria, Estonia, Ireland, Lithuania, Malta, Portugal, Slovenia, Spain, Sweden. 1 is explicitly against: France. The other did not mention monitoring shortages explicitly.

health objective, for example by facilitating product recalls in case medicines defects gets identified after dispensation.

Summing-up, **the convergence of the current end to end verification system into a full track and trace system presents advantages in terms of public health objectives, and most of all by allowing a better monitoring of shortages of medicinal products**. **This specific purpose, however, is outside of the scope of objectives of the FMD and the DR**, which is to combat the introduction of falsified medicines into the legal supply chain. On that note, the French Order of Community Pharmacists (CNOP), has developed a system a cost effective system allowing for the monitoring of shortages without relying on a track and trace system: when pharmacies do not receive a delivery of medicines 48 hours after the order was passed to the supplier, which corresponds to the definition of a medicine shortage in the French legislation, an alert is automatically send to the CNOP.

4.5 Relevance of the establishment, management, and access of the repository (governance)

The DR (EU) 2016/161 establishes the **stakeholder-led model of governance for repositories system**[54]. The main purpose of these repository systems is to serve as the verification platforms that pharmacies or other registered parties – such as wholesalers, self-dispensing physicians or hospital pharmacies – use to check the authenticity of a product[55]. Article 31 of the DR specifies that **the repositories system should be set up and managed by a non-profit legal entity established in the Union by manufacturers and MAHs of medicinal products bearing the safety features**[56]. The DR further requires the industry to bear the costs of the repository system[57]. Wholesalers, persons authorised or entitled to supply medicinal products to the public, and NCAs are encouraged to be involved in the legal entity on a voluntary basis, at no cost[58]. In particular, NCAs may participate in the management board of the legal entities managing those repositories to the extent of up to one-third of the members of the board[59]. Moreover, NCAs have a supervisory role of the NMVS of their respective Member State, for which they are allowed to access the NMVS[60].

The structure of the EMVS is **divided into 2 main levels**:

- At EU level, **the EMVS is represented by the European Medicines Verification Organisation (EMVO),** also which runs the EU-hub. EMVO is responsible for assisting pharmaceutical companies and parallel importers in establishing their connections to the EU-Hub. The governance of the EMVO relies on the collaboration of the key stakeholders in the supply chain represented at European level by the organisations mentioned in brackets, i.e.: manufacturers (EFPIA and Medicine for Europe), parallel distributors (Affordable Medicines Europe), wholesalers (GIRP), pharmacists (PGEU) and hospitals, (EAHP and HOPE). The EAHP (European Association of Hospital Pharmacists) and the HOPE (European Hospital and Healthcare Federation) are affiliated stakeholders. Each of these organisations appoints one member to serve on the EMVO board and these members have voting rights, except EAHP and HOPE which participate in the organisation as observers, therefore they do not have voting rights[61].
- At the national level, **the governance of the NMVOs replicate the governance of the EMVO** with some national specifies reflecting the structure of the local industry.

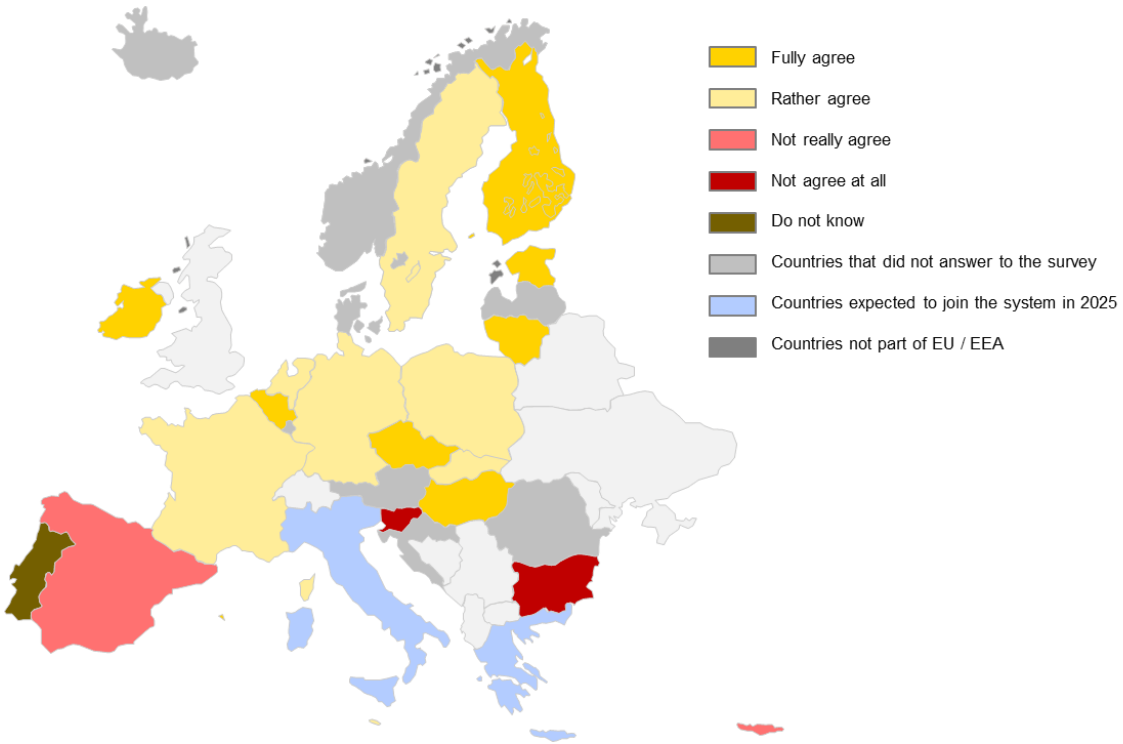
4.5.1 The choice of a stakeholder-led governance model was appropriate by directly involving stakeholders concerned by the measures

Feedback from the 19 participating NCAs in the survey indicates that the majority of them either fully or rather agree that both the EU-Hub's repository system and the NMVS repository system meet their expectations. Specifically, 13 NCAs fully/ rather agree that the EU-Hub's repository system meets their expectations, while 15 fully/ rather agree on the same for what concerns the NMVS' repository system. In addition, **12 NCAs fully/ rather agree that a non-profit organisation driven by private stakeholders is the most suitable entity** for managing the establishment of the EU-Hub, while 14 NCAs fully/ rather agree on the same for the NMVS.

[54] DR
[55] https://emvo-medicines.eu/mission/emvs/
[56] Article 31 DR
[57] Ibid, paragraph 5
[58] Ibid paragraph 3
[59] Ibid paragraph 5
[60] Article 39 DR
[61] As non-voting members, EAHP and HOPE only pay a fraction of the fees normally paid by stakeholders to participate to EMVOs' Board (500 euros according to HOPE).

With regard to the involvement of all relevant stakeholders in the pharmaceutical sector and public authorities in the governance of the EMVO, **13 NCAs fully/ rather agree that this inclusion is adequate and effective**, however the number of NCAs that fully/ rather agree drops to 10 with regard to the same statement vis-à-vis the governance of the NMVO. In contrast, only 7 NCAs fully/ rather agree that the representation of the different stakeholders of the pharmaceutical sector and the public authorities at the governing board of the EMVO is balanced and allows for the achievement of the objectives of the FMD, while 8 NCAs fully/ rather agree on the same statement for what concerns the governance of the NMVO.

Figure 14 Q12 "To what extent do you agree with the following assertions regarding the adequacy of the stakeholder-led governance, as defined in the DR? "A non-profit organisation driven by private stakeholders is the most adequate type of entity to be in charge of the establishment and management of the repository system in your country (i.e., the NMVS")"



Source: Survey to NCA – EY elaboration

The views of the stakeholders regarding the governance system were similar to those of the NCAs. 169 out of 205 (83%) stakeholders surveyed did not consider that governance problems (e.g., conflict of interest between member of the NMVO/EMVO boards) could hinder the achievement of the objectives of the DR and the FMD. On the contrary, a vast majority of the stakeholders praised the principles of the governance system. At the national level, the stakeholders unanimously recognized that a stakeholder-led governance is a driver of swift implementation and engagement, as it directly involves the actors responsible for implementing the verification system.

At the European level, while the actors interviewed also recognized the virtue of the system in term of effectiveness of implementation of the verification system, they have also noted some challenges. All the European stakeholders' associations interviewed mentioned that diverging views among stakeholders **could hinder EMVO's board ability to strategic decisions.** Concerns were also raised about the lack of enforcement powers given to EMVO.

In conclusion, the stakeholder-led model of governance was therefore the most appropriate of the options considered. It represents a unusual approach to ensuring the authenticity of medicinal products across EU/EEA. Such a stakeholders-driven model seeks to involve the most concerned actors of the supply chain in order to engage them in implementing the DR 2016/161 framework, by defining the technical options and by co-building the system in appropriate wat. As per Recital 3 of the DR, "*the policy options identified as the most cost-effective have been introduced as core elements of [the] Regulation.*" The current governance system is also an

innovative organisation, unprecedented at the EU/EEA level, to supervise the implementation and day to day monitoring of a public health policy.

Benchmark Focus

In comparison, both the **Italian and the Greek medicine verification systems are State owned, publicly funded, and supervised by the national competent authorities**: AIFA (Agenzia italiana del farmaco) in Italy and EOF (National Organization for Medicines) in Greece. Stakeholders of the pharmaceutical supply chain participate to the system in their respective role (e.g., manufacturers or MAH place the "authenticity sticker" on medicinal packs, pharmacists decommission medicinal packs at the end of the supply chain, etc.), but do not contribute to the supervision of the system in both Italy and Greece, unlike in the EMVS. Still, AIFA and EOF can request the support of stakeholders for investigation purposes.

According to the NCAs' representatives interviewed, **both Italy and Greece are planning to join the European Medicine Verification System.** They argued that integrating the medicine verification system of all the EU/EEA Member States is not only a legal requirement, it would also increase the safety of European patients by uniformizing medicine verification standards and processes, making it harder for falsifiers to exploit eventual loopholes.

To be compliant with the FMD and the DR, the integration of Italy and Greece to the EMVS **will require some important governance change**. Most of all, local stakeholders of the pharmaceutical supply chain will need to participate to the governance and the funding of the system, while the NCA will no longer be in position to operate it. In practice, the stepping down of the AIFA and the EOF was not raised as a challenge during interviews with both actors. In Greece, the NMVO has already been formed.

4.6 Relevance of the architecture and scope of the repositories system

CONTEXT BEFORE DR

Prior to the DR, some EU Member States such as Belgium[62] were already operating data bases monitoring medicinal packs with bar codes on them for the purposes of authentication and traceability. As highlighted in the 2015 Impact Assessment, however, these data bases were not interconnected and were thus unable to recognise the bar code system used in the other countries. As such, it was for example difficult to trace electronically a medicinal pack produced in Greece and sold in Belgium.

4.6.1 The design of the repositories system (two-tier architecture) has been well thought out but it makes investigation more difficult in case of IMT alerts

The Article 32 of the DR (EU) 2016/161 states that the repositories system has to be structured around two levels:

- **The hub** (in practice, the "EU-Hub") is owned and managed by the European Medicines Verification Organization (EMVO). The EU-hub acts like a router, i.e a networking device that forwards data packets between computer networks between the national systems and MAH.
- **National repositories** must be implemented in each participating country by a National Medicine Verification Organization (NVMO), which runs and manages them. The national repository holds the relevant safety features data for the national markets, receive data from the EU-Hub and serve as a verification platform for pharmacies, wholesalers, and other registered parties to check the authenticity of a product. Multiple MS can also share the same "supranational repository" (e.g., Belgium and Luxembourg both use the Belgian Medicines Verification System).

National authorities and actors consulted (e.g., stakeholders of all EU/EEA and NCA) judged it as **overall relevant and functional**[63]. Operations between the EU Hub and the NMVS seem to flow rather smoothly and all the actors met testified to the speed of the requests sent.

Intermarket transactions (IMT) are good examples of this two-tier architecture of the system. This transaction is triggered when a pack is scanned in a country while the pack's UI is stored in the NMVS of another country. According to stakeholders, this type of transaction is rather rare but can happen in specific situation, for instance, when an end-user location is next to border and has medicines supplied by either country. According to EMVO, less than 1% of the transactions were IMTs in 202264. In an IMT, the pack's 2D barcode is sent to the EU Hub and then to the local market for verification, and the response is sent back. **Overall, stakeholders'**

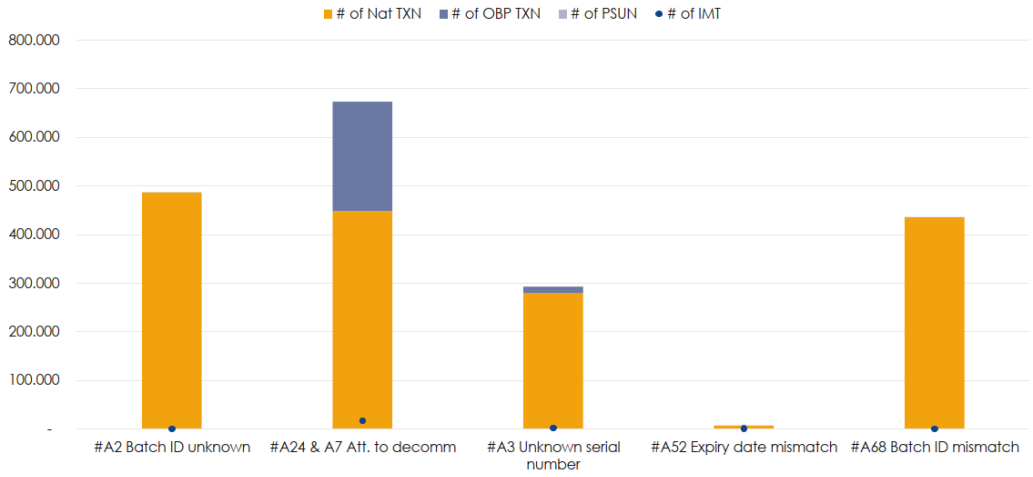
[62] It was also the case for Italy and Greece, where the DR does not apply as of 2023.

[63] For example, out of the 19 NCAs who answered to the survey question "Is the repositories system easy to operate", 4 fully agreed (Bulgaria, Estonia, Hungary, Poland), 8 rather agreed (Belgium, Cyprus, Czech Republic, Germany, Slovakia, Slovenia, Sweden, Ireland), 2 did not really agree (Lithuania, Spain), and 4 did not know (Finland, France Malta, Netherlands).

[64] EMVS Performance Review EU CCB May 2023.

opinion on the link between IMT and alerts are mixed: out of 98 respondents, 51 believe that IMT increase the risk of receiving alerts compared to national transactions, 33 believe that this risk is limited, 10 do not think this is a risk at all and 4 do not know. That being said, IMT are only involved with a marginal of the alerts effectively triggered in the system. The figure below presents the number of alerts per categories in the EU/EEA in September 2023, with those related to IMT.

Figure 15 Absolute number of alerts in September 2023 in all countries



Source: EMVO Monitoring Report for September 2023

Still on that topic of IMT, EFPIA and Medicines for Europe note two main drawbacks regarding this specific type of transaction in their Discussion Report (November 2023): *"(i) it permits inscrupulous manufacturers to load data for their products to one market and allow other markets where the product is legitimately on sale to satisfy verification and decommission requests using the IMT functionality rather than using the local EMVS; (ii) it allows products to be moved freely across market borders without the physical need for repacking, thus allowing a product that is licensed for use in one market but not actually licensed for use in another to be traded across borders without the required re-packaging process being undertaken […] in short, this aspect of the system design inadvertently supports the practice of illegal parallel trade"*[65]. These drawbacks were not discussed by other actors during the data collection of the evaluation and cannot be triangulated by other data sources. As a result, the Study team cannot draw clear conclusions due to the lack of additional data on these findings from the manufacturers' side.

On another note, some NMVOs mention that **this two-tier architecture makes data accessibility more complex.** According to Claude Farrugia (MAMVO) and Ita Gordon (IMVO) in EMVO October 2022 newsletter: "*the local NMVO can only see the events that happened locally but not events that happened in other markets, such as the pack creation details or a change of pack status. For these alerts, collaboration with the NMVO of the fulfilling market is essential to understand the full history of the pack and resolve the alert."* Indeed, information (e.g., cause of alerts, full audit trails) of medicinal product originating from another EU/EEA markets are more difficult to retrieve than for product manufactured and distributed in the same country, as reported by the NCAs of Bulgaria and Lithuania.

This it to be linked with the audit trail provision: ss stipulated in Article 35(1)(g) the **audit trail** has to be immediately available to the competent authority of a Member State following a substantiated request by such authority, which would not be the case currently according to different sources.

- According to EMVO, "*NCAs have reported that the Ozempic case demonstrates the need to implement the complete and detailed A1 Report – Full audit trail as soon as possible to enable a faster and more effective investigation across countries"*[66].
- This subject also raises debates. The term "substantiated" has been further explained in a Letter from SANTE.D.2 to EMVO and refers to a request that is made "*in the context of a specific*

[65] These two elements express the opinion of EFPIA and Medicines for Europe and not of the Study team, which does not have additional elements on these subjects to confirm / qualify these comments. These two observations are therefore linked to the nature of these organisations.
[66] Ozempic Report Case EMVO Report.

investigation on a behaviour or product under investigation […] evidence to support the request should be delivered with the request"[67]

- Finally, the Discussion Report from EPFIA[68] and Medicines for Europe states that one issue of concern is "*the non-delivery of the full audit trail at the request of NCA and the persistent blockage by some EMVO members to meet the legitimate request of NCA*".

These documents and sources were provided to the evaluation team at the end of the evaluation process (after the final project report) and this topic was not really addressed by the actors interviewed during the evaluation collection. Thus, if **these few testimonies tend to demonstrate that the accessibility of full audit trails are not guaranteed, the evaluation team cannot conclude on the extent of this problem**.

Summing-up, **this two-tier architecture (NMVS – EU-Hub) is relevant as it allows for national data to be stored and managed nationally and permits transfer of information when needed**. This structure also leaves the possibility to MS to adapt the system to national specificities. Nevertheless, this **two-tier architecture makes investigations make more difficult** in case of alerts raised via IMT. This is because of the limited information that would be available to the local NMVO. **Should the audit trails not be consistently and immediately available, it constitutes a notable pitfall**.

4.6.2 The scope of the repositories system is relevant towards the fight against falsified medicines but access to data remains unclear for some stakeholders

Two elements must be considered when assessing the relevance of the scope of the repositories system: (1) which actors have access to the system and (2) what for.

As regard to the second element, the main tasks the repositories system should provide for, as stated in Article 32 (3) of the DR, are to:

> *"(a) upload, collate, process, modify and store the information on the safety features that enables the verification of the authenticity and identification of medicinal products;*
>
> *(b) identify an individual pack of a medicinal product bearing the safety features and verify the authenticity of the unique identifier on that pack and decommission it at any point of the legal supply chain."*

Besides, **the repositories system should be accessible to NCAs** for a number of purposes. As stated in Article 39 of the DR, EMVO or the relevant NMVO "*shall grant access to [the repositories system] and to the information contained therein, to competent authorities of that Member State for the following purposes: (i)* ***supervising*** *the functioning of the repositories and* ***investigating*** *potential incidents of falsification; (ii)* ***reimbursement****; and (iii)* ***pharmacovigilance*** *or* ***pharmacoepidemiology***."

By allowing for the identification and authentication of medicinal packs, as stated in Article 32 of the DR, **the medicine verification system directly meets the objective to combat the introduction of falsified medicines into the legal supply chain.** Indeed, verifications must allow for the identification of falsified medicine prior to the delivery to patients. As an illustration, the Bulgarian Drug Agency reported that a company responsible for repacking medicinal products destined for the Dutch market identified falsified packs of Keytruda (an anti-cancer medicine) in June 2022, as the repositories system triggered an alert for inconsistent batch number during verifications.

Debates were raised among NCAs regarding the scope of <u>purposes</u> of the repositories system, as listed in Article 39 of the DR.

- Firstly, **the four purposes indicated were unequally used by the NCAs**, with all of the 19 consulted using it for investigation purposes, and only 3 for pharmacovigilance or pharmacoepidemiology (see table below). This shows the adequacy of the scope of the repositories to its objective of combatting falsified medicines, to which NCAs contribute by using it for investigating into suspected cases of falsification.
- Secondly, 10 out of 19 NCAs[69] consulted recommended extending the scope of utilization of the repositories system to **shortage monitoring**. This evolution as discussed in section 4.4.5, could

[67] Letter to EMVO 06/10/2023 Commission Delegated Regulation (EU) 2016/161 – My reply to Ms Passarani PGEU Secretary General of 13 November 2022.
[68] Discussion Report November 2023, EFPIA, Medicines for Europe
[69] Belgium, Bulgaria, Estonia, Ireland, Lithuania, Malta, Portugal, Slovenia, Spain and Sweden.

serve an objective of public health protection, but would part from the initial objective of the DR and the FMD, which is to secure the legal supply chain from falsified medicines.

Figure 16 Utilization of the Repositories system by the NCAs

	BE	BG	CY	CZ	EE	FI	FR	DE	HU	IE	LT	MT	NL	PL	PT	SK	SL	ES	SE
Supervising	X	X		X						X	X	X		X	X		X	X	X
Investigating	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Reimbursement	X	X													X			X	
Pharmacovigilance or pharmacoepidemiology		X															X	X	

Source: Survey to NCA – EY Elaboration

With regards to the scope of actors <u>having access to</u> the repositories and the data contain therein, in addition to NCAs who can access it for the purposes indicated in Article 39, manufacturers, MAH, wholesalers and person authorized to deliver medicinal products to patients connected to the EMVS can access the repositories system under the condition stated in Article 38 of the DR:

- *"1. Manufacturers, marketing authorisation holders, wholesalers and persons authorised or entitled 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)70 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)."*

<u>On NCAs access to the repositories system</u>, the general practice witness during consultations is that **suspected cases of falsification are flagged to NCAs by their respective NMVO for investigations** and confirmations of the offense. As an illustration, in the 2022 Keytruda case mentioned above, the wholesalers from where the falsification activities originated was identified by analysing audit trails and through additional field investigations. As such, the fact that NCAs can access the repositories system for the purpose, among others, of investigating suspected cases of falsification, seems **entirely consistent with the objective of combating falsified medicines**. In practice, as explained above, **the audit trails would not be consistently and immediately provided to NCA**.

With regards to <u>stakeholders' access to the repositories system</u>, it is necessary to upload and verify UIs, as required in the DR. Nonetheless, the **exact extent to which stakeholders have access to the data contained in the repositories system caused a number of debates** and concerns among the stakeholders consulted. Interviews with EU and national level organisations representing manufacturers, parallel traders and community pharmacies revealed that **data protection can be a critical challenge** in implementing the DR. Indeed, disagreements and concerns can arise between manufacturers and other stakeholders in the supply chain, particularly over the ownership of the data and the extent of transparency if access to the data is granted. This challenge revolves around the access manufacturers would have to commercially sensitive information, such as patient data, stock levels and supply chains information, which in many cases they are not supposed to

70

"(a) the data elements of the unique identifier in accordance with Article 4(b);
(b) the coding scheme of the product code;
(c) the name and the common name of the medicinal product, the pharmaceutical form, the strength, the pack type and the pack size of the medicinal product, in accordance with the terminology referred to in Article 25(1)(b) and
(e) to (g) of the Commission Implementing Regulation (EU) No 520/2012 (1);
(d) the Member State or Member States where the medicinal product is intended to be placed on the market;
(e) where applicable, the code identifying the entry corresponding to the medicinal product bearing the unique identifier in the database referred to in Article 57(1)(l) of Regulation (EC) No 726/2004 of the European Parliament and the Council (2);
(f) the name and address of the manufacturer placing the safety features;
(g) the name and address of the marketing authorisation holder;
(h) a list of wholesalers who are designated by the marketing authorisation holder, by means of a written contract, to store and distribute the products covered by his marketing authorisation on his behalf."

possess[71]. The lack of enforcement and monitoring mechanisms for countries and stakeholders misusing data is another issue in this regard[72]. In countries such as France, concerns about data privacy led community pharmacies to adopt a "connector", which is an intermediary between the NMVS and the IT equipment of pharmacists anonymising data transmitted.

While no proof of breach of data privacy were identified during the study, the concerns expressed by the stakeholders can result either from a lack of enforcement or a lack of awareness of the DR regarding data protection on the repositories system. Indeed, as mentioned above, Article 38(2) specifically provides that stakeholders shall only have access to the data they generate when they interact with the system. In addition, Article 35(h) provides that:

"in accordance with Article 38, its [the repositories system] 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"

Benchmark Focus

In addition to preventing falsified medicinal products to be distributed to patients through the legal supply chain, both the Italian and the Greek verification systems also allows for the monitoring of reimbursements of medicines, pharmacovigilance/ pharmacoepidemiology, but also the monitoring of shortages/ traceability of medicines.

Regarding the ownership and access to data circulating in the system, the Italian system is comparable to the EMVS, as stakeholders are the owners of the data they generate using the system and can always access them. In Greece, the NCA can grant access to the data to third parties depending on their level of confidentiality and the nature of the request (e.g., everyone can verify the status of a medicinal pack using a dedicated platform operated by EOF).

Overall, **when compared to the European System, the Italian and the Greek verification systems cover a larger scope of purposes and grant public authorities a facilitated access to the data contained therein, as they are directly operating it**. These gaps can cause some challenges for the integration of Italy and Greece into the European system. During an interview, a representative of the Italian NCA, the AIFA, acknowledged that the key challenge to address prior to the entry into force of the DR in Italy was the differences in functionalities between the Italian verification system and the EMVS. Reportedly, Italy has sent a proposition to the European Commission to preserve some of the characteristics of its national system after joining the European system. The Italian NCA has also requested to postpone Italy's connection to the European system considering the Commission's proposal for the revision of the EU pharmaceutical legislation. Indeed, an eventual evolution of the legislation may impact the DR, and thus the adjustment Italy will be required to make to join the European verification system.

4.7 Relevance of the reporting system

CONTEXT BEFORE DR	Even prior to the DR, MAH were under the obligation to report to EMA any product quality defect of centrally authorized medicine. In addition, the concerned MAH had to notify the NCA of the Member State where the suspected defective products are distributed[73]. Besides, a rapid alert management system was in place for NCA of different Members States to inform each other of defective medicinal products susceptible to cause serious risk to public health. The UK, for example, used the system as soon as 2007 to notify other NCAs that 72 000 packs of counterfeit Casodex, Plavix and Zyprexa have entered its market and were distributed across Europe, as mentioned in the 2015 Impact Assessment. Prior to that, a communication system based on fax was in place for authorities to exchange information[74]. That being said, no centralised and automated reporting system specific to falsified medicines was in place across the EU/EEA prior to the DR. Notification to EMA were being done by NCAS filling forms, only centrally authorised products were recorded by EMA (which is still the case today), and no dedicated file on falsified medicines were kept by EMA before 2017, as reported by EMA.

[71] In that regard, Recital 37 of the DR states that in order to ensure the protection of personal and commercially confidential data, "manufacturers, marketing authorisation holders, wholesalers and persons authorised or entitled to supply medicinal products to the public should only have ownership of and access to the data they generate when they interact with the repositories system".

[72] EU level stakeholder interviews.

[73] Quality defects and recalls | European Medicines Agency (europa.eu).

[74] According to DG SANTE.

4.7.1 The reporting system based on two alerts mechanisms adds security for the legal supply chain

The DR provides for two alerts (or flagging) mechanisms in the events of a potential case of falsification:

- Articles 18, 24 and 30 refer to a **spontaneous flagging mechanism** should a stakeholder in the supply chain suspects a case of falsification in the stock the stakeholder handles. Where a "manufacturer" (Article 28), a "wholesaler" (Article 24) or a "persons authorized or entitled to supply medicinal products to the public" (Article 30) "*has reason to believe that the packaging of the medicinal product has been tampered with or the verification of the safety measures shows that the product may not be authentic, the manufacturer shall not release the product for sale and shall immediately inform the relevant competent authorities*". Besides, as mentioned in section 4.4.2, end users to perform a simple verification of a "pack at hand", without changing its status. In practice: (i) the operator first scans the pack; (ii) the data scanned are then compared to the data stored in the national system; (iii) the system finally returns the status of the pack.
- Articles 36 and 37 refer to an **automatic alert mechanism triggered by the EMVS itself**. "*The repositories system shall provide for […] the triggering of an alert in the system and in the terminal where the verification of the authenticity of a unique identifier is taking place when such verification fails to confirm that the unique identifier is authentic in accordance with Article 11 [A unique identifier shall be considered authentic when the repositories system contains an active unique identifier with the product code and serial number that are identical to those of the unique identifier being verified]. Such an event shall be flagged in the system as a potential incident of falsification except where the product is indicated in the system as recalled, withdrawn or intended for destruction*"

Alerts or flagging of suspected cases of falsification are then investigated. If confirmed, the cases must be notified to public authorities. As per Article 37 (d), the repositories system should: *"provide for the immediate investigation of all potential incidents of falsification flagged in the system in accordance with Article 36(b) and for the alerting of national competent authorities, the European Medicines Agency and the Commission should the falsification be confirmed;"*

In practice, **investigation work is performed by both the NMVO and the NCA** in the country where the suspected case of falsification was detected. In France for example, the NMVO is first responsible for sorting the alerts triggered and to carry out initial investigations on the les problematic cases. These investigations typically involve contacting the stakeholders responsible for the alerts and addressing technical and human errors. If this initial investigation fails to identify the cause of the alert, the case is then transmitted to the NCA, who conduct further investigation. Overall, NMVOs benefit from a very positive image of their reporting and investigation role, especially from NCAs: 17 out of 19 NCAs surveyed stated that the NMVO has the capacity and capability to investigate and notify real alerts (including 7 "absolutely").

Summing-up, it is fully relevant that the IT system backed by an obligation to carry out compulsory investigations in the event of alerts by the NMVO should be supplemented by an obligation to provide spontaneous information in case of suspicion. Firstly, end users can perform simple verifications of the medicinal packs they handle all along the supply chain. If they suspect a case of falsification, they shall flag the case to the competent authorities. Secondly, the automated alert mechanism should identify cases of suspected falsification at the end of the supply chain, when packs are decommissioned before delivery to patient (or in the cases listed in Article 23 of the DR), should spontaneous verifications have missed the suspicious packs upstream in the supply chain or if such packs get introduced in the chain after verifications are conducted. **Ultimately, such design is adequate with the objective of the DR to prevent falsified medicine to be delivered to patients though the legal supply chain.**

4.7.2 The DR remains unclear about the actual details of the spontaneous alert mechanism

Based on Articles 18, 24 and 30, **a certain lack of clarity can be noted regarding the actual terms and conditions of spontaneous reporting**. These articles mention that in the event of suspicion ("has reason to believe that the packaging of the medicinal product has been tampered with or the verification of the safety measures shows that the product may not be authentic"), the stakeholders "shall immediately inform the relevant competent authorities".

This raises a number of questions:

- **the identity of the person who should be informed**: the DR suggests that this should be the NCA, but in practice the players unanimously turn to the NMVOs, who are their main contacts.

- **the time of reporting**: at what point does a product become suspicious, and when exactly should players report spontaneously?

5 Assessment of the functioning of the measures set out in Delegated Regulation (EU) 2016/161

This chapter is complementary to the first and aims to assess the **functioning of the system** established by DR (EU) 2016/161 in the context of combating falsified medicines. Thus, the relevance of the measures will no longer be studied, but the evaluation instead **focuses on the current implementation of the system and its proper functioning:** what obstacles/good practices can be observed? What is the assessment of the implementation of the system 4 years after the entry into force of the DR? The purpose of this chapter is therefore to answer the set of evaluative questions from the point of view of functioning.

- EQ1.1, the evaluation considered both the functioning of the stakeholder-driven governance of national-level systems, (scrutinising how stakeholders interact within their respective national medicines verification systems), and of EU-level systems (assessing the European Medicines Verification Organisation's role and its interactions with the involved stakeholders). This analysis drew insights from desk research and input gathered through stakeholder consultations, including interviews at national and EU level.
- EQ1.2: the evaluation studied the respect of the technical specificities set out in the DR. The quality of the UI and specifications for the purpose of limiting fraud was also assessed.
- EQ1.3: an assessment of the overall operation of the computer system is provided. The connection of users to the system as well as the different uses were also observed.
- EQ1.4: the evaluation also checked whether the checks were actually carried out at the level of the various actors involved.
- EQ1.5: the analysis of the alerts issued was carried out, based in particular on the lessons of Topic 1 of the Study questions (Trends and developments in the market of falsified medicines.

This chapter also provides answers to Study Questions Q5 to Q7 (Topic 2):

- Q5: How many notifications of suspected falsified medicinal products were reported to the European Medicines Agency (EMA) and to the national competent authorities in the EU/EEA? How many of these suspects were eventually confirmed?
- Q6: How many unique identifiers have been decommissioned and how many of these have seen their status reverted to active?

Key findings

Governance

- **The stakeholder-led governance model** has empowered supply chain stakeholders by integrating them directly in the operational decisions and also allowed for a relatively rapid implementation of the EMVS (except for hospital pharmacies).
- However, **challenges have emerged notably pertaining the fulfilment of the supervisory role of NCA.** This is confirmed by the limited number of inspections carried out (only half of the NCA surveyed), their recognition of their lack of expertise (IT, technical) and the small number of NCA sitting at the NMVO Board. Challenges related to transparency and accessibility of NMVO data also remain points of concern, as well as the lack of leverage of public authorities and NMVOs over software providers (e.g., to make fix IT issues in a timely manner).

UI and ATD:

- **Manufacturers comply with the DR requirements with regards to UI** and all medicinal products produced and intended to be placed on the market bear UI. The printing of UI did not generate any consequent problems for manufacturers, even if cost of update / equipment may have been high in the first place especially for small manufacturing firms. **Challenges remain with regards to readability of the UI in specific and limited situations** (ex: when scanning refrigerated medicinal products as the UI can be erased with the condensation) or with specific box formatting (ex: small boxes) that are not to be linked with UI specifications.
- On the other hand, **the lack of standard of ATD undermines its effectiveness, as defined in the DR, to act as a reliable safety feature.** The ATD can be sometimes poorly affixed on devices package material so that it would come off during handling. This has already led to a few cases of falsification.

Repositories system

- Four years after the entry into force of the DR, **the EMVS operates in all EU/EEA countries** (expect Italy and Greece). National repositories system is also operational, except for Belgium and Luxembourg, as well as for Liechtenstein and Switzerland who share two supranational repositories. **All the operations planned in the DR (decommissioning, reversion of UI status, verification, etc.) have been made**

possible for the stakeholders and NCA but the quality of these operations is not yet sufficient as explained below.

- **Data upload** by Onboarding Partners (OBPs) is effectively carried out, but technical problems at this level explain subsequent alerts (input errors during upload, missing information, etc.). **Stakeholders' connection to the EMVS has accelerated over years** but still remains an issue, especially at the hospital pharmacies level (66% of hospital pharmacists in Spain need to be connected, as for 23% in France). Overall and as of September 2023, 0,83% of community pharmacies, 12,67% of hospital pharmacies and 0,31% of wholesalers are not connected to the system. The main reason is the reluctance to participate to a system often deemed unnecessary given the low perception of falsification risks in Europe and the technical difficulties for hospital pharmacies (decommissioning of large volumes of medicines daily).
- When the users are connected, the user experience and **the functionality of the EMVS are hindered to a great extent by the high alert rate, that remain above the level desired** (0,13% in August 2023 for a target rate set at 0,05%). These alerts are **mostly "false" alerts**, linked to technical / IT issues and human error from the end-user's side and not to be linked with the EMVS.

Modalities of verification

- According to data collected and case studies, **verifications of UI are carried out more frequently** but some users are still reluctant to do it in very different proportions from one country to another (ex: in Bulgaria only 51,40% of the packs are decommissioned even though all end users are connected to the EMVS). **In particular, wholesalers do not perform regular verifications, whether required or spontaneous,** and some community pharmacist admitted **decommissioning medicinal packs at the point of entry (e.g., when medicines packs get delivered to the pharmacies).** Still, **verifications along the supply chain allowed for the detection of a few falsified medicines**.

Reporting system

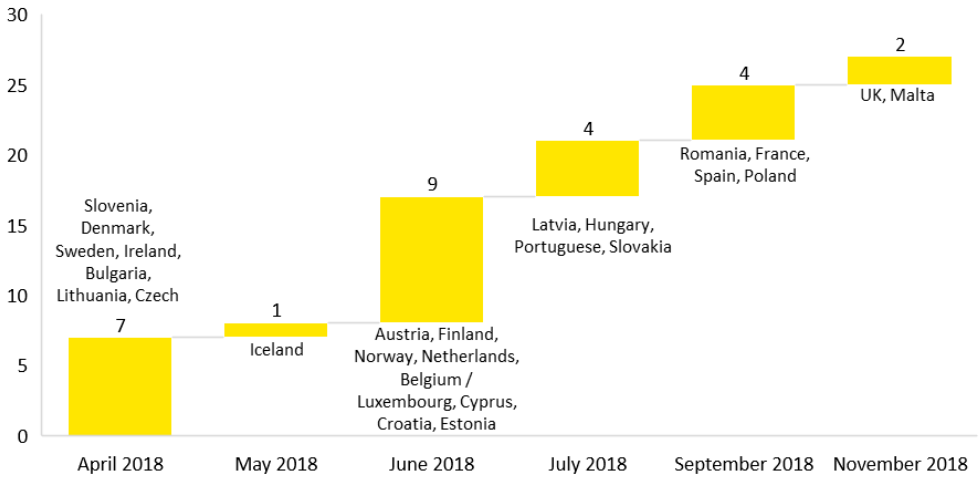
- Alerts emanating from the IT system and not explained by technical problems are **systematically investigated with the support of the NCAs.** However, **there are no homogeneous rules between MS on the follow-up of these alerts** by the NCAs and on the follow-up of suspected and confirmed cases. **Ad hoc and spontaneous information under Articles 18, 24 and 30 of the DR is rare** due to a lack of systematic verifications, the difficulty to detect a suspicion regarding ATD, and above all the lack of clarity of the process.

5.1 Governance: is the stakeholder-driven governance of the system functioning well?

5.1.1 Stakeholder-led governance was efficiently set up, yielding satisfactory results despite diverging stakeholder opinions

To implement the EMVS, all NMVS needed to be connected to the EU-Hub prior to the start of the Operational Phase on 9 February 2019. This objective was achieved, as shown in the graph below.

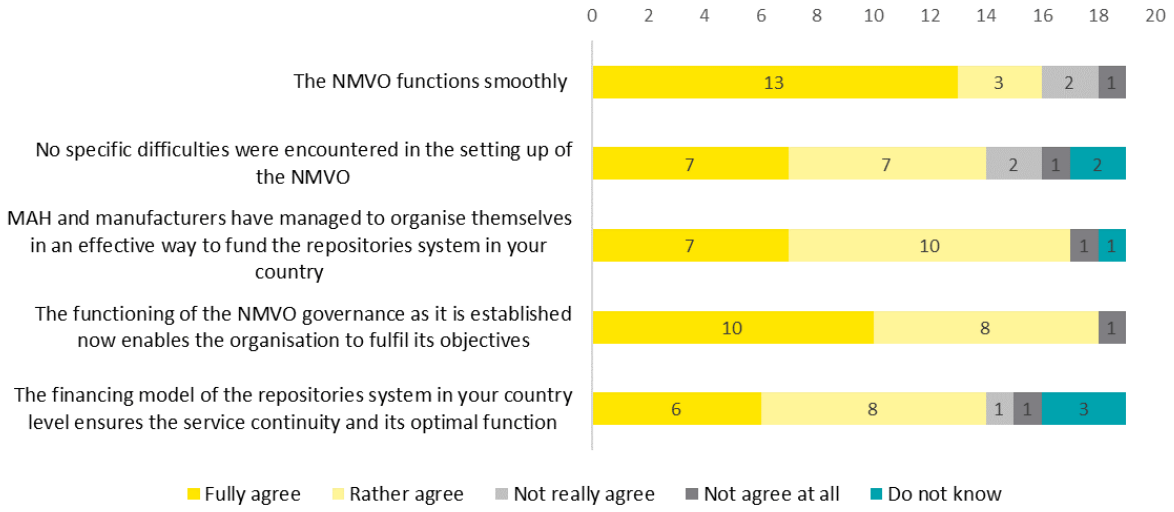
Figure 17 Breakdown of the countries according to the connection date of their NMVS to the EU Hub



Source: EMVO website – EY Elaboration. Note: The list of countries by month is shown in chronological order of connection.

With regards to setting up the NMVOs, most of the NCAs that took part to the survey reported that **this has not posed difficulties for most countries,** and manufacturers have managed to organise themselves to finance and manage the system.

Figure 18 To what extent do you agree with the following assertions regarding the functioning of the stakeholder-led governance at national level, as defined in the DR?



Source: Survey to NCA – EY Elaboration

Regarding the **financing model**, through the NCA survey 13 NCAs either fully/ rather agree that the financing model of the repository system at the EU/EEA level ensures service continuity and optimal function. Similarly, up to 14 NCAs express similar agreement at the national level. Furthermore, 13 NCAs indicate they fully/ rather agree with the appropriateness of the current EMVO governance structure, believing it enables the organisation to achieve its objectives at the EU level. For what concerns the NMVO structure, this view is shared by up to 18 NCAs.

Delving deeper into the assessment of the 8 countries which are the focus of this evaluation, **the representation of stakeholders within the NMVO board is generally balanced.** All categories of stakeholders involved in the deployment, such as manufacturers, wholesalers, and end-suppliers of the DR, are present within the NMVO. Hospital pharmacies are represented in 5 out of 8 NMVO countries, and parallel traders are also typically included on the board, except for Estonia and Spain. The most significant difference arises with NCAs, where only four out of 8 are involved in the NMVO.

The table below provides a more detailed breakdown of the types of actors within the NMVOs of the 8 countries under assessment.

	NCA	Organisation representing				
		manufacturers	wholesalers	parallel traders	community pharmacists	Hospital pharmacists
Belgium	Yes	3	1	1	2	1
Bulgaria	No	2	1	1	1	0
Denmark	Yes	2	1	1	1	1
Estonia	No	1	1	0	1	1
France	Yes	2	2	1	2	3
Ireland	No	2	1	1	1	0
Poland	No	3	1	1	2	1
Spain	Yes	2	1	0	1	0

Source: NMVOs websites

The audits carried out by the NCAs on the NMVO confirm the proper functioning of the NMVO. The Czech Republic, Estonia, Germany and Hungary inspected NMVOs and have not observed serious faults. Belgium and Cyprus are planning to have an audit. Also, the EMVO has audited several NMVOs but did not report results.

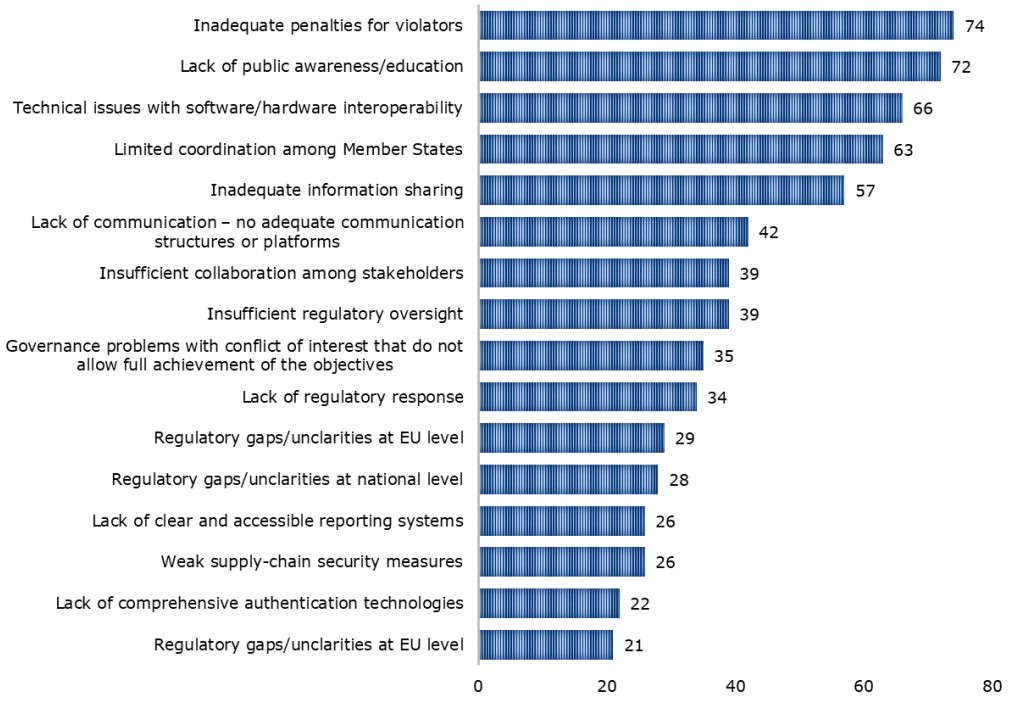
The analysis of the 8 countries studied also highlights **differences in the functioning and functionality of governance.** Indeed, the establishment of NMVO and their subsequent operation have been **facilitated in two main cases:**

- **in countries with a history of legislation related to falsified medicines**. In Belgium, the governance of the NMVO is described by all stakeholders and public authorities as notably well-functioning. This situation is reportedly due to the proximity between the different stakeholders, their history of cooperation on securing the pharmaceutical supply chain, and Belgium's acquaintance with a mixed governance model.
- **in countries with a limited number of stakeholders in the pharmaceutical supply chain**. In Estonia for instance, cooperation between stakeholders is described as smooth and well-functioning: the NCA and the stakeholders reportedly work in "intense collaboration", overcoming punctual complex discussions. In Ireland, the NCA highlighted a straightforward and collaborative process in setting up the Irish NMVO.

Summing-up, this model has achieved substantial progress in the effective functioning of the EMVS: feedback from NCAs suggests that the stakeholder-led governance model has generally met their expectations, with many NMVOs functioning effectively, especially in countries with a history of stakeholder collaboration or a streamlined pharmaceutical supply chain. This governance has empowered supply chain stakeholders by integrating them directly in the operational decisions and also allowed for a quite rapid implementation of the EMVS (except for hospital pharmacies). The specificity of this governance model implies the confrontation of divergent opinions that may impact the functioning of NMVO. The interviews were an opportunity to note that **certain subjects were causing tension** on the part of the stakeholders due to contradictory opinions. A good example is that of **data protection**. For instance, pharmacies and parallel traders are often highly protective of their data on trade flows, while manufacturers advocate for more data sharing to reduce the occurrence of false alerts and gain better insights into trade flows. This can result in a lack of responsiveness especially when quick decisions are required. In Spain, difficulties and delays in decision-making processes have been raised as concerns regarding the effectiveness of the stakeholder-driven governance system.

However, dialogue and cooperation generally allow at national level for the resolution of these specific points of tension. Supply chain actors acknowledge these challenges but do not prioritize them as highly compared to other issues. Governance-related problems related to diverging interests rank only 10th in the list of shortcomings and flaws of the current system, according to their perspective.

Figure 19 Are the following examples for potential gaps or deficiencies present in the current system? (n=204, Multiple options possible)



Source: Survey to other stakeholders (Q16) – EY/Ramboll Elaboration

In conclusion, **while stakeholder-led governance enables the involvement of all actors, strong differences of opinion between these actors sometimes affect the functioning of the NMVO and EMVO**. Nonetheless, while there are topics for debate, these appear to be to a large extent constructive and allow the dialogue to move forward in all cases. Besides, it seems logical that shared responsibility can sometimes slow down decision-making.

5.1.2 Most challenges of the governance pertain to the fulfilment of supervisory roles of NCA

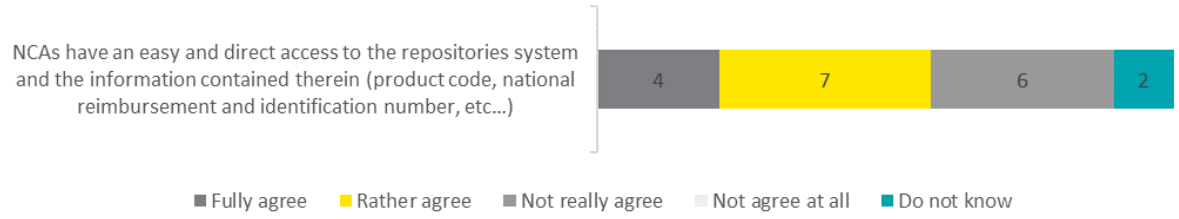
In several countries, **it is difficult for NCA to take on their supervisory role** as confirmed by the NCA survey: **half of the surveyed said they had encountered some problems** in fulfilling their supervisory role. This is reflected in three main observations:

- **the still limited number of inspections carried out**: according to the NCA survey, 9 out of 19 NCAs have not carried out an inspection since the RD came into force. Moreover, among those that have already carried out an inspection, it has often been late in coming: the Czech NCA did not carry out its first inspection until 2022, i.e. 3 years after the start, and in 2021 for Estonia.
- **their recognition of their lack of expertise in supervision mission**: for a number of NCAs (such as such as Hungarian, Lithuanian, Slovenian, Dutch and Spanish NCAs), there are both technical (lack of technical expertise to control repositories) or human (no independent teams able to take on this role) limitations.
- **the small number of NCAs sitting at the NMVO Board**: The survey of NCAs revealed that only five out of the 19 NCAs that replied to the NCA survey are part of the NMVOs. This lack of representation has led to a few NCAs reporting a limited ability to exert influence over the overall functioning of the NMVS and, more specifically, the NMVO boards. For example, in France, the Ministry of Health lacks the means to put pressure on manufacturers into promoting the development of aggregated codes for hospitals, which is considered vital for ensuring compliance with the FMD. Meanwhile, the Bulgarian NCA has recommended the introduction of quotas for representatives from various stakeholders and public authorities, along with enabling government bodies to exercise control over the NMVO Board.

Furthermore, while NCAs have a supervisory role and are permitted to access the repository system and its data for specific purposes outlined in Article 39 of the Falsified Medicines Directive (e.g., to supervise repository

operations, investigate potential falsification incidents, facilitate reimbursement, and support pharmacovigilance or pharmacoepidemiology), **there are challenges related to their actual ability to access and collect data**. Thus, while NCAs consider their obligations adequate, their fulfilment can be more complex in practice. Only 11 NCAs75 out of 19 respondents to the survey use the repositories system to supervise the functioning of repositories. Besides, 6 out of 19 NCAs respondents to the survey said they do not have an easy and direct access to the repositories system and the information therein contained. Most complaints concerned the difficulty for NCAs to extract data sets, that can be a lengthy and tedious process. Investigating suspected falsification activities can require, for example, the downloading of hundreds of audit trails, one by one, of the packs scanned by one suspicious actor.

Figure 20 To what extent do you agree with the following assertion regarding functioning of the repositories system (i.e., as a reminder, the EU Hub and the different NMVS) (Q24, n=19)



Source: NCA survey – EY elaboration

National context and lack of cooperation of stakeholders can also impact their ability to supervise. Some stakeholders may be more reluctant than others to use the system, such as pharmacists in Bulgaria (all connected but not systematic decommissioning). Supervision of the system is therefore more complex in these cases where consensus is hard to reach.

Besides, **the Italian National Competent Authority (AIFA) pointed out that the framework established by DR 2016/161 does not provide NCAs with full real-time access to the NMVS database**, in contrast to the current Italian system. According to AIFA, this limitation may pose challenges to the NCA's supervisory role.

In conclusion, **NCA are not always able to carry out their oversight role**, but this limitation stems from internal problems within the authority (lack of time, human resources, technical expertise), the IT system put in place does not sufficiently consider the competencies and resources of its users. Nonetheless, some evidences of **good practices do exist**: the French NCA for instance, in cooperation with law enforcement authorities and France MVO, use the information of the repositories system to support criminal investigations (e.g., cases of theft of medicines). Also, the Bulgarian Drug Agency (BDA) successfully use the EMVS data to identify suspicious behaviour and orientate investigation (*For more information on these two specific examples, please refer to the Section 6 related to Effectiveness*). Besides, the lack of the NCA's IT expertise can be mitigated to some extent as the DR does not necessarily imply that it is for the NCA to make the computer requests and manipulations: they can make requests directly to the NMVOs and are therefore no longer handicapped by the lack of IT expertise.

5.1.3 Limited operating challenges also exist

i. Fees to participate in the EMVS

Regarding fees for participating in the EMVS, numerous pharmaceutical companies are required to register and pay fees to each NMVOs and EMVO. This situation leads to duplication of costs. This results in the reluctance of some manufacturers and parallel traders to participate in the system. In Finland, some stakeholders did not participate as expected and were then removed from the repositories system. This situation is problematic as that can impact the availability of medicinal products. In Hungary, the problem of MAH refusing to pay fees is critical and appears complex because of the absence of authority of the NMVO (which cannot sanction) and the delicate position of the national authorities who want to avoid stock-outs of medicines. Some countries adopted good practices, such as France where the financing structure is organised around a revenue-based grid, that was reckoned by stakeholders to operate without significant hurdles.

[75] Belgium, Bulgaria, Czech Republic, Ireland, Lithuania, Malta, Poland, Portugal, Slovenia, Spain, and Sweden.

ii. Transparency and accessibility into NMVO data

Additionally, an issue of transparency in NMVO data and activities has been specifically highlighted. For instance, the Bulgarian NCA emphasizes the importance of making transcripts of board meetings, financial reports, and activity reports publicly available. This concern appears to extend to other NMVOs as well. Out of the 15 NMVO websites consulted, only the Czech Republic's NMVO provides annual reports for public access.

iii. Management of software providers

Globally, most actors complained about the **lack of responsiveness of software providers to solve IT issues** and the absence of provisions in the DR regarding software providers. This aspect was regularly mentioned during interviews and surveys, both from public authorities and stakeholders of the supply chain. NCAs have currently no authority to inspect software provider or to require them to address IT issues in a timely manner, nor to implement specific updates. This is exacerbated by the fact that there are only two software providers at the EU/EEA level, adding to **their "market power".**

In France for instance, 95% of alerts are produced by four software providers, and 84% produced by two. Effective management of these software providers would thus significantly reduce the alert rate in France and would also benefit end-users. This example is proof of the need to be able to exercise more control over software providers.

Summing-up, **the management of software providers is indeed an important issue that should not be neglected**, as it has a direct impact on the implementation and effectiveness of the system. nevertheless, this is more a matter of technical/contractual arrangements than possible amendments to the DR, which has no role to play in such matters.

5.2 Unique identifier and anti-tampering device: to what extent do the measures related to the technical UI allow for the effective verification of the authenticity of medicinal products?

5.2.1 Manufacturers comply with the DR as regard to the UI as no medicinal packs concerned by safety features were reported without a UI

In terms of process, following steps have to be followed in compliance with the DR:

- When generating and placing the barcode on the packaging of the medicinal product, the manufacturer must verify that it complies with the DR, that the UI is correct and that it is readable (article 14).
- Before the medicinal product is released for sale or distribution by the manufacturer, the MAH (or the person responsible for placing those medicinal products on the market in case of parallel imported or parallel distributed medicinal products) shall ensure that the information referred to is uploaded to the repositories system and that it is kept up to date thereafter (article 33(1)). In practice, this is undertaken by an On-boarding Partner (OBP), an agent defined by EMVO as a "legal entity authorised to upload UIs and other required information ('OBP Data') on behalf of a MAH, a Parallel Distributors or on its own behalf and who concludes the Participation Agreement with EMVO"[76].

The printing of UI on medicinal products has been deployed in all countries and no medicinal product required to bear safety has been reported without a UI placed on it. No noticeable differences can be distinguished between countries on the display of these safety features. **There is no registry compiling all the data related to the creation/application of UI since 2019** and it is therefore impossible to assess the dynamics.

At country level, all the NCAs surveyed indicate that the technical specifications of the UI are respected by manufacturers in their country. **The generation of UI did not constitute a real problem for manufacturers, since the DR was very specific on the technical details**. The implementation of the DR nevertheless requires substantial initial and on-going investment from manufacturers in serialisation and information technology systems. The cost of complying with these regulations can be burdensome, particularly for smaller manufacturers operating on tight budgets. The Spanish NCA for instance mentioned in the survey that this problem was solved in Spain using pre-printed packs.

Thus, **it appears that UI generation and printing have been effectively implemented**, and in a way that is overall compliant with technical specifications set the DR. But some operational challenges remain, as shown in the next section.

[76] On-boarding Guideline/Manual, EMVO, 2021.

5.2.2 A few challenges remain with regards to readability and upload of the UI into the repositories systems in specific cases

A small number of challenges has been observed throughout the Study, the first one being the **limited readability of the UI:**

- The most common problem is that of **printing the UI on small boxes and other irregular packs** (e.g., vials), as it becomes difficult to scan for end-users.

Benchmark Focus

As a comparison **Greece and Italy use a system of high-quality standardized stickers with authentication information printed on them.** These devices are reportedly easier to place on irregular packs. Both the Italian and the Greek NCAs also reported difficulties at first to place the "authencity stickers" on some irregular packs. In Greece, these issues are handled case by case, leading to the exclusion of some category of products for which the sticker is not adapted and for which the verification is not deemed necessary, such as medicinal gazes and radiopharmaceutical products. In Italy too, medicinal gazes are exempted from bearing an authenticity sticker.

- Reading problems can also be caused by **scanners' malfunction**. Two of the pharmacies consulted in France mentioned for example that some UIs were not easily readable by the average pharmacy scanners. EMVO's September 2023 monitoring report indicated in that sense that a number of alerts were triggered by scanners incorrectly reading "-" or "_" or "/", and "Z" for "Y". These scanning errors are also linked with software issues, as reported by EMVO.
- **Print quality issue**: for instance for refrigerated medicinal products. Having to scan the medicines means taking the boxes out of their refrigerated environment, inducing a change in temperature. This change creates condensation covering medicinal packs and sometimes erases the data matrix, making it impossible to read. According to the estimates of a French pharmacist interviewed, around 5% of refrigerated boxes are impossible to scan.
- **Difficulties in scanning**: a limited number of pharmacists raised issues scanning data matrix containing non-Latin letters (e.g., cyclic alphabet).

Furthermore, a **certain number of alerts are due to encoding and upload issues**. A2 alerts (missing or unknown batch ID issue), A3 alerts (Unknown or missing serial number), A52 alerts (expiry date mismatch), and A68 alerts (batch ID mismatch), which respectively account for 391 348 (30% of all alerts), 219 014 (17% of all alerts), 5 480 (less than 1% of all alerts) and 341 024 (26% of all alerts)77 alerts triggered in the EMVS in September 2023, have been linked, among other root causes identified by NMVOs and EMVO, with missing or incorrect information upload from On Boarding Partner (i.e., incorrect upload of the batch ID, expiry date or other information regarding the pack being scanned).

There is no data to qualify the root causes. It is therefore impossible to know if these types of alerts are caused by the UI itself, because of internal IT problems in the system or because of human errors during the upload (forgetting a number, adding an unintentional space etc.). However, according to estimates provided by EMVO based on feedback from NCAs, **the vast majority of UI upload errors are related to human error**. *For more information on alerts and root causes, see Section 5.3.3.*

Based on these observations, we can conclude that, **while the UI's printing processes are generally adequate and the technical specifications are respected, some operational problems are still encountered by end-users due to parameters external to the EMVS** (scanners malfunctions, etc.) Thus, these problems do not imply changes in the legislation but rather **operational and equipment evolvements**: updating scanners, printing the UI on plastic to prevent it from being erased in case of condensation, etc.

5.2.3 The lack of harmonization of the ATD is a loophole that has already been exploited by falsifiers

As mentioned in the Relevance part, **the DR does not specify physical standards for the ATD**. That has consequences on its reliability. A small number of wholesalers and end-users indeed stated in interviews that **the ATD was sometimes poorly affixed on devices package material** so that it would come off during handling (e.g., on glass or plastic liquid containers used for liquids). Even when properly placed on medicine packs, stakeholders confirmed that the ATD can sometimes be circumvented, as was for instance the case with a pack of "Enbrel" (etanercept) found in 2022 by a German repacked (the syringes were removed from the pack and replaced with crayons without apparent damage to the ATD). Besides, Affordable Medicines reported in an

[77] EMVO (2023), *EMVO Monitoring Report – September 2023.*

email that **not all packs of medicines have currently ATD on all sides of the box**, meaning that boxes can be easily opened and the content exchanged without leaving noticeable traces (when re-gluing it).

Indeed, the view of distributors and wholesalers responding to the targeted survey was that there is a lack of clarity at the EU level regarding the types of ATDs that can be used on packaging. Parallel traders responding to the survey **called for the focus to be placed on the ATD and the UI as a pair**, as in practice the UI can be applied by sticker, whereas the best method for verification is the ATD which has to be sufficient for leaving traces of tampering.

Thus, while the ATD is a necessary feature, this lack of standard prevents the ATD, as defined in the DR, from acting as a reliable safety feature. This is also a reminder that the system can work correctly **only if both safety features (UI and ATD) are implemented.**

A few suggestions were mentioned by stakeholders to improve the design of the ATD. The use of holographic labels instead of transparent stickers or the complete wrapping of the medicine packs were mentioned by some stakeholders. Other more sophisticated alternatives have been suggested by the literature, such as a "smart tracking system" able to record events occurring along a product's lifespan in real time and remotely[78]. However, manufacturers consulted, and especially manufacturers of generic medicines, were worried that the cost of a sophisticated ATD could be too high for low price and high-volume medicines.

5.3 Repositories system: to what extent is the repositories system as a whole suitable and functional?

As of November 2023, four years after the entry into force of the DR, the EMVS operates in all EU/EEA countries (except for Greece and Italy). Each country has its own national repositories system (except for Belgium and Luxembourg, as well as for Liechtenstein and Switzerland, who share two supranational repositories). The entire IT component of the system has been created and implemented by the software providers. It is dominated by two main IT service providers involved across the different countries:

- Solidsoft operates for the EU-hub and is active in 13 countries
- Arvato is active in 17 connected countries

The functionality of EMVS should be judged according to the 3 main types of usage it proposes: (i) connection of stakeholders, (ii) activity volumes and operations allowed and (iii) alerts. Besides, the evaluation should assess the stability and reliability of the EMVS as such. Finally, the user satisfaction must be assessed. Please note that the cost-effectiveness of EMVS cannot be assessed based on data provided by EMVO (topic currently under discussion).

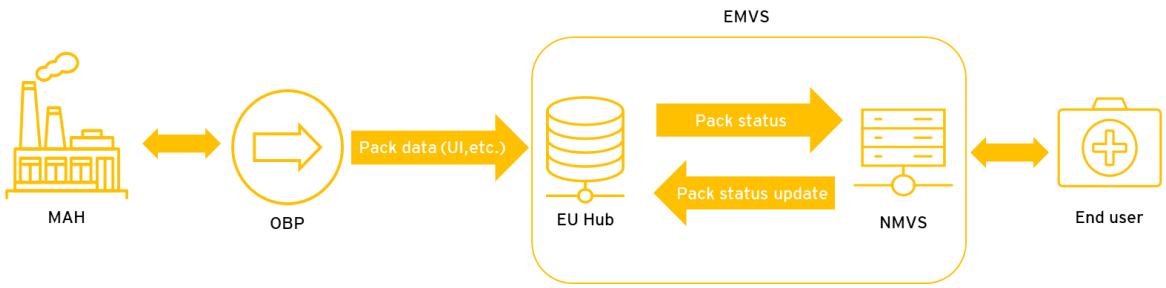
5.3.1 Usage 1: Connection of stakeholders

Overall, **stakeholders' connection to the EMVS has accelerated over years but still remains an issue**, especially at the hospital pharmacies level.

OBP / MAH / Manufacturers

Manufacturers are in charge, through OBP, to upload the data into the EU-Hub, as shown in the graph below.

Figure 21 Simplified Illustration of the functioning the Repositories Systems



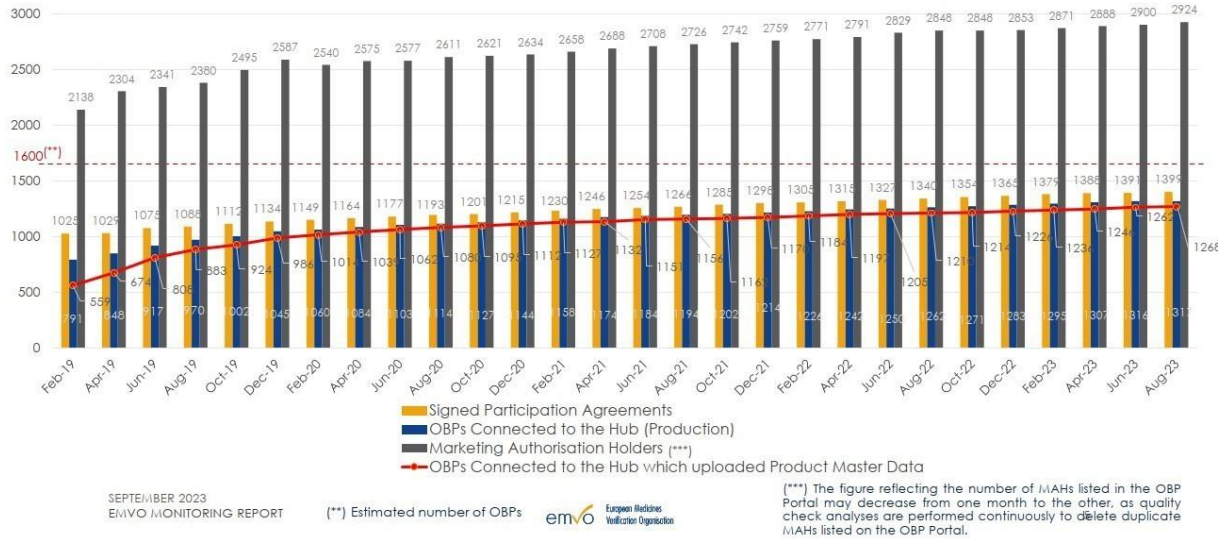
Sources: EMVO's documentation - EY Elaboration

[78] Rich Quelch (2019), *The future of tamper-proof pharmaceutical packaging (europeanpharmaceuticalreview.com)*

Connection of manufacturers to the system was slow. Five months into the operational phase of EMVS (July 2019), EMVO stated in a note[79] that **two fifths (40%) of manufacturers had not yet connected to the EMVS**. That explains that as early as July 2019, EMVO encouraged, through this same note, the NCA to start enforcing the primary requirements of the FMD and DR and undertake inspections on all supply chain stakeholders.

Learning how to upload data took even longer, as illustrated in the graph below: in February 2019, the number of OBPs connected to the EU Hub was not equivalent to the number of OBPs connected to the Hub and uploading data. It took 1 year (February 2020) for the two statuses (connected OBP / connected OBP and downloading data) to be almost similar.

Figure 22 Status OBP / MAH Onboarding



Source: EMVO monitoring report September 2023

It is worth noticing that, as of September 2023:

- **Approximately 20% of the expected OBP are not yet connected to the EMVS**. EMVO estimates the target for OBP at around 1600, while only 1296 OBP are connected.
- **49 OBPs, out of the 1296 connected, do not upload data** according to EMVO data, ie approximately 4% of connected OBP[80].

These difficulties in connecting and uploading data are perceived by the NCAs: 10 NCAs[81] surveyed explicitly mentioned upload issues as obstacle to the good functioning of the repositories system.

They can be caused by a variety of reasons:

- **Errors caused by the MAH themselves during upload**: most of the causes mentioned by NCA relate to missing uploaded information (e.g., batch number, expiry date). In turn, these uploading issues are linked with a of proportion of alerts, triggered at the decommissioning stage by pharmacies. For example, in September 2023, "A2 unknown batch ID", "A3 unknown serial number", "A52 expiry date mismatch" and "A68 batch ID mismatch" alerts represented respectively, 30%, 17%, 0,4% and 26% of all the L5 alerts triggered in the month. In its Monitoring Report for September 2023, EMVO identified incomplete or incorrect data upload by OBP/MAH as one of the root causes of these specific alerts.

  These human errors linked to manufacturers are **minimized** in the Discussion report from EFPIA and Medicines for Europe, which makes them rather marginal compared to other types of errors: "*When asked to define the volumes and nature of the alerts being generated, all the manufacturers questioned admitted that on occasions, some alerts were self-inflicted alerts due to internal*

[79] EMVO stakeholder's consideration on enforcement and inspections under the FMD 2011/62/EU and its Delegated Regulation, 10th July 2019

[80] Please note that the estimated number of OBP and MAH include Greece and Italy.

[81] Bulgaria, Estonia, Finland, France, Hungary, Ireland, Spain, Slovenia, Slovakia, and Sweden.

operational issues. However, all were able to show that the number of self-inflicted alerts were extremely small"[82].

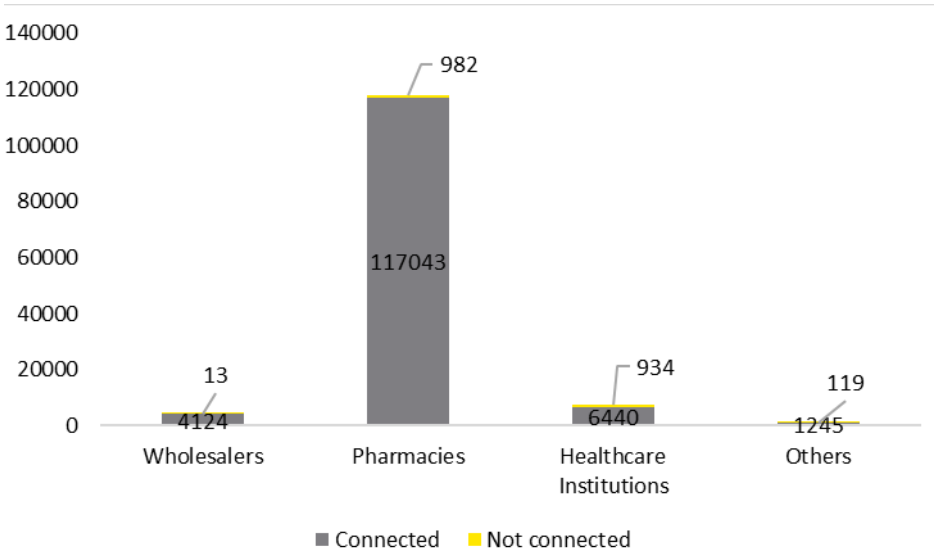
- **Technical issues related to the EMVS itself**: NCAs also mentioned MAH facing difficulties uploading the information attached to large volumes of packs (above 100 000).

As a result, the French NCA mentioned that some batches (no quantification disclosed) were released and distributed without having been loaded in the system, indicating a problem of compliance with processes at the level of the MAH/OBP/manufacturer.

End-users (wholesalers, pharmacies and healthcare institutions)

According to EMVO's September 2023 figures, 0,83% of community pharmacies, 12,67% of hospitals pharmacists and 0,31% of wholesalers are not connected to the system. Absolute figures are presented in the graph below.

Figure 23 End users' connection to the EMVS as of September 2023



Source: EMVO Monitoring Report for September 2023 – EY elaboration

Connexion rates tend to vary across Member States:

- **Wholesalers**: almost all of the wholesalers are connected to the EMVS across the different Member States. Only 4 out of 114 in Belgium, 4 out of 238 in Poland, 4 out of 38 in Northern Ireland and 1 out of 7 in Luxembourg still need to connect as of September 2023 according to EMVO.
- **Community pharmacies**: all pharmacies in the countries concerned by the DR are connected to the system except in 3 countries: firstly France (4,7% of pharmacies still to be connected), Malta (0,43%), and Slovakia (0,19%). Though, in 6 months, France has managed to connect almost 3000 pharmacies, i.e., 15% of the total of French pharmacy. This is the combined effect of the unions' injunctions, pressures from DG SANTE and the coercive measures put in place though fines and, above all the compliance monitoring from the European Commission.
- **Hospital pharmacies**: 7 countries still need to connect a diverse number of hospital pharmacies, led by Spain (66% of hospital pharmacies still to be connected), France (23%), Malta (7%), Slovakia (4%), Portugal (2%) and Liechtenstein (1%). Hospitals pharmacies remain problematic as their connection rate is slowing increasing in France and not increasing in Spain (66% of hospital pharmacies remained to be connected in January 2023 in Spain, and 26% for France). In Spain, public hospitals are not connected while the private one are connected.

Some reasons can be brought forward to explain stakeholders' connection difficulties by assessing the situation in France. Firstly, an overall reluctance to use the system because was identified in France because of its alleged uselessness and observed operational issues. This was reflected in the large proportion of false alerts being triggered by the system. Several pharmacies in France, supported by a trade union of the same opinion, believe that the system is of no use because of the lack of risks in their supply chain: thus, they refused to

[82] Discussion Report, November 2023, EFPIA, Medicines for Europe

connect to the system at first. Secondly, pharmacies are pointing at the additional costs involved with using the system: the purchase of scanners, new software, the adaptation of their pharmaceutical robots when, etc. which are not subsidies by the States. The 2015 Impact Assessment estimated these costs at 530 euros per year per pharmacy. These justifications were also put forward by pharmacists in other countries.

Besides the elements mentioned above, **the size of the market and the connections between the stakeholders also appear to impact the connection rate of end users**. In Ireland, for example, a relatively small market with approximately 1 900 community pharmacies and 100 hospital pharmacies, and where manufacturers, wholesalers, pharmacies and the public authorities work closely together, the connection of rate reached nearly 100% in the first month after the implementation of the DR. In September 2019, already 95% of the wholesalers, 99% of the community pharmacies and 100% of the hospital pharmacies were connected to the EMVS according to EMVO. In France however, a relatively large market with more than 20 000 community pharmacies and 2 200 hospitals, and with looser ties between stakeholders, only 45% of the hospital pharmacies and 72% of the hospital pharmacies were connected to the EMVS in September 2022, according to EMVO. **Overall, a small and tight market seems to facilitate the organisation of stakeholders**, pair control, and enforcement by public authorities, enabling the rapid deployment of the EMVS. A situation that was present in Ireland but lacking in France.

In conclusion, **the connection rate of the end users to the EMVS is close to completion**. The remaining unconnected end users are mostly community and hospital pharmacies in France and Spain. Regarding community pharmacies, the main obstacles are the equipment costs to perform the verification, although this argument is mostly true for small pharmacies considering the relatively low costs involved, and the reluctance to participate to a system often deem unnecessary given the low perception of falsification risks in Europe. Besides, France and Spain are relatively large markets where the organisation of end users and enforcement of connection requirement is structurally more challenging than in smaller markets.

5.3.2 Usage 2: Activity volumes and operations allowed

The actual functioning of the repositories system in the light of what was provided for in the legislation may be judged on the basis of **Article 36, which lays down the minimum operations the repositories system shall provide for:** (i) Repeated verification of the authenticity of an active UI, decommission of an UI, and combination of verification / decommission of an UI (including by manually querying the system), (ii) Reading of the information contained in the Data matrix, (iii) Reversion of UI status from decommissioned to active, (iv) Indication on the decommission status of an UI and about the potential withdrawn, recall, thefts, etc, synchronisation of the status of an UI between national or supranational repositories, (v) Triggering of an alert in the system, (vi) Immediate provision of information concerning a given UI to the NCA and the EMA upon request and (vii) Creation of reports that allow NCA to verify compliance of individual MAH, manufacturers, wholesalers and end-users.

The stakeholders, depending on their position and role in the supply chain, **interact differently with the repositories system and the different operations mentioned above.** A table is provided below, describing the use cases supported by the EMVS and their relation to the different stakeholders. *(source: EMVO documentation[83]).*

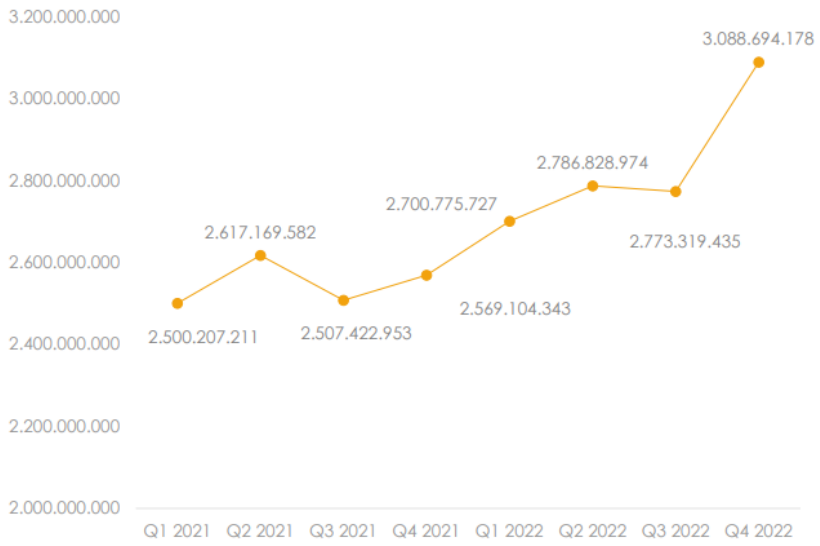
Use Case	Manufacturer	Parallel Distributor	Pharmacist	Wholesaler	Administrator
Upload product master data	X	X			
Upload product pack data	X	X			
Recall batch	X	X			
Verify pack	X	X	X	X	
Dispense pack	X	X	X	X	
Decommission pack	X	X			
Export pack from the EU	X			X	

[83] EMVO Requirements for the EMVS – URS Lite, 2017

Request report	X	X	X	X	X
Withdraw product	X	X			
Mark pack a stolen	X	X		X	
Mark pack as intended for destruction	X	X		X	
Mark pack as free sample	X	X			
Mark pack as sample (NCA)	X	X	X	X	
Mark pack as locked	X	X		X	

All of these operations are possible and can be activated by the stakeholders, who have indeed the possibility to verify, decommission, reverse a UI status, etc. Overall, **all these operations have been carried out in an increasing way**, as evidenced by the graph below produced by EMVO.

Figure 24 Number of transactions done by End-Users



Source: EMVS Performance Review May 2023

In December 2022 only, **the EMVS recorded more than 977 million of scans**, translating into billions of bits of data recorded. Nevertheless, the quality of these operations, 4 years after the implementation of the system, can still be improved in certain respects as explained in the next section related to Alerts.

Table 4 Focus on specific operations: reversion of the status of a UI

The reversion of a UI ("UI reverted to active") is an operation that is well identified and carried out by the actors encountered. However, as this operation is not monitored either by EMVO or at national level, specific figures cannot be provided on this topic (volumes, etc).

Still the interviews did provide some qualitative appreciation, such as the 10-day period mentioned in Article 13 of DR[84] which, in the eyes of the community pharmacies, seems too short and has a direct impact on their inventory management.

For more information on the upload of data: please see Section 5.3.1. For more information on decommissioned packs: please see Section 5.4

5.3.3 Usage 3: Alerts

The EMVS notifies stakeholders and handles potential case of falsified medicinal products by analysing exceptions (i.e., event that disrupts the normal flow of a process) and by producing notifications (i.e., when a system in the EMVS informs a recipient of the occurrence of an exception) and alerts. According to EMVO, alert relates to an exception that is deemed critical (i.e., with a potential case of falsification) and should be notified[85]. All exceptions for "Potential Suspect of Falsification" occurring in a given market are sent to the relevant NVMO and the EU-hub (except for duplicate serial number). The EU-Hub subsequently alerts the concerned manufacturer, who is then responsible to check and confirm the suspected falsification regarding the packs he handles.

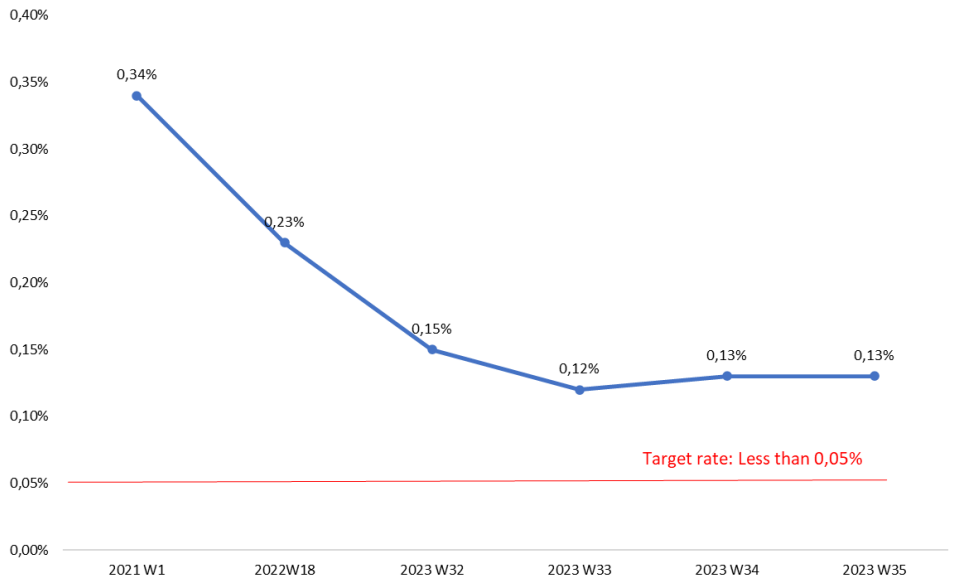
Short glossary on the terms used by EMVO regarding the reporting and alert system:

- **Exception**: an event that disrupts the normal flow of a process.
- **Alert**: exception which is deemed as critical and therefore should be notified. Alerts therefore produce notifications.
- **Notification**: where a system in the EMVS provides information to a recipient informing them of the occurrence of an exception.
- **Potential Suspect Falsification pack:** a medical product pack that may deliberately or fraudulently misrepresent its identity, source or history.
- **Falsification pack**: a medical product pack that deliberately or fraudulently misrepresent its identity, source or history.

Source: EMVO (2020), EMVS Alerts and Notifications

Even if the trends in terms of alerts issued are constantly decreasing (the alert volume has decreased in approximately 15% between 2021 and 2022), **the alert rate remains high and above the level desired (0,05%).**

Figure 25 Total number of alerts in relation to the total number of scans in all countries (%)

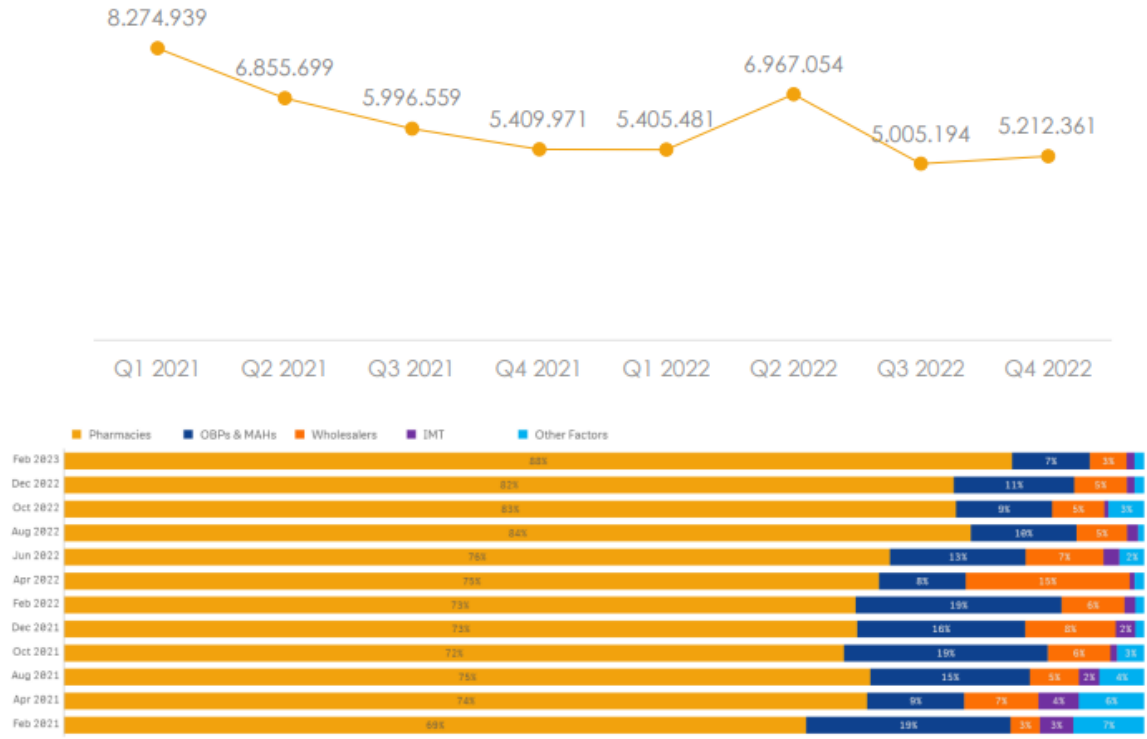


Source: EMVO Monitoring Report September 2023 – EY Elaboration

[84] Article 13 Reversing the status of a decommissioned unique identifier "[…] b) the reverting of the status takes place not more than 10 days after the unique identifier was decommissioned […]".
[85] EMVO (2020), EMVS Alerts and Notifications.

Pharmacists are the most affected by alerts, as confirmed on both NCA and stakeholders' surveys and EMVO monitoring reports. In France for example, out of the approximately 320 000 alerts that were raised in December 2022, around 300 000 were triggered by community pharmacies[86].

Figure 26 Alerts per responsible entity and total volume of alerts (Q1 2021 - Q4 2022)



Source: EMVS Performance Review May 2023. In orange: pharmacists, dark blue: OBPs and MAH, dark orange: Wholesalers, purple: IMT, light blue: Other.

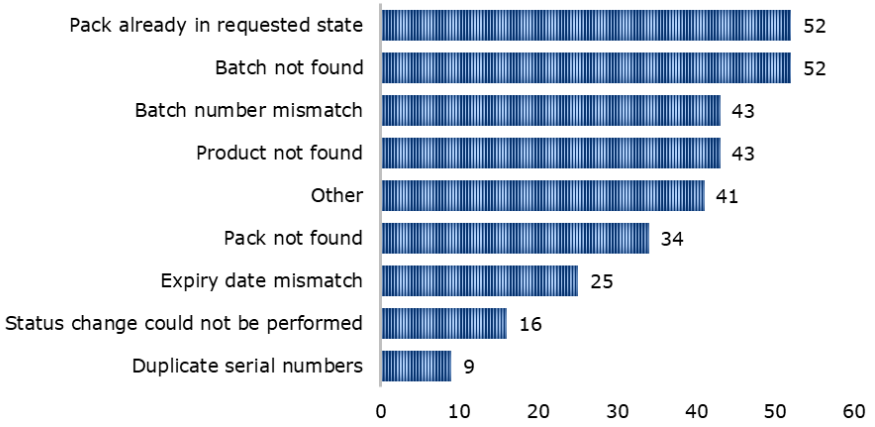
Five alert categories are monitored in EMVO reports. They correspond to "Potential Suspect of Falsification", triggering an L5 alert by the system (the most severe type of alert). EMVO describes these alerts as follows[87]:

- **#A2 Batch ID unknow**: indicates that the product code exists in the European Hub, but the batch identifier does not exist. This reveals that the OBP did not upload the batch to the European Hub, and therefore the serial number cannot be located.
- #**A24 & #A7 Attempt to decommission an already decommissioned pack**: indicates that an attempt has been made to change the state of a pack when the pack is already in that state (A7) or when the pack is in another state (A24). If the National System determines that the attempt is suspicious based on rules defined by the stakeholders, it raises an alert.
- #**A3 Unknown serial number:** indicates that the supplied serial number cannot be found. This exception can only occur in a National System. It can occur when an attempt is made to verify a unique identifier or to update the state of a pack.
- **#A52 Expiry date mismatch**: indicates that the value of the expiry date provided for a single pack made using non-manual data entry does not match the expiry date included with the pack identifier recorded in the EMVS. The pack is identified as potentially falsified.
- **#A68 Batch ID mismatch**: indicates that the supplied batch (lot) identifier does not match the batch identifier recorded in the EMVS for the given product code and serial number. This exception can only occur in a National System when an attempt is made to verify a unique identifier or to update the state of a pack. In the case of a bulk-of-pack transaction, separate exceptions are generated for each unique identifier in the request.

[86] EMVO (2023), *EMVO Monitoring Report – January 2023* and FMVO (2023), *Alerts Monitoring – Week 33 2023*
[87] EMVO (2020), *EMVS Alerts and Notifications*

According to EMVO's data from the Monitoring report, the most frequently encountered alerts by actors are those #A2 Batch ID unknown, #A68 Batch ID mismatch and #A24 / #A7 Attempt to decommission an already decommissioned product. That is consistent with the stakeholders' feedbacks from the survey.

Figure 27 What types of alerts / exceptions do you encounter most? (multiple options possible)



Source: Survey to other stakeholders – EY/Ramboll elaboration

As mentioned earlier, **there is no precise data on the quantification of these root causes**. NMVOs, who collect data on alerts and their root causes on their territory, do not systematically and consistently report this information to EMVO. **It is therefore impossible to quantify in which proportion these types of alerts are due to misconfiguration of the repositories system or because of human and technical errors**. While no precise data were submitted, EMVO still mentioned that three issues were causing the most alerts across the EU/EEA:

- data uploaded or incorrectly uploaded by OBP/MAH
- scanners' issues
- double decommission

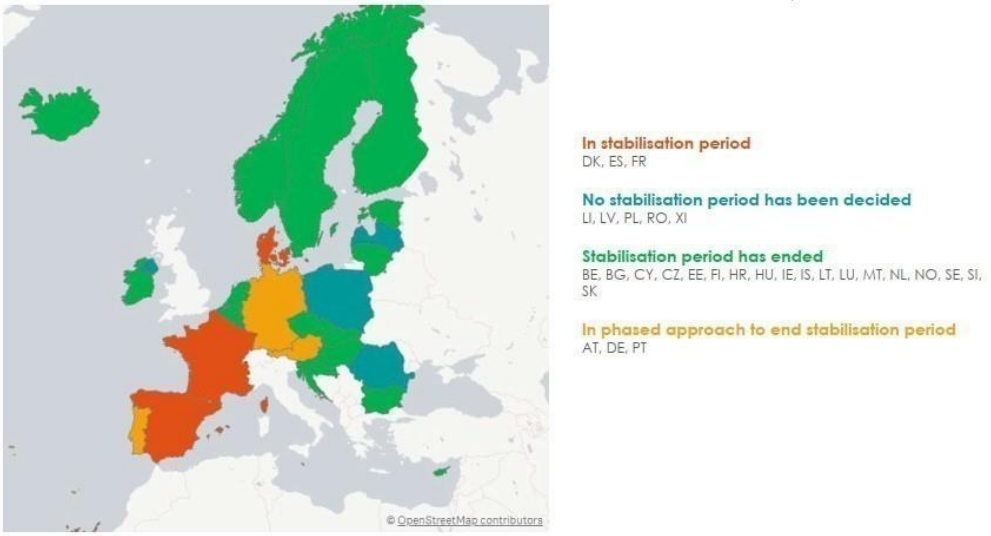
In face of the numerous difficulties with the system implementation (scanners and software malfunctions causing many false alerts, etc.), EMVO introduced a "**stabilization period"** beyond the regular transition phase initially planned in the DR (which ended in February 2019). During this period, pharmacies were allowed by their NCA (acting under the recommendation of EMVO) **to dispense medicinal products even if an alert was triggered**, provided that there were no indication of falsification and as long as the product was obtained through the legal supply chain. The purpose of this "stabilization period" was to avoid a sudden shortfall in medicinal products supply and to allow stakeholders to familiarize themselves with the system while identifying failures.

This period was extended several times in the context of the COVID pandemic and as implementation difficulties endured[88]. As of November 2023, the stabilization period is still practiced in Austria, Denmark, France, Germany, Portugal and Spain, **indicating that the EMVS is not working as designed across all the concerned countries.** Indeed, some of these countries are still subject to a high number of alerts[89]. On that note, it is important to mention that **the Stabilization period is formally non-compliant with the EU legislation** as the DR, which does not mention this period, is applicable in all the countries of the Union since February 2019 (except for Italy and Greece).

[88] See for example MaMVO's Statement: "The Pharmaceutical Supply Chain in the Post-Stabilisation Period – Pharmacies", July 2020.

[89] For week 35 of 2023 alone, the alert rate of Spain (0,34%), France (0,13%), Germany (0,11%), and Portugal (0,10%) was above EMVO's target of 0,05% (EMVO Monitoring Report for September 2023). Austria and Denmark, where the alert rate is below 0,05% (0,01% and 0,03% respectively for week 35 of 2023), are currently in the process of ending the Stabilization period.

Figure 28 Stabilisation periods overview



Source: EMVO Monitoring Report for September 2023

It is in this context of high alert rate that countries like Estonia have decided to **set up an additional alert management system,** specific to their country, and which allows to sort alerts before addressing them. The example of the REK-IS system, implemented efficiently in Estonia and developed as part of a specific case study, is summarised below. **The existence of a collateral alerting systems is the very proof of the system's current inability to generate reliable alerts.**

Figure 29 The Estonian Alert system: REK-IS

The decision to establish an additional alert management system was based on several reasons, the main one being that the large number of alerts made it very difficult for end-users and investigation procedures to work. In addition, since alerts mainly emanate from technical incidents and human errors, it seemed appropriate to create a system to sub-filter alerts.
Thus, Estonia developed its own standalone IT-based alert management system known as 'REK-IS.' This system is developed and owned by REKS, the Estonian NCA, and it is designed to assist end users in managing alerts generated within the medicines verification system. Within the REK-IS system, when an alert is initiated and subsequently determined not to stem from a technical or human error, a process of validation is carried out by the end user. This validation involves scrutinising the alert type and ascertaining whether it was triggered by a scanner malfunction or an oversight on the part of the end user. An example of such an oversight could be neglecting to update a password in the user system, potentially leading to alert notifications.
In practice the REK-IS system is widely embraced by the majority, if not all, of Estonian general pharmacies, notably because of its efficiency: the interviewed stakeholder from the pharmaceutical sector emphasised that a stand-alone automated Alert Management System significantly assists end-users in resolving recurring alerts associated with medicines and specific batches. The success rate for alert management through this system is estimated to exceed 90%, eliminating the need for repetitive manual investigations that have already been conducted. The fact that the system is national, and not European, was also an asset according to the actors consulted because it made it possible to overcome the language barrier, REK-IS being completely in Estonian. Communication and alert management have thus been much more effective.

Sources: Interviews with representatives of the Estonian pharmaceutical industry / public authorities, desktop review

5.3.4 EMVS Technical Stability and Availability

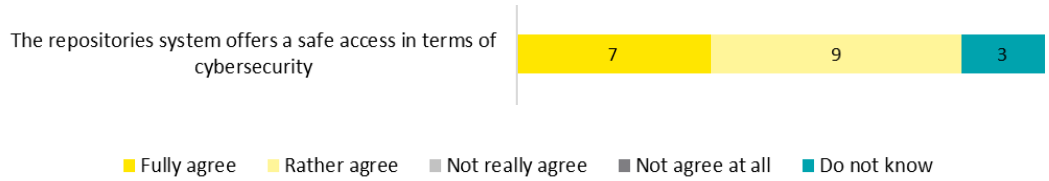
In addition to these 3 different uses, the functionality of EMVS can also be judged based on IT and technical criteria relating to its stability and reliability. These criteria include:

- **System availability**: all the systems have been available more than 99% of the time and no downtimes were observed during 2022[90].
- **Cybersecurity** and capacity to contain a large volume of data: in this respect, all the feedbacks from NCAs that responded to the survey were positive on the topic of safe access / cybersecurity,

[90] Ibid

with the exception of 3 NCA who indicated that they did not know. Some stakeholders nonetheless expressed concerns about the level of access to the data they generate using the system. More particular, community pharmacist and parallel traders were opposed to letting other stakeholders, and especially manufacturers, having openly access to their data though the EMVS.

Figure 30 To what extent do you agree with the following assertions regarding functioning of the repositories system? (n=19)



Source: Survey to NCA – EY elaboration

Thus, **the repositories system makes it possible to effectively and securely contain a large volume of information and is efficient in terms of cybersecurity.**

The EMVS Performance Review also provides further details on the functionality of the system, although the Study team is not in a position to judge them because of the lack of initial targets set.

- A total of 88 incidents in PROD has been registered since the go-live on 9th February 2019 and until 31st December 2022
- A total of 26 emergency changes was logged in the same period (4 in 2020, 14 in 2021 and 8 in 2022)

In order to improve its functionality, routines changes were implemented in 2022 (39 in total, 28 of which were directly related to the EU Hub).

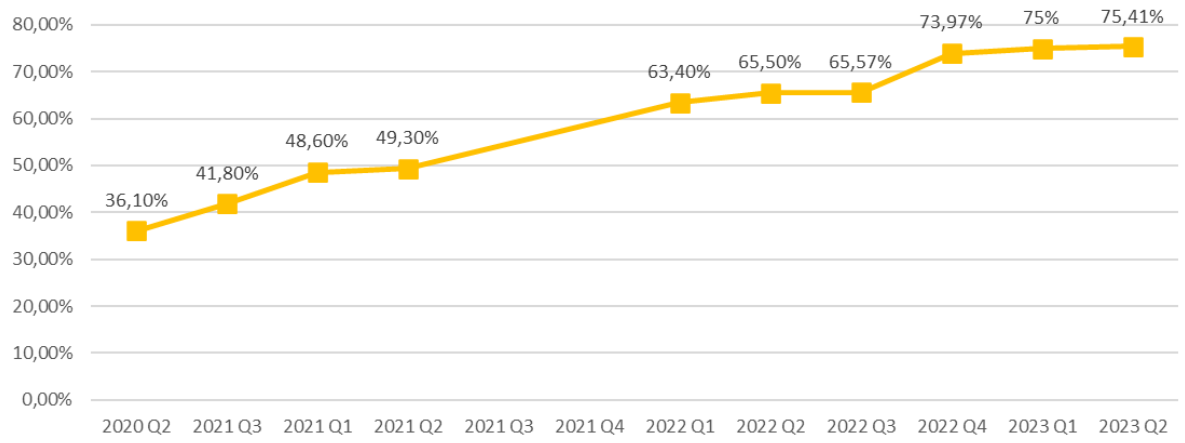
5.4 Verification of the safety features: to what extent are the modalities for the verification of the safety features well implemented?

5.4.1 Verifications of UI are increasingly carried out but a (reducing) number of users are still reluctant to do it

Several observations can be made regarding the implementation of verifications of UI.

First, even if decommission rate progresses (in 2023 Q2 75,41% of the medicine packs were being decommissioned in the countries of the EMVS while it was the case for only 36,10% of the packs in 2020 Q2), **still 26% of the medicines bearing safety features are not being decommissioned as of September 2023**.

Figure 31 Evolution of the decommission rate in all MS (2020-2023)



Source: EMVO reports (data lacking for some periods) – EY elaboration

Second, **wholesalers do not perform regular verifications, whether obliged or spontaneous**. The NCA of Portugal, for example, detected that all wholesalers were not compliant with the obligation to check the UI when buying from another supplier than the designated wholesaler or a MAH (as required in Article 20 of the DR). Also, when asked in the survey if the wholesalers respondents carry out frequently or occasionally spontaneous verification even when not required to do so, only 19 out of 38 stakeholders answered positively. Wholesalers are indeed generally reluctant to perform all the verifications required by the DR because of the additional workload they create and the relative uselessness they perceive from these operations. Most describe their security system as already well established and system checks as redundancies.

Third, **even when complying with the obligation to verify and decommission UI, some pharmacists do it in an irregular way without it being possible to quantify this phenomenon precisely**. To save time and resources, some community pharmacist admitted **decommissioning medicinal packs at the point of entry** (i.e., when packs get delivered to the pharmacy) instead of at the point of dispense, as required in Article 25 (1) of the DR. This is also a way to **secure the dispensing to patients and guaranteeing a good customer relationship,** as many say that the system is damaging the latter as explained below.

- In the survey distributed throughout the study, 27 out of 44 stakeholders complained that the EMVS was deteriorating their customer relationship (when 17 believed it did not). When asked why, the stakeholders mentioned delays, workflow interruptions, and false alerts caused by the verification process, which in turn fuel patient dissatisfaction.
- Research carried out with pharmacies in Ireland[91], for example, uncovered the view that FMD requirements had led to increased waiting times for patients (82% of respondents) and reduced the time available for direct patient interaction (65% of respondents). The additional task of medicines decommissioning was seen as a time-consuming diversion from critical clinical checks, potentially heightening the risk of errors.

This inconsistency to verify can lead to falsified medicines being distributed to patients, as it has been the case for the Ozempic Case (semaglutide, already described in this Report) according to EPFIA and Medicines for Europe in their Discussion Report: "*the recent Ozempic case shows clearly that some parties are not verifying product as they are legally obliged to*".

Thus, even if the verifications are well carried out by the bulk of stakeholders of the supply chain, the latter are not always respected despite the entry into force of the DR. Based on the observations presented above, there are several reasons for this non-compliance. The stakeholders can indeed be:

- not connected to the system
- reluctant to use the system (like pharmacies in France for example who put forward the argument of a deterioration of the customer relationship)
- not equipped with scanners to perform verifications (the argument of the high cost of these tools have often been mentioned by pharmacists)

[91] Dalton, K., Connery, C., Murphy, K.D. and O'Neill, D., 2022. Pharmacists' views on the impact of the Falsified Medicines Directive on community pharmacies: A cross-sectional survey. Exploratory Research in Clinical and Social Pharmacy, 5, p.100127.

- not well informed / aware of their duties and therefore do not make spontaneous checks (for wholesalers)

To conclude, **even if the assessment of the deterioration of the customer relationship by pharmacists is exaggerated to a certain extent, it should not obscure the fact that the high alert rate remains an important problem** that needs to be solved. **The argument of the high cost of scanner equipment also seems exaggerated** for the vast majority of cases.

5.4.2 Verifications along the supply allowed for the detection of a few numbers of falsified medicines

According to EMVO, **a few cases of falsification reported (no precise quantification possible) were detected during simple verifications** along the supply chain. Some cases were mentioned in this report: 3 falsified packs of Keytruda were as such discovered in the Netherlands during repacking in 2022, one pack of Enbrel (etanercept) filled with pencils detected in the same year during repackaging, and falsified packs of Avastin were detected in 2019 during an investigation conducted by a Dutch wholesaler.

Several conclusions can be drawn from this observation. Firstly, as mentioned in section 4.7, it shows that **the double alert mechanisms, and especially the spontaneous verification mechanism, is an effective system** preventing the deliverance of falsified medicine to patients if properly implemented. The fact that very few to none of the cases of falsification identified were found at the moment of dispensation, typically when pharmacies decommission packs, indicates that most if not all the identifiable falsified packs were caught earlier along the supply chain. Secondly, and drawing from the first conclusion, this observation shows that a track and trace system is not necessarily required to detect the introduction of falsification. In fact, verification requirements in between both ends of the supply chain, at the wholesale level for example, can be adjusted according to the risk of falsification to secure the chain without having to impose systematic checks at each stage of the chain. This system, while meeting the objective of the DR of securing the supply chain, is also the most cost effective and acceptable by the stakeholders. *More information about the actual detections of falsified medicines is provided in the section related to the Effects of the measures.*

5.5 Reporting system: to what extent is the reporting system effective in contributing to secure the legal supply chain of medicinal products?

5.5.1 The alerts emanate mostly from the IT system and not spontaneously from the stakeholders

As seen previously, a huge number of alerts emanates from the IT system weekly. The table below highlights the proportion of alerts and scans per week in 10 countries. **The majority of respondents to the survey to other stakeholders (108/152) answered that they have never suspected the existence of falsification** of a medicinal product and made a spontaneous alert to a competent authority. Only 18 respondents answered that they had, of which 10 were NMVOs originating from Austria, Bulgaria, Croatia, Estonia, Hungary, Latvia, Netherlands, Romania and Slovenia. 26 did not know. This was confirmed in interviews with NCAs and NMVOs, who affirmed that they rarely or never receive spontaneous alerts from stakeholders of the supply chain.

With regards to spontaneous notifications, **the lack of monitoring and data from NMVO and NCAs on the subject prevents the Study team from making general constants and comparisons between countries**. Nevertheless, the analysis was possible for a small number of countries, whose results are highlighted in the table below.

Table 5 Number of scans, alerts, suspected and confirmed falsified medicines in a selection of countries

Country	**Total scans** per week[92]	**Total alerts** per week[93]	**Suspected cases** of falsified medicine directly reported by the NMVO to its NCA since 2019	**Confirmed cases** of falsified medicine according to the **NCA** since 2019	**Confirmed cases** of falsified medicine according to **EMA** since 2019
Bulgaria	2 266 000	3 184	0	0	2

[92] Weekly average of the number of boxes of medicinal product scanned during December 2022 rounded to the thousands (except for Lithuania).
[93] Weekly average of the number of alerts triggered by the EMVS/NMVS when scanning boxes during December 2022.

Croatia	3 329 000	2 271	0	0	0
Czech Republic	8 419 000	2 570	1	0	1
Estonia	970 000	464	0	0	0
France	27 704 000	80 447	40[94]	0	0
Hungary	8 018 000	2 312	1	0	4
Lithuania	1 270	11	59	0	2
Netherlands	6 451 000	48 932	63	0	2
Portugal	5 497 000	10 366	3	0	0
Slovenia	1 004 000	122	342	0	0

Sources: NCAs, EMA and EMVO – EY Elaboration

This table clearly highlights the lack of precision of the EMVS alert system, given the low proportion of confirmed cases of falsification compared to alerts issued.

5.5.2 The reporting system suffers from the lack of clear and shared definitions of "suspected case" and "confirmed case" of falsification, as well as the lack of centralization of falsification data

Several observations can be made regarding the functioning of the reporting system.

Firstly, as said in Section 5.5.2, **the reporting of suspected and confirmed cases of falsification is often partial and inconstancies were detected** between reports across European and national authorities. Out of the 28 NCAs contacted, 12 have not responded to our demand to share data on confirmed cases of falsification, and 18 have either not responded or are not recording the number of suspected cases of falsification reported to them by their NMVO. At the European level, EMA only records cases of falsification involving medicine with a European marketing authorisation, and not nationally authorised products. More generally, due to a "**lack of awareness of the phenomenon",** there seems to be a **lack of willingness to consistently records data** and to share information on medicine falsification and diversion, as reported by Marco Dugato, a researcher at Transcrime and the Università Cattolica del Sacro Cuore[95].

Secondly, even when submitted, **inconstancies were detected between reports across European and National authorities.** For example, the Hungarian NCA has reported 0 confirmed case of falsification since 2019, against 4 according to EMA. These gaps are exacerbated by the lack of common standards between countries and between authorities to qualify a case as a confirmed falsified medicinal product. For example, a case considered as confirmed by the Belgian NCA may need validation by a court ruling to be officially treated as such, generating "pending" confirmed cases. The scope of products considered sometimes also differ between authorities (e.g., as mentioned above, EMA only records centrally authorised products). Overall, the lack of standard procedures to qualify cases as confirmed falsification and the lack of centralised files reporting all cases across the EU/EEA make comparisons and trend analysis particularly difficult. Even when recorded, the reliability of the data submitted was sometimes questioned.

Thirdly, **records do not always differentiate between falsification cases and other incidents involving medicines.** Some NCAs pointed out that the same database was used to record cases of falsification in the legal supply chain, cases of falsifications in the illegal supply chain and cases of stolen medicinal packs, as these situations were often difficult to distinguish.

[94] Estimation provided by the NCA
[95] Contrasto al traffico illecito di farmaci: appello alla condivisione dei dati - AboutPharma

6 Assessment of the effects of the measures

This chapter aims first to answer **EQ2: To what extent have the objectives of DR (EU) 2016/161 been achieved?** The approach to answer EQ2 relies on the evidence gathered in evaluation questions 1.1 to 1.5 as well as broader evidence gathered on the system as a whole.

Key findings

- **Operational objectives have been achieved in a differentiated manner:** while the efficiency of the characteristics and technical specifications of the UI has been quite effectively ensured, the introduction of proportionate verification of the safety features and the interoperability and functioning of the system are still ongoing.
- **The incomplete implementation of the EMVS, as well as the lack of data, limit the accurate assessment of the effectiveness of the FMD and DR in the fight against falsified medicines**. As the reporting system has significant shortcomings, and as all stakeholders do not consistently verify medicinal pack, it is possible that a number of falsified medicinal products have circulated in the legal supply chain without being detected by the EMVS.
- **Still**, the detection of some cases of falsification, either directly, or indirectly in conjunction with the work of investigators, indicate that **the verification system can prevent falsified medicines to reach patients under some circumstances**. In other words, if the FMD and DR framework does not currently allow for the detection of all cases of falsification given its partial implementation, it can already detect some cases. Besides, **the FMD and the DR exert a deterrent effect on falsification** (although difficultly quantifiable) by making it more costly for criminals to introduce falsified medicines into the legal chains, due to tighter controls and added safety features on medicinal packs. Moreover, **the system represents a powerful source of data for investigator to track falsifying activities**.
- **In this context, the current FMD and DR framework deserves to be consolidated, promoted, and used to its full potential.** Extending the system, for example for monitoring shortages, does not seem appropriate at this stage given the incomplete implementation of the DR. Still, the existing features of the system can already be used extensively to optimize its impacts. This is the case, for example, for the collaborative exploitation of the EMVS data by NMV0, NCAs and law enforcement authorities to identify and tracks falsification activities.

6.1 Operational objectives have been achieved in a differentiated manner

The achievement of operational objectives must be assessed in a differentiated manner.

i. To ensure efficient and effective characteristics and technical specifications of the UI

This operational objective can be considered as achieved. A UI harmonized in terms of format and content has been put in place in all the countries concerned by the DR. Every medicinal product on the market now carries this UI, and the alerts related to UI / upload of data etc mainly pertain to human errors and not defects in UI design and effectiveness.

On the other hand, the ATD (even if it is not directly mentioned in this objective) is deficient due to its non-harmonisation.

ii. To introduce proportionate verification of the safety features to combat falsified medicines

This objective is still **in the process of being achieved**. The verification procedures are proportionate: they avoid excessive burdens for the stakeholders while combating the introduction of falsified medicines in the legal chain. Nevertheless, some actors are still not connected to the system (0,83% of community pharmacies, 12,67% of hospitals pharmacists and 0,31% of wholesalers as of September 2023) or are connected but do not decommission medicines. Checks are therefore not always carried out or these are conducted in an inappropriate way, such as decommissioning of packs when they are delivered to the pharmacy instead of when they are dispensed to the patient. Nevertheless, over time, thanks to the awareness of actors on the importance of their role and the performance of verifications, and the generalisation of certain technical progresses (e.g., code aggregation and bulk verification), this objective should be achieved in the short term.

iii. To ensure interoperability of the repositories system, free movement of medicines and supervision by the competent authorities

This objective is **also in the process of being achieved**. The high alert rate remains a major problem of the system that harms its operation, even though these alerts are most of the time not of its own fault but rather

the result of human error and technical problems with additional equipment (e.g., malfunction of scanners). The interoperability of national systems is indeed possible via IMT, which generates alerts, but in no greater proportion than other actions. Supervision by competent authorities is contrasted due to a very uneven use of EMVS between authorities, some of which point to their lack of technical expertise and ability to influence.

6.2 Incomplete implementation of the EMVS as well as lack of data limit the accurate assessment of the effectiveness of the FMD and DR in the fight against falsified medicines

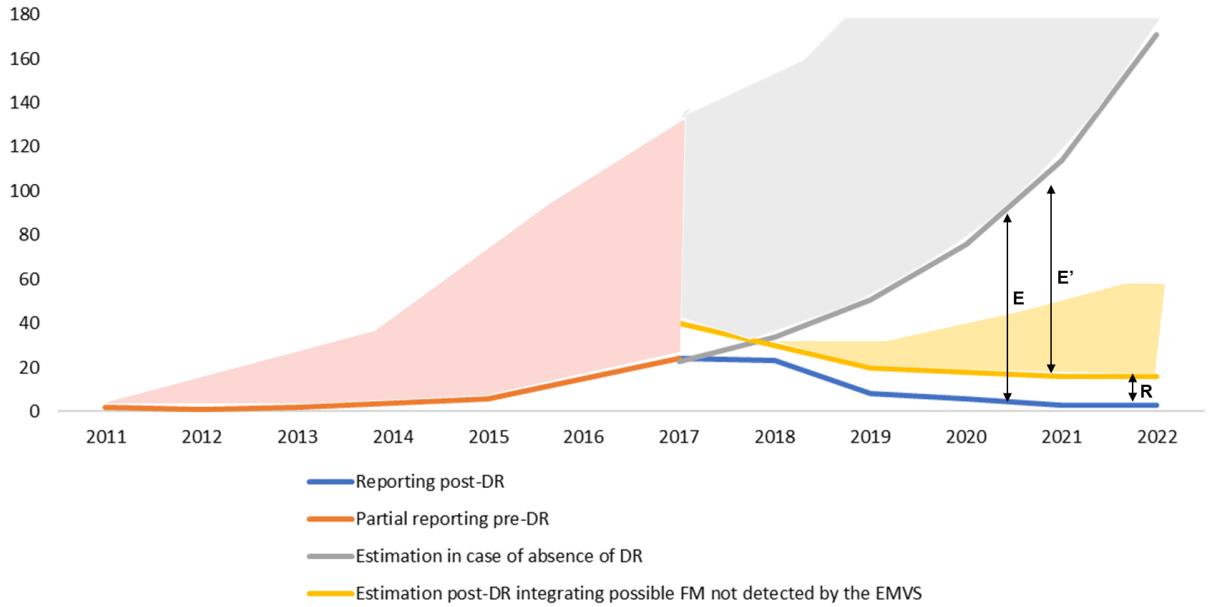
Firstly, **it seems premature to comment on the effectiveness of the system as the latter is not fully implemented yet.** The connection of the stakeholders (both end-users and MAH /OBP) to the system is incomplete, heterogenous, and even problematic for hospital pharmacies (as reminder, more than half of the pharmacies in Spain remain to be connected) Moreover, verifications and decommissions are not carried out systematically by end-users. In addition, due to the stabilization period, medicinal products can still be dispensed even in the event of alerts or observations of minor defects on the ATD. Lastly, although the number of alerts is decreasing, they still have **a direct impact on the functioning of the system and affect the willingness of the end-users to participate in it.**

In addition, as mentioned above, **the reporting system has significant shortcomings** (lack of harmonised definition, lack of centralisation of data) which make the available data partly unreliable concerning the precise number of falsified medicines detected by the system. Thus, it is possible that an unquantifiable number of falsified products have circulated in the legal chain without being detected by the system.

Under these conditions, **it is impossible to precisely predict what the impact of DR is and what the trends would have been without the legislation**. Nevertheless, we propose a schematic and purely indicative graph below on the basis of two assumptions:

- In view of the increasing trend in the number of falsified medicines over the period 2011-2016 (confirmed by the literature, the Impact Assessment 2008 and 2015), we assume that the trend will continue increasing over the period 2016-2022 without the entry into force of the DR.
- In view of the incomplete implementation of the system, we accept the hypothesis that a small number of medicines circulate in the legal chain without being detected by the system.

Figure 32 Graph of trends in falsified medicines before and after DR based on both figures collected and estimations (2011-2022)



Source: "Reporting post-DR" and "Partial reporting pre-DR" are based on EMA figures. "Estimation in case of absence of DR" and "Estimation post-DR integrating possible FM not detected by the EMVS" are hypothetical projections made by EY. These are purely illustrative and don't rely on proved figures. solid fields represent the potential margin of error due to (i) the lack of reliable data for the pre-DR figures and (ii) the projectional nature of the post-DR data invented by EY.

The desired measure of effectiveness of the FMD and DR in this evaluation is equivalent to measuring R, which symbolizes the delta between the number of falsified medicinal products detected by the EMVS based on the numbers provided and the actual number of falsified medicinal products (including possible non-detection by the EMVS). **In the case where FMD and DR are fully effective, R is equal to zero**. For the reasons mentioned above, we cannot conclude on the scope of R at this time.

Regarding the impact of the DR, it can be measured in theory in two ways:

- **E'**, which symbolizes the delta between the number of falsified medicines in the legal supply chain at a given time without the legislation put in place and the same number with the legislation and with the hypothesis that some falsified medicines are circulating undetected. It is therefore a measure that is based on two unknown figures.
- **E**, i.e. the delta between the number of falsified medicines in the legal supply chain at a given time without the legislation put in place and the same number with the legislation and with the assumption that the system detects all medicines.

For the same reason than for the measure of effectiveness, we cannot conclude on the scope of E and E' at this time.

It is important to note that the risk in making the number of falsified medicinal products detected by the EMVS the indicator to demonstrate its effectiveness is to declare that the system is useless because it has detected only a handful of falsified cases. Indeed, with preventive measures as those required by the DR, **the added value to stakeholders is usually not proven until something actually goes wrong, which has not been the case so far**. Besides, such a demonstration does not account for the deterrent effect of the FMD and the DR, which can contribute to the low number of falsified medicines detected (this specific issue is further discussed in section 6.4)

A comparison with the UK's ability to detect and report falsified medicines

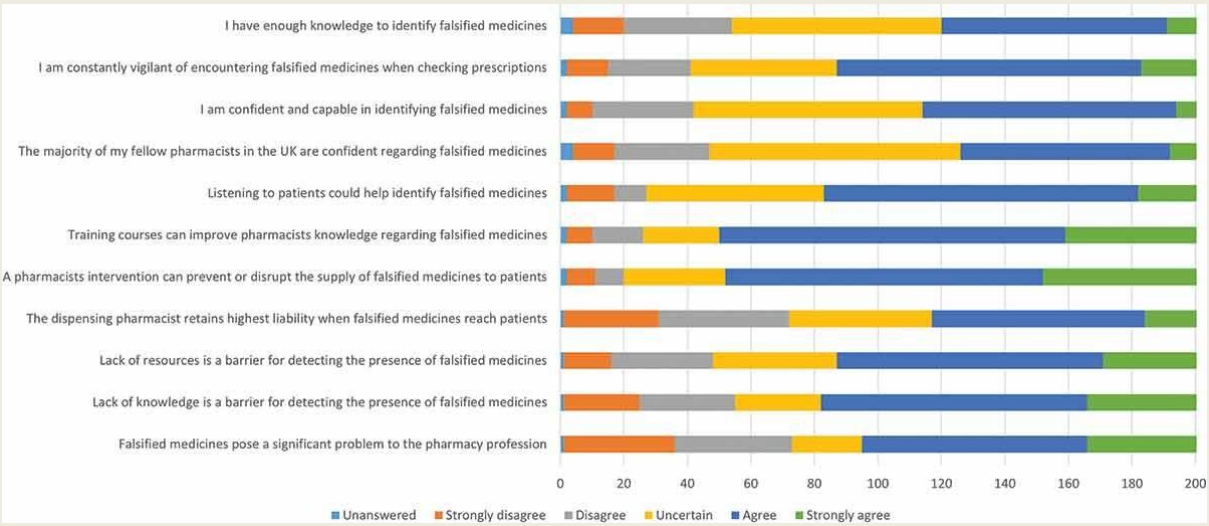
A study has been conducted in 2022[96] assessing UK's pharmacies readiness to detect and report falsified medicines in the absence of a similar framework as the FMD and the DR. At the time of writing, the UK had no dedicated system to detect and report falsified medicines in the legal supply chain, apart from the WHO's Yellow Card Reports (YCR) system, a "spontaneous reporting pharmacovigilance system, which invites reports of suspected side effects to medicines, vaccines, e-cigarettes, medical device incidents, and defective or falsified (fake) products to the Medicines and Healthcare products Regulatory Agency (MHRA)", and which is reportedly underutilized.

The report shows that out of the 207 pharmacies surveyed, 7 had identified a falsified medicines in the past, and only one reported it to the local NCA (the MHRA). The report also shows that pharmacist' opinions were mixed as regard to their ability to detect falsified medicines. For example, less than half of the pharmacist surveyed reported having enough knowledge to identify falsified medicines (see figure below). Overall, **these reports show the relative unpreparedness of UK's pharmacists to detect and report falsified medicines in the absence of framework similar to the FMD-DR**, which requires medicine packs to bear safety features, verifications to be systematically conducted, and incidents to be reported automatically.

Coherently, 68,7% of the pharmacists surveyed stated that the preparation measures required by the FMD would have improved patient safety. The author of the report concludes by saying that, in that context, **an FMD or equivalent framework needs to be reinstated in the UK to better protect the legal pharmaceutical supply chain from falsified medicines**.

[96] Ravina Barrett (2022), A cross-sectional study on substandard and falsified medicines (fake or counterfeit drugs) in UK pharmacies during the COVID-19 pandemic (tandfonline.com).

Figure 33 Self-efficacy scale for community pharmacists about their own and other pharmacists' ability to identify and manage Sub standards and falsified medicines



Source: Ravina Barrett (2022), A cross-sectional study on substandard and falsified medicines (fake or counterfeit drugs) in UK pharmacies during the COVID-19 pandemic

6.3 While conclusions can hardly be drawn about its overall effectiveness, the EMVS has nonetheless contributed to the detection and investigation of a few cases of falsification

Given the limitations presented in the previous section, **the "success stories" described below cannot be used as a basis for generalising an assessment of the effectiveness of the system.** These examples can **only prove that the system is indeed able to detect some cases of falsification in the legal supply chain**.

That being said, the cases investigated as part of the evaluation demonstrate the EMVS' ability to detect falsified medicines in the legal supply chain **in two ways: (i) direct detection through alerts and (ii) indirect detection through suspicious activities.**

i. Direct detection

Regarding the Avastin case (April 2019), four packs were scanned, raising an alert with the message "unknown badge number". This alert was associated with the first pack of Avastin, while the subsequent three packs triggered a message saying, "double verify in group." Consequently, the operator, alerted by these messages, examined the situation and identified that the serialisation numbers for all four packs were identical, prompting the system to raise an alert. In addition to the serial numbers, the packs were also checked for visible differences and defects, of which a number of characteristics were observed. For instance, the colouring and text on the packages differed from the authentic version, and the labelling was positioned lower compared to the original version. In this case, the system correctly detected the falsification by identifying packs with identical serial numbers and an expired batch.

In 2022, the Bulgarian Drug Agency (BDA) noticed by analysing EMVS reports from 2022 that hundreds of packs of oncology medicines were decommissioned in one Bulgarian hospital, then in another one, triggering A24 and A27 alerts. On-site investigations in January 2023 revealed that these packs, after being decommissioned in the first hospital, were being stollen and then illegally resold to a wholesaler, who latter resupplied the medicine to the second hospital. As such, A24 and A7 alerts reports can be useful indicators of suspicious activities, that must be completed with the extraction of further audit trails reports and investigations.

ii. Indirect detection

Another impact of EMVS is to **assist in the detection and tracking of falsification cases once a suspicious activity is identified.**

Regarding the 2022 Keytruda Case, 3 falsified packs of Keytruda were discovered in the Netherlands during repacking. The batch number between the first and the second pack was different, leading to an investigation by the BDA. The audit trail and the investigation revealed that the packs, while being physically in the Netherlands,

were being scanned in Bulgaria by suspicious wholesalers using pictures of the UI of the packs of Keytruda. However, the EMVS alone did not detect the falsification. The spontaneous alert was triggered by the company repacking the boxes of Keytruda in the Netherlands. Then, a field investigation was conducted to reveal the unfolding of the falsification scheme.

The same goes for the 2022 Enbrel Case: one pack of Enbrel (Etanercept) filled with pencils was detected in 2022 during repackaging in Germany (see picture below). The audit trail extracted from the EMVS revealed that the pack was an authentic one which UI was previously uploaded in the EMVS. The UI of the pack was then scanned by a Bulgarian wholesaler to check if its status was active and thus fit for sale, and then laundered by a second local wholesaler who sold the product in the Netherlands. The pack was finally supplied in Germany, were the repacking company noticed the falsification.

Figure 34 EMVS audit trail and actual trail of Enbrel

Source: Bulgarian Drug Agency – EY elaboration

In these two examples, the EMVS provided valuable data to retrace the journey of the packs and to identify suspicious behaviours (i.e., the unexpected scanning by a third-party pharmacy, the back and forth of the pack between the hospital and wholesalers, etc.). The limit to this type of use of EMVS is the technical ability of the users (in this case NCA) to use the system and track the information.

This use of the data and the potential of EMVS can go even further in the case of cooperation with law enforcement authorities (see section 5.1.2).

Whether in category (i) or (ii), these detections indicate that the system is combating the introduction of falsified medicines into the legal supply chain. However, due to the limitations presented in the previous section, the precise measurement of the detection capacity and scope (i.e., the ability of the system to detect all falsified medicines introduced into the legal supply chain) of the system cannot be assessed.

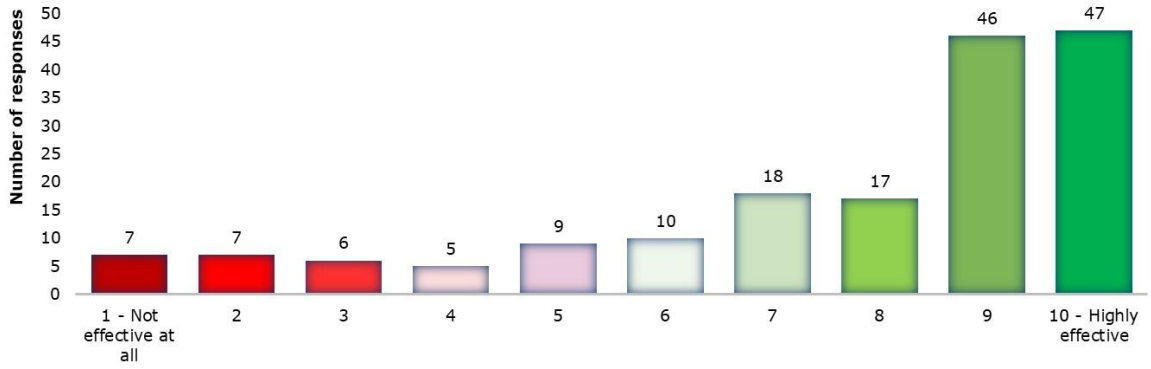
6.4 FMD and DR have a theoretical deterrent effect (even if not absolute)

Regardless of whether or not the EMVS consistently detects cases of falsification, **the FMD and the DR have a theoretical deterrent effect by increasing the cost of falsification for criminals.**

One of the main impacts of the DR is indeed that the investment in falsification for criminals becomes more and more expensive in terms of equipment. The system plays a deterrent role by reinforcing barriers to entry into the legal supply chain (e.g., through systematic verifications of medicinal products entering and exiting the chain), which combine with "natural" barriers to falsification of medicines (e.g., high equipment / material costs to manufacture falsified medicines and safety features).

The opinions of the stakeholders surveyed (see graph below) are aligned with the view of the industry described in the Discussion report from EFPIA and Medicines for Europe[97]: "*A view held by many within the industry is that the low rate of positive detection of falsified products by the EMVS is a result of its deterrent impact*".

Figure 35 From a scale of 1 to 10 (10 being highly effective and 1 being not effective at all), how effective do you think these national measures are in preventing or helping to prevent the entry of falsified medicinal products into the legal supply-chain? (n=172, one option possible)



Source: Survey to stakeholders of the pharmaceutical supply chain – EY/Ramboll elaboration

Experts and academia consulted also agreed that traceability and regulation on medicinal products remain fundamental factors against medicine falsification. In their view, and in accordance with the **Crime opportunity theory**[98], falsification tend to increase (1) for those medicinal products with high prices, (2) when medicinal products (expensive or not) are in shortage, (3) and when the inspections on the production of medicinal products are marginal.

Therefore, **it becomes easier for a criminal to steal and/or divert medicines packs from the legal supply chain and resell them in the illegal circuit** (which is not controlled), than to try to reintroduce falsified boxes into the legal circuit (that is tightly controlled thanks to the DR).

However, **this deterrent effect is not absolute given that cases of falsification have still been detected** in recent years.

6.5 Rather than an evolution towards a track and trace system, the current framework deserves to be consolidated, promoted, and used to its full potential

The system must first be consolidated to reach its full potential. Indeed, as described above, the implementation of the system is still partial as many stakeholders need to be connected. Besides, the system is still in the middle of a learning curve as stakeholder are gradually integrating it into their practices (e.g., many pharmacists are still not consistently or properly conducting verifications and decommissions). **Time is therefore required to perfect its implementation and achieve the desired level of efficiency**. With this in mind, at this stage, **an evolution towards a track and trace system does not seem to be appropriate**.

In addition, **the system deserves to benefit from increased publicity among stakeholders in terms of its objectives, its results and the limits set.** Indeed, a significant number of criticisms made by actors consist in claiming that the system is useless because (i) it does not detect falsified packs in the legal chain and (ii) it does not address the real problem of falsification which is concentrated in the illegal chain. Both elements can be easily counteracted with the help of targeted communication that would recall (i) the precise objectives of the DR and the need to distinguish between the fight against falsification in the legal/illegal supply chain and (ii) the incomplete implementation of the system.

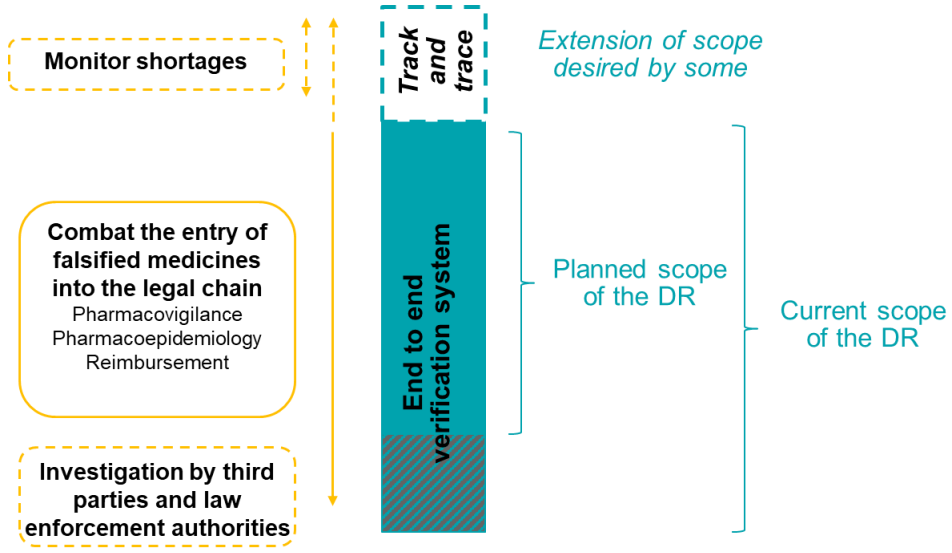
Finally, it **could prove useful to capitalise the system's already functioning features, and to use it in extensive ways.** In this respect, a best practice has been identified in France where the EMVS data is helping

[97] Four years of the European Medicines Verification System and th Falsified Medicines Directive: A Discussion Report, November 2023, EFPIA, Medicines for Europe

[98] Crime opportunity theory claims that criminals act rationally and thus choose targets offering high reward with little effort and risk. The occurrence of crimes depends on the existence of a motivated offender and a favourable environment to commit that crime (source: Hindelang, Michael (1978), *Victims of personal crime: an empirical foundation for a theory of personal victimization*).

law enforcement authorities during criminal investigation. Today in practice, France MVO is approached approximately once a week by police forces though a judicial requisition, after the authorisation of the NCA, and requested to submit information about packs of medicines seized. The law enforcement authorities transmit photos of the UI of the packs seized, so that France MVO can extract the corresponding audit trail from the EMVS. This information can help investigators track the last actor having scanned the pack seized, and eventually identify patterns of diversions. In March 2023, for example, the law enforcement authorities have seized 30 packs of anaesthetic cream modified with uronic acid. One of the packs was decommissioned, allowing the investigators to identify the community pharmacy from where the packs originated.

Figure 36 Simplified diagram of current, planned and desired scope of the DR



Source: EY elaboration

7 Conclusions

This concluding chapter synthesises the main conclusions set out in the previous sections of the report (which highlight the associated observations and findings). In particular, it identifies the main lessons to be learned from the evaluation.

Regarding the **trends and developments in the market of falsified medicines**, **available data reflect a bell curve shaped trend in the number of falsified medicinal products found in the European legal chain in recent years**: on the rise before the adoption of the DR(EU)2016/161 and decreasing afterwards. However, collected data on nationally authorised medicinal products, which are based on published studies and questionnaires collected from public authorities during this evaluation, are **too partial and inconsistent to draw robust conclusions on falsification trends in the EU/EEA**. For instance, differences in definition of a confirmed case of falsified medicinal products between countries and between authorities can be noticed and a case considered as confirmed by an NCA may need validation by a court ruling to be officially treated as such, generating "pending" confirmed cases. Besides, tracking and recording processes diverge across national authorities and EMA because of the different scope of the products considered (e.g., the EMA focuses on medicinal products with a European marketing authorization, while national authorities treat all products with a marketing authorisation).

Some conclusions however stand out according to data and qualitative inputs collected: **falsified medicines are mainly traded in the illegal supply chain and pertain to expensive and lifestyle medicines** (as they promise the highest profits for fraudsters). Most respondents to surveys (both NCA and stakeholders) agree that the online and illegal markets are the most concerned about falsification. **Both trends were also observed in Greece and Italy.**

Regarding the relevance of the measures set out in the DR, these appear fit for purpose and do not seem to require amendments to the legal texts, except on specific points that call for clarification (described below). **These measures are considered by NCAs and stakeholders as relevant vis-à-vis the objective of combating falsified medicines**, except for a limited number of end-users who claim that the legislation is not targeting the heart of the issue (i.e., falsified medicines in the illegal supply chain). This criticism is however

not relevant in the context of this study as the fight against falsification in legal and illegal distribution circuits are two complementary but different approaches.

The **UI** in particular is considered by both NCA and stakeholders of the supply chain[99] as a **very relevant safety feature because of its full harmonization**. **Its technical specifications allow indeed for the secured identification of legitimate medicinal products**, thus preventing the introduction of falsified medicines into the legal supply chain, while **unifying national product coding systems** across Member States. The purpose of the **anti-tampering device (ATD),** that is to guarantee that medicinal packs have not been tampered with, is **compromised by the lack of standards for physical specificities**. ATD currently suffers from strong disparities between manufacturers (who are in charge of their production) and therefore weakens the fight against falsification by opening loopholes for potential criminals. This is reflected in the perceptions of stakeholders of the supply chain surveyed: the opinion is overall positive but less than for the UI (70% - 112 out of 157 - of the respondents considered the ATD to be adequate or fully adequate; 85% for the UI). In comparison, both Italy and Greece require manufactures and MAH to place a unique authenticity sticker on medicinal packs instead of a UI. This sticker is directly produced by public authorities (or under public supervision) and has strict characteristics (in terms of size, material, etc.).

The end-to-end verification procedures are the most adequate to guarantee both the proportionality (i.e., avoiding an excessive verification burden for the stakeholders) **and effectiveness of the measures, assuming that the system is fully and well implemented in all Member States** and that wholesalers are compliant with risk-based verifications**.** Compared to the "simple" end-to-end verification" option discussed during the drafting of the DR (which did not provide for risk-based verifications by wholesalers), these verification methods add extra security and also allow for faster detection of falsified medicines as verifications are provided not only at the end of the supply chain. In comparison, the Greek and Italian verification system also allows for the decommission of medicinal products at the end of the supply chain and verifications along the chain. **These verifications procedures can nevertheless be not adapted and flexible enough to fit the particularities of hospital pharmacies**, which handle large volumes of packs of medicines daily thus causing practical challenges. In that respect, bulk verification using "aggregated codes" or "consolidated codes"[100] has been developed and needs to be promoted. Finally, verifications of the ATD are complicated because of the absence of specific guidelines on how to conduct them, resulting in a lack of awareness among stakeholders towards the importance of these verifications.

The reporting system is also relevant to the objective of the FMD as the double reporting mechanism, relying on automatic IT alerts and spontaneous flagging by stakeholders, **multiply chances of detecting falsified medicine before reaching patients.** However, **the DR is unclear about the actual details of the spontaneous alert mechanism** and needs further specifications (who needs to be informed in case of suspicion of falsification and at what time). Finally, **there are no homogeneous rules** between MS on the follow-up of these alerts by the NCAs and on the follow-up of suspected and confirmed cases.

Overall, **the opinion of the NCAs on the system is very positive**, although it should be noted that **most NCAs believe that the national supply chain was already secure** before the entry into force of the FMD and DR. These conclusions were also drawn by European and national stakeholders towards the middle and the end of the supply chain (i.e., mainly wholesalers and pharmacists), leading some stakeholders to question the utility or relevance of the verification system. On the other hand, stakeholders at the beginning of the supply chain (i.e., mainly manufacturers), see the introduction of falsified medicinal products in the legal supply chain as a real threat for patient safety and support the reinforcement of verifications and the convergence of the current verification system into a "track and trace system" to better monitor the movement of medicinal products across the EU/EEA. This proposition has received the support of some NCAs, who believe that such the modified a system could be used to monitor shortages of medicines across Europe. Most of the other stakeholders do not share the same opinion. In comparison, **both the Greek and Italian verification system can be used to monitor eventual shortages of medicines,** in addition to the traditional usages (securing the supply chain from falsified medicines, monitoring reimbursement of medicines, etc.). **This divergence in purposes with the European system represents the main challenge for the integration of Greece and Italy to the FMD and DR framework** (due in early 2025). In that context, Italy has made a proposition to the Commission to accommodate for some of the specificities of its national system.

[99] Regarding perceptions of the actors consulted, the majority of these ones were satisfied with the current design of the safety features. More than 85% (137 out of 157) of the respondents to the survey to stakeholders considered the Unique Identifier (UI) to be adequate or fully adequate. As for the NCA, all the answers received were positive in this respect.

[100] Aggregated codes are used to verify and decommission the UI of multiple medicine packs simultaneously. In practice, a supplier sends a shipment of products with their UIs and other relevant information (product name, expiry date, etc.) listed in a standardised data file. This data file can be matched to the shipment with an additional barcode, or "aggregated code", that is send along the shipment using a parallel repositories system to the EMVS. Once the hospital pharmacy has received the shipment and matched it with the corresponding data file using the aggregated code, it can decommission all products in the shipment without the need to scan each individual UI.

The choice of a stakeholder-led governance is appropriate and seeks to involve the most concerned stakeholders of the supply chain in order to engage them in implementing the DR framework, by defining the technical options and co-building the system in a cost-effective way. This allowed for a rather rapid implementation of the EMVS (except for hospital pharmacies) but **diverging views remain strong at EMVO level and could hinder EMVO's board ability to take strategic decisions**. Challenges related to transparency and accessibility of NMVO data also remain points of concern (few board minutes are available on websites for instance), as well as the management of software providers to make them act in a timely manner. In comparison, **the medicine verification systems in Greece and Italy are owned and operated by public authorities**, who have a direct access to the data circulating within it.

Finally, the **relevance of the design of the repositories system is proved** as it allows for national data to be stored and managed nationally and permits transfer of information when needed without increasing the risk of the introduction of falsified medicines. However, in case of investigation the process can be complicated by this two-tier architecture as full audit trail are not immediately available to competent authority, even though this was stipulated in the DR (Article 35(1)(g)).

Regarding the **actual functioning of the measures set out in the DR**, even if these ones are relevant **their application has been complicated and full compliance with the obligations in the DR is not yet achieved**.

First of all, **the connection of both OBP and end-users to the system has been slow and continues to be incomplete today**, 4 years after the entry into force of the DR. **Verifications are not systematic at the level of wholesalers as well as for pharmacists**, because the latter are not connected of the system or, when they are connected, because they are reluctant to do it. That is especially true for **hospital pharmacies** who face major technical challenges in decommissioning as they handle daily large volumes of medicines. Besides, **the number of "false" alerts remains high despite a continuous downward trend in recent years and contributes both to discouraging actors from participating in the system and to drowning out "real" alerts.** According to EMVO, these false alerts are to be linked to technical / IT issues from the end-user's side essentially, and not with the EMVS itself. Finally, medicines can still be dispensed in the event of an alert in the countries where a **"stabilization period"** is ongoing. This period, which is not mentioned in the FMD and the DR and is thus not compliant with EU legislation, was initiated by EMVO to avoid a sudden shortfall in medicinal products supply in countries where the alert rate is still high. This period was extended several times due to the disruption caused by the COVID-19 pandemic and difficulties with the implementation endured in some countries. This is considered as non-compliance towards the legislation.

Due to this incomplete implementation and the major shortcoming of the reporting system (e.g., lack of centralised monitoring, lack of common definition of falsified medicines), **it is premature to *quantify* the global effectiveness and impact of the FMD and DR**: it is indeed possible that an unquantifiable number of falsified medicinal products has circulated in the legal supply chain without being detected by the EMVS. Thus, while it is possible to highlight examples of success in detecting cases of falsification, it is not possible to conclude on the effectiveness of the system and its scale (i.e., whether the EMVS detected all the cases that should have been detected).

That being said, it is possible to ***qualify* the impact of the FMD and DR**. Indeed, the entry into force of the FMD and DR **has two main impacts**: firstly, **it has a theoretical deterrent effect** as it becomes more costly for criminals to introduce falsified medicines into the legal chain due to stricter controls. This deterrent effect, however, cannot be measured with precision. Secondly, it also constitutes a **powerful source of data for investigator to track falsifying activities.** The EMVS provided several times valuable data to retrace the journey of the packs and to identify suspicious behaviours (i.e., the unexpected scanning by a third-party pharmacy, the back and forth of the pack between the hospital and wholesalers, etc.). The detection of some cases of falsification, either directly, or indirectly in conjunction with the work of investigators, indicate that **the verification system can prevent falsified medicines to reach patients under some circumstances**. In other words, if the FMD and DR framework does not currently allow for the detection of all cases of falsification given its partial implementation, it can already detect some cases.In this sense, **the current framework deserves to be consolidated, promoted, and used to its full potential**. The EMVS is indeed in the middle of a learning curve and time is required to perfect its implementation and achieve the desired level of efficiency. As such, **an evolution towards a track and trace system, if it was to be considered, does not seem appropriate at this time**. Still, the existing features of the system can already be used extensively to optimize its impacts. This is the case, for example, for the collaborative exploitation of the EMVS data by NMV0, NCAs and law enforcement authorities to identify and tracks falsification activities.

Synthesis and prospective

On the basis of the conclusions mentioned throughout this report, a few major issues and risks stand out and could be addressed.

- Firstly, **the lack of physical standards of the ATD constitutes a major loophole** and is detrimental to the security of the legal supply chain. The verification process of the ATD is also problematic since it is not specified in the legislation, and thus unevenly performed by end-users. In this context, **it would prove useful to harmonize the technical specificities of the ATD and to specify its verification and reporting methods in the event of suspicion**. In practice, precise physical specifications for the ATD, as well as verification and reporting methods in case of suspicions of ATD breach could be inscribed in the appropriate legal/regulatory text, or in the form of guidelines.
- Secondly, **NCAs are only partially able to exercise their supervisory and control role over** (i) the repositories system (because of a reportedly lack of IT expertise) and (ii) software providers (e.g., to make them fix in a timely manner technical issues preventing the repositories system to function properly). Here again, several mitigation options can be considered to ensure the effective supervision role of NCAs. On the one hand, **precise supervision activities** (e.g., regular audits of the repositories system, if needed, by IT specialists; all transcripts of NMVO Board meetings or activity reports could be made available to NCAs) **and responsibilities** (e.g., presence of NCAs at NMVOs boards) for NCAs could be made **mandatory** in the appropriate text. On the other hand, the responsibilities of software providers should be better formalized, for example through **guidelines or "standard contracts" between NMVOs and software providers** indicating the minimum obligations that the latter must comply with, or by directly mentioning software providers and their responsibilities in the legislation.
- Thirdly, **an important number of users are still not connected to the system**. Beyond incentives to encourage connection, coercive measures (e.g., **fines**) could for instance be more systematically enforced by the appropriate level of authority (Member States, regions, etc.), to push the connection rate towards 100%. More specifically **the low connection rate of hospital pharmacies remains problematic**. This is linked, according to the hospital pharmacists consulted, to the practical difficulties to verify one by one the large volumes of medicines products they manage on a daily basis. This challenge could be mitigated by **promoting technical solutions allowing for the quick and easy verification of medicinal packs.** This, in turn, would encourage hospital pharmacies to connect and use the system. One practical solution put forward by many of the actors consulted is the **generalization of aggregated codes and bulk verification**. This solution is already widely deployed in Ireland and could be extended in the other Member States
- Fourth, **technical errors in uploading and scanning still exist** among EMVS users, even four years after the entry into force of the DR. As such, **it appears necessary to upskill the end users responsible for performing verification operations**, which would reduce the proportions of alerts related to human error. In that sense, **training courses** already initiated by EMVO and NMVOs could be strengthened in the area causing the most alerts (e.g., incorrect uploading of data in the EU hub, double decommissioning, etc.).
- Finally, the **lack of standardized and centralized monitoring of falsification cases (suspected and confirmed)** hinders the assessment of the effectiveness of the verification framework. Again, several options could be considered to mitigate this challenge. **Clear procedures to qualify cases** as confirmed falsified medicines could be determined and circulated across MS and public authorities. **EMA could also be made responsible for recording all cases of falsification**, including of nationally authorised products.

8 Annexes

8.1 Annex 1 - Glossary

Term	Definition	Source
API (Active pharmaceutical ingredient)	Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product.	EMA
ATD (Anti-Tampering Device)	The safety feature allowing the verification of whether the packaging of a medicinal product has been tampered with.	DR (EU) 2016/161
Decommissioning of a UI	The operation changing the active status of a UI in the repositories system referred to in Article 31 of the DR (EU) 2016/161 to a status impeding any further successful verification of the authenticity of that UI.	DR (EU) 2016/161
EAMS (European Alert Management System)	A system which aims to maximise the efficiency of alert management in the EMVS when the level of alert rate reaches a steady state (target 0,05%). The EAMS supports EMVS users (OBPs, MAHs, NMVOs and end-users) to change alert statuses and communicate with other parties involved in an alert investigation, depending also on the landscape at national level in each Member State. It is composed of the AMS Hub developed by EMVO and the National AMSs.	
EMVO (European Medicines Verification Organisation)	A non-profit legal entity that is responsible to set up and manage a central information and data router ('hub') in accordance with the provisions of the EU Directive on Falsified Medicines and the Delegated Regulation.	EMVO
EMVS (European Medicines Verification System)	he system for medicines verification that has been set up and is managed in accordance with Chapter VII of the Delegated Regulation; it consists of the European Hub and the National Systems, and allows the End-Users to verify the authenticity of medicinal products in accordance with the provisions of the EU Directive on Falsified Medicines and the Delegated Regulation.	EMVO
End-User	Any wholesaler, pharmacy or other person authorized or entitled to supply medicinal products to the public as foreseen under the EU Directive on Falsified Medicines and the Delegated Regulation or as otherwise foreseen under applicable law.	EMVO
Excipient	Constituent of a medicine other than the active substance, added in the formulation for a specific purpose. These must be declared in the labelling and package leaflet of the medicine for its safe use.	EMA
Healthcare institution	A hospital, in- or outpatient clinic or health centre.	DR (EU) 2016/161
MAH (Marketing Authorisation Holder)	The organisation which owns the serialisation data and which is accountable for uploading the data to the EU Hub (e.g. XYZ Sales Company in EU member country). Possibly an affiliate of the OBP; for smaller companies, the MAH and OBP could be the same.	EMVO
NCA (National Competent Authority)	A medicines regulatory authority in a EEA Member State that is, amongst others, primarily responsible for the authorisation of medicines available in the EEA that do not pass through the centralised procedure.	EMVO
NMVO (National Medicines Verification Organisation)	The non-profit legal entity (entities) that is (are) responsible to set up and manage a national and/or supranational repository(ies) in accordance with the provisions of the EU Directive on Falsified Medicines and the Delegated Regulation.	EMVO
NMVS (National Medicines Verification System)	The national or supranational repository of the EMVS according to Article 32, para. 1, b) of the Delegated Regulation under the responsibility of one NMVO; it is connected to the European Hub and allows the End-Users to verify the authenticity of medicinal products in accordance with the provisions of the EU Directive on Falsified Medicines and the Delegated Regulation.	EMVO
OBP (On-Boarding-Partner)	The company or organisation which is the contracting party of EMVO in the Participation Agreement and represents the affiliated entities that hold marketing authorisations for products for which the OBP uploads product and pack data to the EU Hub to be transferred to the National Systems.	EMVO
Parallel Distributor	A holder of either specific product authorisations issued by national competent authorities in an abbreviated procedure or the holder of an EMA distribution notice.	EMVO
Parallel importers	Parallel importers buy products marketed by the original manufacturer at a lower price in one country and sell them at a higher price in another country. Before selling the product in the country of destination, they may need to remove the outer packaging and ensure a repackaging.	Impact assessment of Directive (EC) 2001/83
Participation Agreement	The agreement that establishes the contractual framework and conditions for its on-boarding on the EU Hub and EMVS, including the conditions for the grant of rights that are necessary for the performance thereof.	EMVO
Stakeholders of the supply chain	The term "stakeholder" unless otherwise stated, refers to the private actors that constitute the legal pharmaceutical supply chain, and notably, manufacturers, importers, parallel traders, wholesalers, hospital and community pharmacists.	EY
UI (Unique Identifier)	The safety feature enabling the verification of the authenticity and the identification of an individual pack of a medicinal product.	DR (EU) 2016/161

8.2 Annex 2 - Targeted Interviews

Interviews conducted during the consultation phase

Country/Region	Organisation	Date
EU / International level		
EU	AME (Affordable Medicines Europe)	19/06/2023
EU	DG TAXUD	19/04/2023
EU	EAEP (European Association of E-Pharmacies)	07/07/2023
EU	EAHP (The European Association of Hospital Pharmacists)	27/06/2023
EU	EFPIA (European Federation of Pharmaceutical Industries and Associations)	28/06/2023
EU	EIPG (European Industrial Pharmacists Group)	17/07/2023
EU	EMA	22/09/2023 and 21/02/2023
EU	EMVO	02/2023
EU	GIRP (The European Healthcare Distribution Association)	22/06/2023
EU	HOPE (The European Hospital and Healthcare Federation)	20/06/2023
EU	Medecines for Europe	22/08/2023
EU	PGEU (Pharmaceutical Group of the European Union)	20/06/2023
EU	WHO	02/2023
International	University of Oxford	22/06/2023
International	University of Dublin	04/07/2023
National level		
Belgium	APB (Association Pharmaceutique Belge)	16/06/2023
Belgium	Bapie (Belgium Association of Parallel Importers and Exporters)	27/06/2023
Belgium	Belgium MVO	16/06/2023
Belgium	FAGG (Federal Agency for Medicines and Health Products)	03/05/2023
Belgium	Pharma.Be	16/06/2023
Bulgaria	ARPharM (The Association of the Research-based Pharmaceutical Manufacturers in Bulgaria)	30/06/2023
Bulgaria	BAMPTD (Bulgarian Association for Medicines Parallel Trade Development)	29/08/2023
Bulgaria	BDA (Bulgarian Drug Agency)	24/05/2023
Bulgaria	BgMVO (Bulgarian NMVO)	15/06/2023
Denmark	Danish Medicines Verification Organisation	12/07/2023
Denmark	NovoNordisk	13/09/2023
Estonia	Estonian Association of Pharmaceutical Wholesalers	01/06/2023
Estonia	Estonian Pharmacy Association	02/06/2023
Estonia	RAVIMIAMET (Estonian Agency of Medicines)	09/05/2023
Estonia	REKS (Estonian NMVO)	01/06/2023
France	ANSM (Agence Nationale de Sécurité du Médicament et des Produits de Santé)	31/05/2023
France	CSRP (Chambre Syndicale de Répartition Pharmaceutique)	13/06/2023
France	France MVO	02/06/2023
France	France MVO/ SNPHPU (Syndicat National des Pharmaciens Hospitaliers et Praticiens Universitaires)	08/06/2023
France	OCLAESP (Office central de lutte contre les atteintes à l'environnement et à la santé publique)	30/06/2023
France	USPO (Union de syndicats de pharmaciens d'officine)	15/06/2023
Greece	EOF (Grec NCA)	02/11/2023
Ireland	FMD Expert group	31/05/2023

Ireland	Irish Medicines Verification Organisation	07/07/2023
Ireland	Irish Pharmacy Union	12/07/2023
Ireland	Medicines for Ireland	13/07/2023
Italy	AIFA (Italian Medicines Agency)	24/10/2023
Poland	GIF (Poland's Chief Pharmaceutical Inspectorate)	15/05/2023
Poland	INFARMA (Employers' Union of Innovative Pharmaceutical Companies)	12/09/2023
Poland	PLMVO	20/07/2023
Poland	PZPPF (Polish Association of Pharmaceutical Industry Employers)	11/09/2023
Spain	Farmaceuticos (Consejo General de Colegios Farmaceuticos)	19/07/2023
Spain	FARMAINDUSTRIA	22/06/2023
Spain	Fedifar	17/07/2023
Spain	FMD Expert group	05/06/2023
Spain	Spanish Medicines Verification System (SEVeM)	21/06/2023

Interviews conducted for the case studies

Country	Organisation	Date
Belgium	Special Investigation Unit	21/09/2023
Bulgaria	Bulgarian Drug Agency	22/09/2023 And 17/08/2023
Estonia	Estonian Association of Pharmaceutical Wholesalers	21/09/2023
Estonia	Estonian State Agency of Medicines	21/09/2023
France	CHU Lyon	22/08/2023
France	CNOP (Conseil National de l'Ordre des Pharmaciens)	13/10/2023
France	Community pharmacy/ Fédération des syndicats pharmaceutiques de France (FSPF)	13/09/2023
France	Community pharmacy/ USPO	25/08/2023
France	France MVO	08/09/2023
France	France MVO/ SNPHPU (Syndicat National des Pharmaciens Hospitaliers et Praticiens Universitaires)	30/08/2023
France	OCLAESP (Office central de lutte contre les atteintes à l'environnement et à la santé publique)	30/06/2023
France	USPO	23/08/2023
Ireland	IMVO	19/09/2023
Ireland	Mater Misericordiae University Hospital	25/09/2023
Ireland	Mater Private	08/09/2023
Netherlands	NCA	10/2023
Netherlands	NMVO (Stichting Nederlandse Medicijnen Verificatie Organisatie)	25/09/2023
Spain	Farmaceuticos (Consejo General de Colegios Farmaceuticos)	19/07/23
Spain	Fedifar	17/07/23

8.3 Annex 3 - Survey Questionnaires

8.3.1 Survey Questionnaire to NCAs

Survey to National Competent Authorities on the implementation and effects of Directive 2011/62/EU and Delegated Regulation 2016/161/EU on falsified medicinal products

The European Commission has mandated EY to undertake a Study to assess the implementation and effects of Directive 2011/62/EU on the falsification of medicinal products (FMD) and measures laid down in Delegated Regulation 2016/161/EU (DR).

The Study will provide inputs for the Commission to prepare the report required according to Article 3 of FMD. The report will cover two key components, i.e.: (i) an analysis of the trends in the falsification of medicinal products, and (ii) the adequacy and functioning of the system in place, including the effects of the traceability mechanisms and obligatory safety features as part of the outer packaging of medicinal products.

This questionnaire aims to collect key inputs from you, as the National competent authority (NCA) in your country. More specifically, it aims to:

- **Gather relevant information on the implementation of the measures** set by the EU legislative framework in your country (such as the traceability system and the Unique Identifier and Anti-tampering device placed on medicine packs), including existing national specificities and challenges;
- **Collect your perceptions on the adequacy and functioning of these measures** (considering each measure separately);
- **Collect inputs** on past and current trends with regards to the falsification of medicinal products in your country;
- **Receive your suggestions and recommendations** on how to improve the functionality of the system to better address potential remaining risks and overcome existing barriers and constraints.

This questionnaire contains **52 closed and open-ended questions** divided into four sections:

1. *The implementation of the EU legal framework in your country and your role as an NCA*
2. *Adequacy and effects of the measures laid down by the* EU Legal Framework*EU legal framework*
3. *Trends of falsification in your country*
4. *General opinion*

Remarks:

- Questions are distinguished between **first tier questions (in red)**, and second tier questions (in black). While both categories of questions are necessary for the study, you can **prioritize** answering to first tier questions should you be time constrained.
- Please note that all responses will be kept **confidential** and used for research purposes only
- You are invited to **respond directly on this Word document**. This Word format allows you to transfer the document between structures/divisions of your institution if more than one person has to complete the questionnaire. We except **one Word questionnaire per structure**.

- You are expected to answer either by ticking boxes or by explaining directly in the boxes provided under the questions. Even in the case of questions to be ticked, you are invited to elaborate in the box provided.
- In order to guide you on certain topics, blue boxes recalling the key points of the Regulation on these topics have been inserted at the beginning of the parts.
- We will **request some data to support your answers on a separate document.**

Acronyms:

- DR: Delegated Regulation 2016/161/EU
- EMA: European Medicines Agency
- EAMS: European Alert Management System
- EU: European Union
- FMD: Directive 2011/62/EU on the falsification of medicinal products
- NCA: National Competent Authority
- NMVO: National Medicines Verification Organisation
- NMVS: National Medicines Verification System
- MAH: Marketing Authorization Holder
- MS: Member State
- OBP: Onboarding Partner
- UI: Unique Identifier

The implementation of the EU legal framework in your country and your role as an NCA

National state of play before the entry into force of the EU legal framework

1. Before the entry into force of the 2011 FMD and the 2016 DR, was there already a system in place in your country allowing the verification of medicines' authenticity?

☐ Yes

☐ No

☐ Do not know

2. If you replied yes to question No. 1, what were the characteristics of the system in place in your country prior to the entry into force of the FMD and the DR?

- Where medicinal products systematically verified along the supply chain?
- Were falsified medicinal products reported and registered?
- Based on obligatory safety features of medicines?
- IT-based system?
- Characteristics of the UI?
- Role of the stakeholders?
- Reporting system?
- Registration of cases of falsified medicines?

Please answer here

3. Are there any characteristics of your former system that could have been maintained in the FMD and the DR? Or have the EU rules improved the previous system and if they have, with which features?

Please answer here

Scope of the DR

"This Regulation applies to:
(a) medicinal products subject to prescription which shall bear safety features on their packaging pursuant to Article 54a(1) of Directive 2001/83/EC, unless included in the list set out in Annex I to this Regulation;
(b) medicinal products not subject to prescription included in the list set out in Annex II to this Regulation;
(c) medicinal products to which Member States have extended the scope of application of the unique identifier or of the anti-tampering device in accordance with Article 54a(5) of Directive 2001/83/EC.
(Article 2 of DR 2016/161/UE)

4. **Do you consider the scope as defined in the DR relevant to achieve the objectives of the FMD?**
   - ☐ Yes, fully relevant
   - ☐ Yes, rather relevant
   - ☐ Not really
   - ☐ Not at all
   - ☐ Do not know

Please elaborate if needed

5. **Do you see challenges or difficulties coming from the fact that the list of products subject to prescription may differ from one MS to another? Do you see challenges or difficulties coming from the fact that MS can extend/ reduce the scope at national level?**

Please answer here

6. **Have you already notified the Commission about non-prescription medicinal products and/or prescription medicinal products not deemed at risk of falsification that your country judged at risk of falsification?**
   - ☐ Yes
   - ☐ No
   - ☐ Do not know

7. **If you have answered "Yes" to the previous question, have you performed a risk-based assessment or any other form of analysis?**
   - ☐ Yes
   - ☐ No
   - ☐ Do not know

8. **Could you explain the criteria that were included in this risk assessment or analysis (e.g., potential risk to public health, previous occurrence of falsification, etc.)? Which of these mostly influenced the decision, if any in particular?**

Please answer here

9. Did the Commission handle the notification in a satisfactory manner? What could have been done better?

☐ Very satisfactory

☐ Satisfactory

☐ Not satisfactory

☐ Very unsatisfactory

☐ Do not know

Please elaborate

10. Has your country extended the scope of application of the unique identifier to any medicinal product for the purposes of:

-	- Yes	- No	- Do not know
- pharmacovigilance	- ☐	- ☐	- ☐
- reimbursement	- ☐	- ☐	- ☐

Please elaborate

11. Has your country extended the scope of application of the anti-tampering device to any medicinal product for the purposes of patient safety?

☐ Yes

☐ No

☐ Do not know

Please elaborate

Governance of the system

The establishment of the NMVS relies on a stakeholder-led governance which involves manufacturers, distributors, and suppliers as well as NCAs.
"1. The repositories system where the information on the safety features shall be contained, pursuant to Article 54a(2)(e) of Directive 2001/83/EC, shall be set up and managed by a non-profit legal entity or non-profit legal entities established in the Union by manufacturers and marketing authorisation holders of medicinal products bearing the safety features.
2. In setting up the repositories system, the legal entity or entities referred to in paragraph 1 shall consult at least wholesalers, persons authorised or entitled to supply medicinal products to the public and relevant national competent authorities.
3. Wholesalers and persons authorised or entitled to supply medicinal products to the public are entitled to participate in the legal entity or entities referred to in paragraph 1, on a voluntary basis, at no cost."
(Article 31 of the DR 2016/161/UE)

"A legal entity establishing and managing a repository used to verify the authenticity of or 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 following purposes:
(a) supervising the functioning of the repositories and investigating potential incidents of falsification;
(b) reimbursement;
(c) pharmacovigilance or pharmacoepidemiology."
(Article 39 of the DR 2016/161/UE)

12. To what extent do you agree with the following assertions regarding the adequacy of the stakeholder-led governance, as defined in the DR?

-	- F ully agree	- R ather agree	- ot really agree	- ot agree at all	- o not know
-	**Adequacy at EU/EEA level**				
- t is adequate and effective (as regard to the objectives of the FMD) to have all relevant stakeholders in the pharmaceutical sector and public authorities involved in the governance of the **EMVO**	- □	- □	-	-	-
- he representation of the different stakeholders of the pharmaceutical sector and the public authorities at the governing board of the **EMVO** is balanced and allows for the achievement of the objectives of the FMD	- □	- □	-	-	-
- non-profit organisation driven by private stakeholders is the most adequate type of entity to be in charge of the establishment and management of the repository system at the	- □	- □	-	-	-

EU/EEA level (i.e., the EU "Hub")					
- he repository system at the **EU/EEA level** meets your expectations	- □	- □	-	-	-
- **Adequacy at national level**					
- It is adequate and effective (as regard to the objectives of the FMD) to have all relevant stakeholders in the pharmaceutical sector and public authorities involved in the governance of the **NMVO**	-	-	-	-	-
- The representation of the different stakeholders of the pharmaceutical sector and the public authorities at the board of the **NMVO** is balanced and allows for the achievement of the objectives of the FMD	-	-	-	-	-
- A non-profit organisation driven by private stakeholders is the most adequate type of entity to be in charge of the establishment and management of the repositories system in **your country** (i.e., the NMVS)	-	-	-	-	-
- The repositories system in **your country** meets your expectations	-	-	-	-	-

Please elaborate here
(And notably, if you don't think that a non-profit organisation driven by private stakeholders is the most adequate, would public stakeholders be a better option in your view?)

13. To what extent do you agree with the following assertions regarding the functioning of the stakeholder-led governance, as defined in the DR?

-	- ully agree	- ather agree	- ot really agree	- ot agree at all	- o not know
-	**Functioning at EU/EEA level**				
- he **EMVO** functions smoothly	-	- □	-	-	-
- o specific difficulties were encountered in the setting up of the **EMVO**	-	- □	-	-	-
- AH and manufacturers have managed to organise themselves in an effective way to fund the repositories system at the **EU/EEA level**	-	- □	-	-	-
- he functioning of the **EMVO** governance as it is established now enables the organisation to fulfil its objectives	-	- □	-	-	-
- he financing model of the repositories system at the **EU/EEA level** ensures the service continuity and its optimal function	-	- □	-	-	-
-	**Functioning at national level**				
- he **NMVO** functions smoothly in your country	-	- □	-	-	-
- o specific difficulties were encountered in the setting up of the **NMVO** in your country	-	- □	-	-	-

- AH and manufacturers have managed to organise themselves in an effective way to fund the repositories system in **your country**	-	-	-	-	-
- he functioning of the **NMVO** governance as it is established now enables the organisation to fulfil its objectives	-	-	-	-	-
- he financing model of the repositories system in **your country** ensures the service continuity and its optimal function	-	-	-	-	-

Please elaborate here

14. Would you have any recommendations on how to improve the adequacy and functioning of these governance principles at EU or national level?

Please answer here

Your role as an NCA

"National competent authorities shall make the following information available to the marketing authorisation holders, manufacturers, wholesalers and persons authorised or entitled to supply medicinal products to the public, upon their request:
(a) the medicinal products placed on the market on their territory which shall bear the safety features in accordance with Article 54(o) of Directive 2001/83/EC and this Regulation;
(b) the medicinal products subject to prescription or subject to reimbursement for which the scope of the unique
identifier is extended for the purposes of reimbursement or pharmacovigilance, in accordance with Article 54a(5) of Directive 2001/83/EC;
(c) the medicinal products for which the scope of the anti-tampering device is extended for the purpose of patient safety, in accordance with Article 54a(5) of Directive 2001/83/EC."
(Article 43 of the DR 2016/161/UE)

"1. National competent authorities shall supervise the functioning of any repository physically located in their territory, in order to verify, if necessary by means of inspections, that the repository and the legal entity responsible for the establishment and management of the repository comply with the requirements of this Regulation.

2. A national competent authority may delegate any of its obligations under this Article to the competent authority of another Member State or to a third party, by means of a written agreement.
3. Where a repository not physically located in the territory of a Member State is used for the purpose of verifying the authenticity of medicinal products placed on the market in that Member State, the competent authority of that Member State may observe an inspection of the repository or perform an independent inspection, subject to the agreement of the Member State in which the repository is physically located.
4. A national competent authority shall communicate reports of supervision activities to the European Medicines Agency, which shall make them available to the other national competent authorities and the Commission.
5. National competent authorities may contribute to the management of any repository used to identify medicinal products and verify the authenticity of or decommission the unique identifiers of medicinal products placed on the market in the territory of their Member State.
National competent authorities may participate to the management board of the legal entities managing those repositories to the extent of up to one third of the members of the board."
(Article 44 of the DR 2016/161/UE)

15. Are you a member of the NMVO management board?

☐ Yes

☐ No

16. Do you consider the obligations required from the DR with regards to NCA's supervision of the repositories system adequate and functioning to achieve the objectives of the FMD?

☐ Yes, fully adequate

☐ Yes, rather adequate

☐ Not really

☐ Not at all

☐ Do not know

Please elaborate here

17. Have you encountered any challenges in fulfilling these obligations (e.g., in supervising the functioning of the repository located in your country)?

☐ Yes, many

☐Yes, some

☐ No

☐ Do not know/ NA

Please elaborate (specify in case you have delegated these obligations to the NCA of another MS or to a third party)

18. Which type of actions is your institution deploying with respect to the supervision of the NMVO/ NMVS? Please report whether other actions are planned to be deployed in the future.

4.

Please answer here

19. Have you carried out inspections since the entry into force of the DR in 2019? If yes, what have been the main issues you have reported (e.g., technical incident, actual case of falsification, etc.) Have you taken any measures to solve these issues?

Please answer here

Adequacy and effects of the measures laid down by the EU Legal Framework

Functioning of the safety features

" 'Unique identifier' means the safety feature enabling the verification of the authenticity and the identification of an individual pack of a medicinal product; *'anti-tampering device' means the safety feature allowing the verification of whether the packaging of a medicinal product has been tampered with. "* *(Articles 3 of DR 2016/161/UE)* *"The manufacturer shall place on the packaging of a medicinal product a unique identifier which complies with the following technical specifications:* *(a) The unique identifier shall be a sequence of numeric or alphanumeric characters that is unique to a given pack of a medicinal product.* *(b) The unique identifier shall consist of the following data elements:* *(i) a code allowing the identification of at least the name, the common name, the pharmaceutical form, the strength, the pack size and the pack type of the medicinal product bearing the unique identifier ('product code');* *(ii) a numeric or alphanumeric sequence of maximum 20 characters, generated by a deterministic or a non-deterministic randomisation algorithm ('serial number');* *(iii) a national reimbursement number or other national number identifying the medicinal product, if required by the Member State where the product is intended to be placed on the market;* *(iv) the batch number;* *(v) the expiry date.* *(c) The probability that the serial number can be guessed shall be negligible and in any case lower than one in ten thousand.* *(d) The character sequence resulting from the combination of the product code and the serial number shall be unique to a given pack of a medicinal product until at least one year after the expiry date of the pack or five years after the pack has been released for sale or distribution in accordance with Article 51(3) of Directive 2001/83/EC, whichever is the longer period.* *(e) Where the national reimbursement number or other national number identifying the medicinal product is contained in the product code, it is not required to be repeated within the unique identifier."* *(Articles 4 of DR 2016/161/UE)*

20. To what extent do you agree with the following assumptions related to the safety features?

-

-	- ully agree	- R ather agree	- ot really agree	- ot agree at all	- o not know
- **EU/EEA level**					
- T he technical specifications of UI are adequate to secure the legal supply chain of medicinal products in Europe	-	- □	-	-	-
- O verall, the composition of the UI is sufficient to allow the verification of the authenticity	-	- □	-	-	-

of the medicinal products					
- Overall, the probability for a serial number to be guessed is negligeable	-	- □	-	-	-
- The Anti-Tampering Device is adequate to secure the legal supply chain of medicinal products in Europe	-	- □	-	-	-
- **National level**					
- The technical specifications of UI are adequate to secure the legal supply chain of medicinal products in your country	-	- □	-	-	-
- The composition of the UI is sufficient to allow the verification of the authenticity of the medicinal products in your country	-	- □	-	-	-
- The probability for a serial number to be guessed is negligeable in your country	-	- □	-	-	-
- The technical specifications of the UI, as stated in Article 4 of the DR, are respected by the manufacturers in your country	-	- □	-	-	-
- The Anti-Tampering Device is adequate to secure the legal supply chain of medicinal products in your country	-	- □	-	-	-

-

Please elaborate here if needed

-

21. Are you aware of <u>any difficulties or technical problems</u> encountered?

- **by the manufacturers** to generate the UI and place the anti-tampering device
- **by the MAH / OBP**[101] to upload the information to the repositories system (in that case, the EU Hub)

Please answer here by specifying who encountered the problem, how he was affected, and what solutions were implemented.

22. Have you requested to include <u>additional information</u> than the UI on the packaging?

☐ Yes

☐ No

☐ Do not know/ NA

For what purpose? If yes, what information?

23. Have the stakeholders requested the inclusion of other information in your country and been granted your approval?

☐ Yes

☐ No

☐ Do not know/ NA

What information? For what purpose? Was the approval eventually granted?

Functioning of the repositories system

"The repositories system shall be composed of the following electronic repositories:
(a) a central information and data router ('hub');
(b) repositories which serve the territory of one Member State ('national repositories') or the territory of multiple Member States ('supranational repositories'). Those repositories shall be connected to the hub."
(Article 32 of DR 2016/161/UE)

"The repositories system shall provide for at least the following operations:
(a) the repeated verification of the authenticity of an active unique in accordance with Article 11;
(b) the triggering of an alert in the system and in the terminal where the verification of the authenticity of a unique identifier is taking place when such verification fails to confirm that the unique identifier is authentic in accordance with Article 11. Such an event shall be flagged in the system as a potential incident of falsification except where the product is indicated in the system as recalled, withdrawn or intended for destruction;
(c) the decommissioning of a unique identifier in accordance with the requirements of this Regulation;
(d) the combined operations of identification of a pack of a medicinal product bearing a unique identifier and verification of the authenticity and decommissioning of that unique identifier;
(e) the identification of a pack of a medicinal product bearing a unique identifier and the verification of the authenticity and the decommissioning of that unique identifier in a Member State which is not the Member State where the medicinal product bearing that unique identifier was placed on the market;
(f) the reading of the information contained in the two-dimensional barcode encoding the unique identifier, the identification of the medicinal product carrying the barcode and the verification of the status of the unique identifier, without triggering the alert referred to in point (b) of this Article […]"
(Article 36 of DR 2016/161/UE)

"A legal entity establishing and managing a repository used to verify the authenticity of or decommission the unique identifiers of medicinal products placed on the market in a Member State shall grant access to that

[101] The On-Boarding Partner (OBP) "represents the Marketing Authorization Holders (MAH) on behalf of which it will
upload data for in the European Hub" (source: EMVO, OBP *On-Boarding Presentation*)

repository and to the information contained therein, to competent authorities of that Member State for the following purposes:
(a) supervising the functioning of the repositories and investigating potential incidents of falsification;
(b) reimbursement;
(c) pharmacovigilance or pharmacoepidemiology
(Article 39 of DR 2016/161/UE)

24. To what extent do you agree with the following assertion regarding <u>functioning of the repositories system</u> (i.e., as a reminder, the EU Hub and the different NMVS)

-	- F ully agree	- R ather agree	- ot really agree	- ot agree at all	- o not know
- T he repositories system is easy to operate (user-friendly interface, etc.)	-	- ☐	-	-	-
- T he repositories system offers a safe access in terms of cybersecurity	-	- ☐	-	-	-
- T he repositories system reports alarms efficiently and consistently	-	- ☐	-	-	-
- N CAs have an easy and direct access to the repositories system and the information contained therein (product code, national reimbursement and identification number, batch number and expiry date…)	-	- ☐	-	-	-

Please elaborate here

25. For what purpose do you use the information contained in the repositories system?

☐ for the purposes of reimbursement

☐ for the purposes of pharmacovigilance

☐ for the purposes of pharmacoepidemiology

☐ for the purposes of supervising the functioning of the repositories

☐ for investigating potential incidents of falsification

☐ for other purposes, please specify:

Please answer here

26. Would you have any recommendation with respect to the extension of the scope of the repositories?

-	- Yes	- No	- Don't know	- Please elaborate
- Extension for other purposes (purposes not mentioned in DR article 39)	- ☐	- ☐	- ☐	-
- Extension for other medicinal products (products not mentioned in DR article 2)	- ☐	- ☐	- ☐	-

Please elaborate

27. Would you have any recommendation regarding the supervision of the repositories system?

Please answer here

Modalities of verification

"The authenticity and integrity of the safety features placed on the packaging of a medicinal product at the beginning of the supply chain should be verified at the time the medicinal product is supplied to the public, although certain derogations may apply. However, medicinal products at higher risk of falsification should be additionally verified by wholesalers throughout the supply chain, to minimise the risk of falsified medicinal products circulating undetected for lengthy periods of time.
The verification of the authenticity of a unique identifier should be performed by comparing that unique identifier with the legitimate unique identifiers stored in a repositories system. When the pack is supplied to the public, or is distributed outside the Union, or in other specific situations, the unique identifier on that pack should be decommissioned in the repositories system so any other pack bearing the same unique identifier could not be successfully verified."
(Recital 4 of DR 2016/161/UE)

28. To what extent do you agree with the following assumptions related to <u>the adequacy of the verification modalities?</u>

-	- ully agree	- ather agree R	- ot really agree	- ot agree at all	- o not know
- The end-to-end verification requirements are sufficient to limit the risks of falsification on the legal supply chain	-	- ☐	-	-	-
- The verification requirements are proportionate to	-	- ☐	-	-	-

the risks of falsification					
- The modalities of verification are aligned with other EU and national legal obligations	-	- ☐	-	-	-
- Reversing the status of a decommissioned UI does not bring more risks than benefits	-	- ☐	-	-	-

Please elaborate here

29. What challenges/ difficulties have you identified regarding the verification? (who faced them, were they structural, etc.)

Please answer here

30. Has your country used the possibility to <u>adapt the verification modalities</u> of the safety measures to the specificities of your national legal supply chain (as permitted by the article 23 of the Delegated Regulation 2016/161)?

☐ Yes

☐ No

☐ Do not know/ NA

31. If so, in which cases are wholesalers also required to verify the safety features and decommissions the UI of a medicinal product?

☐ Before it is supplied to persons authorised or entitled to supply medicinal products to the public who do not operate within a healthcare institution or within a pharmacy.

☐ Before it is supplied to veterinarians and retailers of veterinary medicinal products.

☐ Before it is supplied to dental practitioners.

☐ Before it is supplied to optometrists and opticians.

☐ Before it is supplied to paramedics and emergency medical practitioners.

☐ Before it is supplied to armed forces, police and other governmental institutions maintaining stocks of medicinal products for the purposes of civil protection and disaster control.

☐ Before it is supplied to universities and other higher education establishments using medicinal products for the purposes of research and education, with the exceptions of healthcare institutions.

☐ Before it is supplied to prisons.

☐ Before it is supplied to schools.

☐ Before it is supplied to hospices.

☐ Before it is supplied to nursing homes.

☐Other, please specify :

Please elaborate here

Management of alerts

The DR provides for two alerts (or flagging) mechanisms in the events of a potential case of falsification:

- Articles 18, 24 and 30 refer to a spontaneous flagging mechanism should a stakeholder in the supply chain suspects a case of falsification in the stock he handles.
- Articles 36 and 37 refer to an automatic alert mechanism triggered by the system itself.

Where a "manufacturer" (Article 28), a "wholesaler" (Article 24) or a "persons authorized or entitled to supply medicinal products to the public" (Article 30) "has reason to believe that the packaging of the medicinal product has been tampered with or the verification of the safety measures shows that the product may not be authentic, the manufacturer shall not release the product for sale and shall immediately inform the relevant competent authorities"
(Articles 18, 24 and 30 of DR 2016/161/UE)
"The repositories system shall provide for […] the triggering of an alert in the system and in the terminal where the verification of the authenticity of a unique identifier is taking place when such verification fails to confirm that the unique identifier is authentic in accordance with Article 11 [A unique identifier shall be considered authentic when the repositories system contains an active unique identifier with the product code and serial number that are identical to those of the unique identifier being verified]. Such an event shall be flagged in the system as a potential incident of falsification except where the product is indicated in the system as recalled, withdrawn or intended for destruction";
(Article 36 of DR 2016/161/UE)
"Any legal entity establishing and managing a repository which is part of the repositories system shall […] continuously monitor the repository for events alerting to potential incidents of falsification, […] provide for the alerting of national competent authorities, the European Medicines Agency and the Commission should the falsification be confirmed."(Article 37 of DR 2016/161/UE)

32. As an NCA, are you consistently notified of all the alerts…

-	- Yes	- No	- Don't know	- Please elaborate
- …spontaneously flagged by manufacturers, wholesalers, or other stakeholders	- ☐	- ☐	- ☐	-
- …detected by the repositories system	- ☐	- ☐	- ☐	-

***33.* When / for which types of errors are you alerted *(e.g., only if there is a serious suspicion of falsification, etc)?* Does this NCA alert level seem relevant / adequate to you?**

Please elaborate here: • *Definition of "alert" in your country: when are you alerted? Which types of errors?: ….* • *Relevance and adequacy of this alert level: ……*

34. At which <u>level</u> of the legal supply chain are alerts triggered the most often?

☐ Manufacturers

☐ Distributors

☐ Full-line wholesalers

☐ Designated wholesalers

☐ Importers

☐ Parallel traders

☐ Brokers

☐ Hospitals

☐ Pharmacists

☐ Other actors:

Add precisions if needed

35. What is the main cause triggering alerts?

☐ Technical incidents (e.g., software or hardware malfunction)

☐ End users mistake (e.g., double scanning by a pharmacist)

☐ Actual case of falsification

☐ Other:

Add precisions if needed

36. How often do you encounter alerts related to intermarket transactions (i.e., transactions between MS of the EU or the EEA)?

☐ Frequently

☐ Occasionally

☐ Rarely

☐ Never

☐ Do not know/Not applicable

37. What measures do you take when notified of an alert by the repositories system and of spontaneous alerts from end-users? Do you follow the same course of action in each case? (e.g., is an investigation undertaken following every alerts?)

Please answer here

38. How is the coordination with other entities (incl. EMA) realised on the management of suspected cases? Have you identified any coordination challenges between stakeholders when managing suspected cases of falsification (at both EU and national level)?

Please explain briefly the process in place when an alert is triggered, including the timeline until a resolution of the suspicion.
Description of eventual challenges

39. To what extent do you agree with the following assumptions related to the adequacy and functioning of the management of alerts and reporting system?

-	- F ully agree	- R ather agree	- ot really agree	- ot agree at all	- o not know
- he legislation framework is specific enough with respect to the actions to be taken in case of suspected identified cases	- □	- □	-	-	-
- he legislation framework is specific enough with respect to the actions to be taken in case of confirmed identified cases	- □	- □	-	-	-
- he report of incidents is adequate to prevent the supply of falsified medicinal products	- □	- □	-	-	-
- he report of incidents is adequate to detect cases of falsification and take timely actions	- □	- □	-	-	-
- he NMVO has the capacity and capability to investigate and notify real alerts	- □	- □	-	-	-

40. Do you have any suggestions to improve the current European notification framework and its articulation with national systems?

10.

Please answer here

41. The EMVO is currently deploying a European Alert Management System (EAMS). Is your country planning the join this initiative? What are the considerations taken into account?

☐ Yes

☐ No, excluded

☐ We are considering it

Please elaborate here

Trends of falsification in your country

Please note that specific data will be requested on a separate document regarding trends

42. How would you <u>assess the trends</u> in terms of falsification of medicines in your country and especially since the implementation of the DR? How did the trends in medicines falsification evolve in your country since the entry into force of the DRin 2019? *(Please answer for each of the category below)*

Number of suspected case (increase/stagnation/decrease)	
Number of confirmed cases (increase/stagnation/decrease)	
Causes of falsification	

***43.* What are the three <u>most commonly falsified medicines</u> traded in the supply chain in your country?**

(These data are also requested separately for use by the study team. If you provide the data on the separate document, you can skip this question.)

Please answer here

44. How do you explain that these medicinal products are particularly falsified? Do they suffer from specific incentives (high price/profit margin, shortage, high demand)?

Please answer here

45. How do you perceive <u>the impact of e-commerce</u> on the market for falsified medicinal products?

In terms of overall perception, estimated share of e-commerce on the total market value for falsified medicinal products in your country, etc.

11.

Please answer here

46. Are medicinal products imported from outside the EU and the European Economic Area (EEA) more concerned about falsification than locally produced products?

☐ Yes

☐ No

☐ Do not know

Please specify in which proportion, and which countries of origin are the most concerned.

47. Do intermarket transactions pose particular challenges in terms of risks of introducing falsified medicinal products into the supply chain of your country?

☐ Yes

☐ No

☐ Do not know

Please elaborate.

48. Do authorities of your country pursue any specific legal actions against falsified medicines (including administrative action and pre-litigation)?

☐Yes
☐No
☐Do not know

Please elaborate here

49. In your view, what are the new challenges or trends in the falsified medicinal products market that have emerged in recent years?

☐ Increased online/Internet sales
☐ Sophistication of forging and adulteration techniques of medicinal products and medicinal packs
☐ Issues related to the globalization of supply chains (e.g., difficult traceability of products, diffusion of accountability, etc.)
☐ Greater involvement of organized crime
☐ High demand in lifestyles products with pharmaceutical claim
☐ Growing demand for high-value medicinal products
☐ Lack of standardization in authentication technologies

☐ Other, please specify below:

Specify here

General opinion

50. To what extent do you think the system laid down by the FMD and the DR reduces the risks of medicines falsification?

12.

Please answer here

51. Do you have any proposal to improve the FMD and the DR and make them more fit for purpose?

Please answer here

52. Do you have specific topics in mind that the Study team should investigate in detail?

Please answer here

Thank you for your participation in this survey.

8.3.2 Survey Questionnaire to stakeholders of the pharmaceutical distribution chain

Survey: Actors of the legal supply-chain of medicinal products

The European Commission has mandated EY and Ramboll to undertake a Study to **assess the implementation and effects of Directive 2011/62/EU (Falsified Medicines Directive)**, aiming at strengthening the fight against falsified medicinal products through tougher rules and new measures to secure their manufacturing, packaging, and ensure that the distribution channels are rigorously controlled. Detailed rules for these safety features have been laid down by **Delegated Regulation (DR) (EU) 2016/161**[102], which introduces an end-to-

[102] Commission Delegated Regulation (EU) 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

end verification **mechanisms and obligatory safety features of medicinal products,** as part of the outer packaging of medicinal products subject to prescription, namely: (i) a **unique identifier** (a 2-dimension barcode), whose authenticity testifies the legitimacy of the manufacturer, and (ii) an **anti-tampering device**, whose integrity demonstrates the authenticity of the medicinal product and its packaging.

The DR became applicable on 9 February 2019 in the EU and the European Economic Area (EEA), with the exception of Italy and Greece[103]. In that context, EY's study will provide inputs for the European Commission's report to the European Parliament and the Council, which, according to Article 3 of Directive 2011/62/EU, covers two key components, i.e.: (i) an analysis of the trends in the falsification of medicinal products, and (ii) the adequacy and functioning of the system in place, including the effects of the traceability mechanisms and obligatory safety features as part of the outer packaging of medicinal products.

The purpose of this survey is to gather information and insights from stakeholders involved in the legal supply-chain of medicinal products, including manufacturers, distributors, wholesalers, importers, brokers, pharmacists/persons authorized or entitled to supply medicinal products to the public. **The information collected will be used to support the Commission's report to the European Parliament and the Council** on trends in the falsification of medicinal products and measures provided according to Directive 2011/62/EU.

The survey contains a series of open and closed questions. For the closed questions, some may only require one answer, while some questions may allow for multiple answers. Each question will state how many options can be selected.

Please note that this survey is **strictly confidential**. Your identity will not be mentioned directly in the study reporting (as the results will be reported at an aggregate level) or disclosed to the Commission. The survey is being conducted by Ramboll Management Consulting, and Ramboll will collect, process, and store the information collected for the purposes of the Assignment for the duration of the contract with DG SANTE. Following completion and termination of the Assignment, Ramboll will systematically delete all personal data which was collected. If you have any specific questions on the protection of your personal data, you can contact the Study Team at FRSH@ramboll.com.

The survey should take approximately [estimated time] to complete and is available in English, French, Spanish and German (see the drop-down menu at the beginning of the questionnaire).

The survey will be closed on XX.

We thank you in advance for your participation in this survey.

[103]Greece and Italy have been granted the option of deferring application of the rules of an additional period of up to 6 years (i.e., until 9 February 2025). Belgium was granted this option but has formally renounced to it and applies the rules as of 9 February 2019.

Introduction: Profiling questions

This first section will ask a series of profiling questions about you/ your organisation.

1. **Which <u>category group</u> do you belong to?** *(filter question, one answer, mandatory)*

☐	Manufacturer
☐	Distributor
☐	Full-line wholesaler
☐	Designated wholesaler
☐	Generic wholesale distributor
☐	Parallel importer
☐	Parallel trader
☐	Broker
☐	Pharmacies/Persons authorised to supply medicinal products
☐	Healthcare provider
☐	Business association
☐	Academia/ Research institution
☐	Non-governmental organisation
☐	Third-party service provider
☐	Other stakeholder

a. If other, please specify below.

2. **Please provide the full name of your organisation/ association below**

3. **In which <u>country</u> in EU/EEA/EFTA is your organisation based? (one option)**

☐	Austria
☐	Belgium
☐	Bulgaria
☐	Croatia
☐	Cyprus
☐	Czech Republic
☐	Denmark
☐	Estonia

☐	Finland
☐	France
☐	Germany
☐	Greece
☐	Hungary
☐	Iceland
☐	Ireland
☐	Italy
☐	Latvia
☐	Liechtenstein
☐	Lithuania
☐	Luxembourg
☐	Malta
☐	Netherlands
☐	Norway
☐	Poland
☐	Portugal
☐	Romania
☐	Slovakia
☐	Slovenia
☐	Spain
☐	Sweden
☐	Switzerland
☐	Other, please specify:

4. **How many employees does your organisation have? (one option)** *[Asked only to those that **did not** answer as a "Business Association"]*

☐	I work alone
☐	Less than 10
☐	Between 10 and 100
☐	Between 101 and 500
☐	More than 500

5. **How many members does your organisation have? (one option)** *[Asked only to those that answered as a "Business Association" and "NGO"]*

☐	Less than 10
☐	Between 10 and 50
☐	Between 51 and 250
☐	More than 250

6. **How long has your organisation been in existence in the supply chain of medicinal products? (one option)**

☐	Less than 5 years
☐	Between 5 and 15 years
☐	Between 15 and 50 years
☐	More than 50 years

7. **How long has your organisation been active in the supply chain of other types products? (if you do not specialise in medical products) (one option)**

☐	Less than 5 years
☐	Between 5 and 15 years
☐	Between 15 and 50 years
☐	More than 50 years
☐	We are not active in the supply chain of other types of products

Common core of questions

Trends in Falsified Medicinal Products Market

This section of the survey will explore trends in the market for falsified medicinal products from an EU/EEA perspective. It focusses on medicinal products with a false representation of their identity (including packaging, labelling, name and composition), their source (including manufacturer, country of manufacturing, country of origin or marketing authorisation holder), or their history (including the records and documents relating to the distribution channels used).
It will gather information on:

- changes in the number of falsified medicinal products identified since the introduction of Directive 2011/62/EU in 2011
- changes in the market for falsified medicinal products since 2019 including the influence of increased e-commerce
- new challenges or trends in the falsified medicinal products market that have emerged in recent years
- specific categories of medicinal products and their indications that are of particular concern or pose a particular temptation in terms of falsification.

8. In your view, has there been a <u>change</u> in the number of identified falsified medicinal products since 2011, when Directive 2011/62/EU was introduced? (one option)

☐	Large increase in falsified medicinal products
☐	Medium increase in falsified medicinal products
☐	Small increase in falsified medicinal products
☐	No change
☐	Small decrease in falsified medicinal products
☐	Medium decrease in falsified medicinal products
☐	Large decrease in falsified medicinal products
☐	Don't know/ not applicable

9. How do you perceive <u>the impact of e-commerce</u> and the development of e-pharmacies on the market for falsified medicinal products?

Please answer here

10. What are the <u>new challenges or trends</u> in the falsified medicinal products market that have emerged in recent years? (Multiple options possible)

☐	Increased online/internet sales in business-to-consumer relationships
☐	Increased online/internet sales in business-to-business relationships
☐	Sophisticated falsification techniques
☐	Globalization of supply chains
☐	Greater involvement of organized crime
☐	Use of cryptocurrencies for transactions
☐	Growing demand for high-value medicinal products
☐	Lack of standardization in authentication technologies
☐	Other (please specify)
☐	Don't know/ not applicable

a. Please specify any other challenges

11. Are there any specific categories of medicinal products subject to the EU safety features that are of particular concern in terms of falsification? (Multiple options possible)

☐	High-risk medicinal products[104] (e.g., cancer drugs, vaccines)
☐	Lifestyle medicinal products (e.g., erectile dysfunction drugs, weight loss drugs)
☐	Medicinal products for rare diseases

[104] High-risk medicinal products are pharmaceuticals that are associated with a higher level of risk due to their intended use, mode of action, or potential side effects. These products may include cancer drugs, vaccines, and other medications that are used to treat serious or life-threatening conditions. High-risk medicinal products are subject to rigorous regulatory oversight and may require special handling, storage, and administration procedures to ensure their safe and effective use.

☐	Medicinal products for chronic conditions (e.g., diabetes drugs, cardiovascular drugs)
☐	Medicinal products authorised or used in other constituencies but non in the EU/EEA
☐	Other (please specify)
☐	Don't know/ not applicable

a. If other, please specify below.

Global perception on measures laid down by the legislation and the system implemented

This section of the survey will explore your global perception of the adequacy and effectiveness of measures under Directive 2011/62/EU and Delegated Regulation 2016/161. The questions will assess your familiarity with the EU legislation. It attempts to gather your views on the adequacy and effectiveness of the measures, the reasons for the system's effectiveness or lack thereof, the extent of implementation across the EU, and identification of gaps or deficiencies in the current measures.

12. How familiar are you with Directive 2011/62/EU and DR 2016/161? (one option)

☐	Familiar to a great extent
☐	Familiar to a certain extent
☐	Familiar to a small extent
☐	Not familiar

13. Overall, how <u>adequate are the measures laid down</u> by the Directive 2011/62/EU (such as the Unique identifier, the Anti-tampering device and the repositories systems that supports the identification of suspicious medicinal products) to prevent the falsification of medicinal products in the supply-chain? (one option)

(This question aims to assess your overall opinion of the system put in place; more specific questions will be asked later in the questionnaire on each of the items)

[Asked only to those that answered as a "Familiar to a great extent", "Familiar to a certain extent", "Familiar to a small extent" in Q12]

☐	Highly Adequate
☐	Adequate
☐	Moderately Adequate
☐	Inadequate
☐	Highly Inadequate
☐	Don't know/ not applicable

14. How effective do you consider the following factors in *preventing the entry* <u>of falsified medicinal products into the supply chain?</u> (*Multiple options possible)*

Factor	Highly ineffective	Ineffective	Moderately effective	Effective	Highly effective
Regulatory framework	☐	☐	☐	☐	☐
Regulatory response	☐	☐	☐	☐	☐
Faithful and timely implementation	☐	☐	☐	☐	☐
Authentication measures	☐	☐	☐	☐	☐
Tracking and tracing	☐	☐	☐	☐	☐
End-to-end verification	☐	☐	☐	☐	☐
Supply chain oversight	☐	☐	☐	☐	☐
Collaboration among stakeholders	☐	☐	☐	☐	☐
Availability of resources	☐	☐	☐	☐	☐

Awareness/training for procedures relating to detection/report of falsified medicinal products	☐	☐	☐	☐	☐
Other	☐	☐	☐	☐	☐

a. Please specify any "other" factors.

15. Are the <u>following examples for potential gaps or deficiencies</u> present in the current system? (Multiple options possible) *[Asked only to those that answered as a "Familiar to a great extent", "Familiar to a certain extent", "Familiar to a small extent" in Q6]*

☐	Lack of comprehensive authentication technologies
☐	Lack of regulatory response
☐	Insufficient regulatory oversight
☐	Weak supply-chain security measures
☐	Inadequate penalties for violators
☐	Limited coordination among Member States
☐	Insufficient collaboration among stakeholders
☐	Inadequate information sharing
☐	Lack of public awareness/education
☐	Regulatory gaps/unclarities at EU level
☐	Technical issues with software/hardware interoperability
☐	Lack of clear and accessible reporting systems
☐	Regulatory gaps/unclarities at EU level
☐	Regulatory gaps/unclarities at national level
☐	Governance problems with conflict of interest that do not allow full achievement of the objectives
☐	Lack of communication – no adequate communication structures or platforms
☐	Training/resources/knowledge
☐	Other (please specify)

a. Are there any other gaps or deficiencies in the current measures that need to be addressed?

b. Based on your experience, which countries are facing structural difficulties with implementing the current measures? *[Asked only to EU-level stakeholders]*

16. Overall, to what extent do you believe that the measures provided by Directive 2011/62/EU are <u>effectively implemented</u> across the EU? (one option)

☐	Effectively implemented to a strong extent
☐	Effectively implemented to a moderate extent
☐	Effectively implemented to a small extent
☐	Ineffectively implemented to a small extent
☐	Ineffectively implemented to a moderate extent
☐	Ineffectively implemented to a strong extent
☐	Don't know/ not applicable

a. Please specify the measures which you believe to be effectively implemented to a small/very limited to no extent. *[Asked only to those that answered as a "Effectively implemented to a small extent" or "Not implemented effectively"]*

National contexts in the supply chains to address falsification of medicinal products

This section explores any national specificities in the scope of measures for combating falsified medicinal products compared to those covered under Directive 2011/62/EU and DR 2016/161/EU. It also investigates the verification modalities implemented in the respondent's country to ensure the authenticity of medicinal products in the legal supply-chain, effectiveness of national measures in preventing the entry of falsified medicinal products, and current challenges or barriers faced by the country in implementing national measures to combat falsified medicinal products.

17. In your view, are there <u>any particular national specificities</u> in the country(-ies) you operate regarding the scope of measures for combating falsified medicinal products compared to those covered under Directive 2011/62/EU? (one option)

☐	Yes, there are national specificities (please specify)
☐	No, there are no national specificities
☐	Don't know/ not applicable

a. If yes, are these national specificities complementary with Directive 2011/62/EU and with the DR or do they create uncertainty? Please explain

18. What are the verification modalities implemented in your country to ensure the authenticity of medicinal products in the legal supply-chain? (*Multiple options possible.)*

☐	Serialisation/Serial Number verification
☐	Tamper-evident packaging
☐	Holograms/Security labels
☐	Barcoding/QR Codes
☐	Track and trace systems
☐	Secure supply chain processes and auditing
☐	Third-party authentication services
☐	Regulatory oversight and inspections
☐	Product authentication training for healthcare professionals
☐	Authentication Technologies (e.g., RFID[105], NFC[106])
☐	Other (please specify)
☐	Don't know/ not applicable

a. Please specify what other modalities are implemented in your country.

19. From a scale of 1 to 10 (10 being highly effective and 1 being not effective at all), how <u>effective</u> do you think these national measures are in preventing or helping to prevent the entry of falsified medicinal products into the legal supply-chain? (one option)

1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Medicinal Products not Intended for Free Circulation

This section explores how medicinal products that are intended for introduction on the territory of EU/EEA but not intended to be released for free circulation are currently managed or regulated in the respondent's country. It investigates the regulatory approval process, distribution channels, authentication measures, supply-chain oversight, monitoring and reporting requirements, and any other measures in place.

20. How are medicinal products that are intended for introduction on the territory of EU/EEA but not intended to be released for free circulation <u>currently managed or regulated</u> in your country/another country you are aware of? *(*Multiple options possible*).*

[105] Radio Frequency Identification is a technology that uses radio waves to wirelessly transmit data between an RFID tag or label and an RFID reader. It can be used to verify the authenticity of products, including medicinal products, within the supply chain.
[106] Near Field Communication is a short-range wireless communication technology that allows devices to establish a connection and exchange data when they are in close proximity to each other, typically within a few centimetres.

☐	Strict regulatory approval process
☐	Specialised distribution channels[107]
☐	Stringent authentication measures
☐	Premises inspections
☐	Robust supply-chain oversight
☐	Legal penalties/criminal charges
☐	Other (please specify)
☐	Don't know/ not applicable

a. If other, please specify below.

21. Are there any challenges or risks associated with such medicinal products in terms of falsification? (Multiple options possible).

☐	Vulnerability to Counterfeiting
☐	Limited Tracking and Tracing Mechanisms
☐	Complex EU Regulatory Requirements
	Complex national Regulatory Requirements
☐	Potential for diversion to illegal markets (i.e., products exiting the legal supply chain through illegal practices such as theft, irregular decommissioning, etc.)
☐	Other (please specify)
☐	Don't know/ not applicable

a. If other, please specify below.

22. Do you believe that the current measures under Directive 2011/62/EU are sufficient in preventing the entry of falsified medicinal products not intended for free circulation into the legal supply-chain? (one option)

☐	Yes, to a great extent
☐	Yes, to a certain extent
☐	Not really
☐	Not at all
☐	Don't know/ not applicable

a. Please specify in what ways the measures are not sufficient. *[Asked only to those that answered as a "No" Q22]*

Impact of Intermarket Transactions

This section explores the cases of alerts arising from intermarket transactions (i.e., transactions involving medicinal products between member states of the EU or the EEA). These alerts correspond to exceptional events (e.g., when a medicine pack is not recognized by the system when scanned, or when a bar code intended for another purpose is mistakenly scanned) detected by the European Medicines Verification System (or by National Verification systems). These require the intervention of a stakeholder (the user, the system administrator, etc.).
This section also investigates challenges or issues related to intermarket transactions in the context of combating falsified medicinal products, including lack of transparency, difficulties in tracking and tracing medicinal products across markets, inadequate authentication measures, complex regulatory requirements, and increased risk of falsified medicinal products entering the legal supply-chain through intermarket transactions.

23. How familiar are you with intermarket transactions and the impact they may have on the creation of alerts in the legal supply-chain of medicinal product? (one option)

Not familiar at all	**Not very familiar**	**Familiar**	**Highly familiar**

[107] Channels designed to ensure that medicinal products are properly managed, distributed, and used in compliance with applicable regulations and requirements.

☐	☐	☐	☐

24. Do Intermarket Transactions increase the risk of receiving alerts compared to transactions within the national repository system? (one option) *[Asked only to those that answered previously as a "Familiar" or "Very Familial"]*

☐	Yes, a lot
☐	yes, rather
☐	Not really
☐	Not at all
☐	Don't know/ not applicable

b. Please explain why. Were these alerts mostly related to technical/IT problems or did it detect confirmed cases of falsification?

25. Have you encountered any challenges or issues related to intermarket transactions in the context of combating falsified medicinal products? (Multiple options possible).

☐	Lack of transparency in intermarket transactions
☐	Difficulty in tracking and tracing medicinal products across markets
☐	Inadequate authentication measures (such as serial number verification, tamper-evident packaging, QR codes)in Intermarket Transactions
☐	Complex regulatory requirements for Intermarket Transactions at the national or EU level
☐	No Challenges
☐	Don't know/ not applicable

Focus on the implementation of the DR (safety measures, verification modalities, etc.)

This section focuses on the implementation of the measures laid out in the DR, and more specifically:

- **the repositories system** (or "European Medicines Verification System"), which refers to the electronic structure composed of the central data router (or "EU Hub") and the different national repositories (or "National Medicines Verification System");
- **the safety features**, which refer to the Unique identifier (UI) and the Anti-tampering device (ATD) places on medicinal packs;
- **the verification requirements** refer to the obligations for stakeholders to verify the authenticity of the UI and/or the integrity of the ATD at different stages of the legal supply chain, as stated in the DR;
- **the alerts mechanism**, which refers to both the system of notifications triggered by the repositories system when incidents are detected, and the spontaneous flagging of incidents detected by the stakeholders of the legal supply chain.

<u>Repositories system</u>

26. Are you currently <u>connected</u> to the repository system[108]? (one option)

☐	Yes
☐	No
☐	Do not know / not concerned

27. In case you are not connected, could you specify what are the reasons? (Multiple options possible)

☐	Lack of information technology/computer equipment
☐	Software related problems
☐	Lack of financial resources

[108] A repository system is a centralized database and infrastructure designed to verify the authenticity of medicinal products and prevent the distribution of falsified or counterfeit drugs within the pharmaceutical supply chain.

☐	Lack of human resources
☐	Other, please specify: …….

Safety features

28. What do you think of the adequacy of unique identifier and other anti-tampering measures in terms of composition and technical specifications, considering the risks and proportionality principles? (one option)

-	- ully adequate	- equate Ad	- ot very adequate	- ot adequate at all	- o not know
- he Unique Identifier	- ☐	- ☐	-	-	-
- he Anti-Tampering Device	- ☐	- ☐	-	-	-

29. Do you think the absence of a clearly defined framework for ATD might facilitate the ATD's falsification and the avoidance strategies put in place by the falsifiers? (one option)

☐	Yes, a lot
☐	yes, rather
☐	Not really
☐	Not at all
☐	Don't know/ not applicable

30. Do you think there is need to require additional verification at other stage(s) of the supply chain and thus to migrate towards a full tracking verification system? (one option)

☐	Yes, completely
☐	Yes, rather
☐	Not really
☐	Not at all
☐	Don't know/ not applicable

Verification and alerts

31. Did you have any difficulties in implementing the following steps regarding the verification measures (one option)

-	- es, a lot	- es, quite	- ot really	- ot at all	- o not know
- Co nnection to the repository system	-	-	-	-	-
- Set up of computer tools (scanners, etc.)	-	-	-	-	-
- Tra ining of teams regarding verification methods	-	-	-	-	-

32. To what extent do you agree with the following assumptions: (one option)

	Fully agree	**Mostly agree**	**Mostly disagree**	**Fully agree**	**Do not know/ NA**
The verification of the authenticity of the UI is adequate to implement	☐	☐	☐	☐	☐
The verification of the authenticity of the UI is easy to implement	☐	☐	☐	☐	☐
The verification of the integrity of the ATD is adequate to implement	☐	☐	☐	☐	☐
The verification of the authenticity of the ATD is easy to implement	☐	☐	☐	☐	☐
The verification requirement are sufficient to prevent falsification attempts	☐	☐	☐	☐	☐
Please elaborate if needed:					

33. How often do you encounter alerts when implementing these verifications? (one option)

☐	Frequently
☐	Occasionally
☐	Rarely
☐	Never
☐	Don't know/Not applicable

34. What types of alerts / exceptions do you encounter most? (multiple options possible)

☐	Product not found
☐	Batch not found
☐	Pack not found
☐	Batch number mismatch
☐	Expiry date mismatch
☐	Pack already in requested state
☐	Status change could not be performed
☐	Duplicate serial numbers
☐	Other

35. How often do you encounter alerts of falsification that are eventually confirmed (e.g. genuine product recalls) in the legal supply-chain of medicinal products due to intermarket transactions? (one option)

☐	Frequently
☐	Occasionally
☐	Rarely
☐	Never

☐	Don't know/Not applicable

36. How many actual cases of falsification have you encountered since the implementation of the EU verification system?

Please answer here:

37. Have you ever suspected the existence of falsification of a medicinal product and made a spontaneous alert to a competent authority? (one option)

☐	Yes
☐	No
☐	Do not know / Not applicable

a. If yes, please elaborate the situation:

38. How often have you conducted a voluntary or mandated recall of products? (one option)

☐	Frequently
☐	Occasionally
☐	Rarely
☐	Never
☐	Don't know/Not applicable

39. Overall, do you think the reporting system in place is adequate to report incidents in the repositories? (one option)

☐	Yes completely
☐	Yes, rather
☐	Not really
☐	Not at all
☐	Do not know / not concerned
Please elaborate here	

40. In addition to the european system, do you have your own alert management system?

☐	Yes
☐	No
☐	Do not know / Not applicable

If "yes", for what purposes and how does it work? Please describe briefly below how it helps you: …

41. Would you recommend that the system evolve from an end-to-end system to a track and tracing system?

☐	Yes, completely
☐	Yes, probably
☐	Not really
☐	Not at all
☐	Do not know / Not applicable

Please elaborate: ….

Specific questions to manufacturers

<u>Safety features</u>

42. To what extent did you already face the following technical / functional difficulties regarding the unique identifier? (one option)

-	- ften	- S ometimes	- arely	- ever	- o not know
- I nability to generate a serial number	-	- □	-	-	-
- I nability to ensure the full composition of the unique identifier	-	- □	-	-	-
- I nability to upload the unique identifier	-	- □	-	-	-

Please elaborate here, particularly in case of other challenges not mentioned above

43. Did you already include other additional information within the two-dimensional data matrix code, when permitted by the national competent authority of your country? (one option)

□	Yes
□	No
□	Do not know / not concerned

In case you answer "Yes", please elaborate here

44. On a scale of 1 to 5 (5 being very easy and 1 not easy at all), how would you rate the ease of implementation of safety features on your medicinal products? (one option)

-	-	-	-	-	-
- U nique identifier	-	-	-	-	-
- An ti-tampering device	-	-	-	-	-

45. Did the fact that the DR does not provide specific and harmonised technical specifications for ATD cause you any problems in its implementation? (one option)

□	Yes completely
□	Yes, rather
□	Not really
□	Not at all
□	Do not know / not concerned

46. How often are you confronted to the following situations? (one option)

-	- ften	- S ometimes	- arely	- ever	- o not know
- R emoving the safety measures and decommission the unique identifier if replaced	-	- ☐	-	-	-
- R epacking or re-labelling the product to use it as authorized investigational medicinal product or auxiliary medicinal product	-	- ☐	-	-	-
- P lacing an equivalent UI to comply with Article 47a of Directive 2001/83/EC	-	- ☐	-	-	-

Repository system

47. In your view, do you think that the current financial model of the repositories systems, which relies exclusively on the contribution of manufacturers, is suitable and sustainable in the long term? (one option)

☐	Yes completely
☐	Yes, rather
☐	Not really
☐	Not at all
☐	Do not know / not concerned

48. Are there any amendments that you could suggest to the current repository system from a financial/governance/regulatory perspective? (one option)

49. Did you have any difficulty in joining an Onboarding partner? (one option)

☐	Yes completely
☐	Yes, rather
☐	Not really
☐	Not at all
☐	Do not know / not concerned

44. Please elaborate your answer:

General questions

50. Are there any specific requirements or regulations in your country for manufacturers to combat falsified medicinal products that go beyond the scope of Directive 2011/62/EU? (one option)

☐	Yes, our country has additional requirements or regulations beyond Directive 2011/62/EU to combat falsified medicinal products.
☐	No, our country does not have any specific requirements or regulations beyond Directive 2011/62/EU to combat falsified medicinal products.
☐	Not sure, I am not aware of any additional requirements or regulations beyond Directive 2011/62/EU in our country.

a. Please specify these requirements or regulations. *[Asked only to those that answered as a "Yes"]*

Specific questions to wholesalers / brokers

Verification modalities

51. How often are you confronted to the following situations? (one option)

-	- ften	- metimes So	- arely	- ever	- o not know
- medicinal product is returned to you by persons authorized (Article 20-a, no decommission)	-	- ☐	- ☐	- ☐	-
- ou receive medicinal products from a wholesaler who is neither the manufacturer nor the wholesaler holding the marketing authorization (Article 20-b)	-	- ☐	- ☐	- ☐	-
- he product is requested as a sample by competent authorities (article 22-d, decommission)	-	- ☐	- ☐	- ☐	-
- he product is intended for destruction	-	- ☐	- ☐	- ☐	-

(Article 22-c, decommission)					
- he product is returned to you by an authorized persons and cannot be returned to saleable stock (Article 22-c, decommission)	-	- □	- □	- □	-
- he product is intended for distribution outside of the EU (Article 22-a, decommission)	-	- □	- □	- □	-

52. Do you carry out spontaneous checks even when not required to do so (i.e. in situations other than those described above) (one option)

□	Often
□	Sometimes
□	Rarely
□	Never
□	Don't know/Not applicable

a. If "Often" "Sometimes" "Rarely" are selected: who did you contact?: .....

b. If "Never" is selected, could you explain why? (lack of time, lack of human resources to do the verifications, etc.): .....

53. As intermediaries / pivots in the value chain, have you been made aware / received training regarding the following? (one option)

-	- Yes, a lot	- Yes, quite	- Not really	- Not at all	- Do not know
- The importance / interest of this Directive and DR (patient protection, fight against falsification, etc.)	- □	- □	-	-	-
- Your strategic role in the verification procedures	- □	- □	-	-	-
- The use of tools and checks during decommission (scanning, etc.)	- □	- □	-	-	-

- The management of alerts issued by the system	-	-	-	-	-
- The issuing of spontaneous alerts if you suspect cases of falsification	-	-	-	-	-

54. How confident are you in the authenticity and integrity of the medicinal products you receive from your suppliers, considering the measures implemented under Directive 2011/62/EU? (one option)

☐	Highly confident
☐	Confident
☐	Moderately confident
☐	Not confident
☐	Don't know/Not applicable

55. As a wholesaler/broker/intermediary, how often have you encountered offers for medical products that seem suspicious in terms of pricing, quantities, and regular availability? (one option)

☐	Often
☐	Sometimes
☐	Rarely
☐	Never
☐	Don't know/Not applicable

56. Have you reported these instances to your national authorities? (one option) *[Asked only to those that answered as a "Often", "Sometimes" or "Rarely"]*

☐	Yes
☐	No

57. How do you ensure the authenticity and integrity of medicinal products in your supply-chain, as required by Directive 2011/62/EU? Multiple choices possible. (multiple options possible)

☐	Regular audits of suppliers
☐	Implementation of authentication technologies
☐	Systematic or random scanning of bar codes
☐	Collaborative efforts with other stakeholders
☐	Compliance with regulatory oversight
☐	Other (please specify)

b. Please specify any "other" measures implemented.

Specific questions to persons authorized or entitled to supply medicinal products to the public

<u>Verification modalities</u>

58. As people authorized / entitled to supply medicinal products to the public and representatives of the "end" of the supply chain, in contact with patients, have you been <u>made aware / received training</u> regarding the following? (one option)

-	- es, a lot	- es, quite	- ot really	- ot at all	- o not know
- T he importance / interest of this Directive and DR (patient protection, fight against falsification, etc.)	-	-	-	-	-
- T he use of tools and checks during the final decommissioning before handing over to patients (scanning, etc.)	-	-	-	-	-
- T he management of alerts issued by the system	-	-	-	-	-
- T he issuing of spontaneous alerts if you suspect a breach of the ATD when it is handed over to patients	-	-	-	-	-
- D ealing with patients in the event of questions / queries from them	-	-	-	-	-

Please elaborate:

59. Do you think that these verification methods have had an <u>impact on the quality</u> of your customer relationship? (too many false alerts, recurring impossibilities to deliver the product to customers) (one option)

☐	Yes completely
☐	Yes, rather
☐	Not really
☐	Not at all
☐	Do not know / not concerned

Please elaborate here

60. How often are you confronted to the following situations when verifying / decommissioning a medicinal product? (one option)

-	- ften	- So metimes	- arely	- ever	- o not know

- he product in your possession cannot be returned to the manufacturer or wholesaler (Article 25-4a)	-	- □	- □	- □	-
- he product in the authorized person's possession is requested as samples by competent authorities (Article 25-4b)	-	- □	- □	- □	-
- ou supply a product as an authorized investigational medicinal product or an authorized auxiliary medicinal product (Article 25-4c)	-	- □	- □	- □	-
- ou supply only a part of a pack of a medicinal product to the public (Article 28)	-	- □	- □	- □	-

61. Did the fact that the DR does not provide specific and harmonised technical specifications for ATD cause you problems during your verifications (different ATDs, uneven quality of ATDs, etc.)? (one option)

□	Yes completely
□	Yes, rather
□	Not really
□	Not at all
□	Do not know / not concerned

62. [if reply "Healthcare provider] at Q1] Can you easily decommission large numbers of grouped products (batches)? (one option)

□	Yes completely
□	Yes, rather
□	Not really
□	Not at all
□	Do not know / not concerned

If you replied "not really", "not at all", please elaborate below about the challenges encountered and how you overcome them:

63. How do you ensure the authenticity and integrity of medicinal products in your supply-chain, as required by Directive 2011/62/EU? Multiple choices possible. (multiple options possible)

☐	Regular audits of suppliers
☐	Implementation of authentication technologies
☐	Systematic or random scanning of bar codes
☐	Collaborative efforts with other stakeholders
☐	Compliance with regulatory oversight
☐	Other (please specify)

c. Please specify any "other" measures implemented.

64. How confident are you in the authenticity and integrity of the medicinal products you receive from your suppliers, considering the measures implemented under Directive 2011/62/EU? (one option)

☐	Highly confident
☐	Confident
☐	Moderately confident
☐	Not confident
☐	Don't know/Not applicable

Closing questions

65. Do you have any proposal to improve the Directive 2011/62/EU and make it more fit for purpose?

66. Do you have any recommendations regarding the areas or subjects the study should investigate?

8.4 Annex 4 - Case Studies Synthesis Table

Case Study	Questions addressed	Interviews conducted[109]	Problems encountered and solutions found
E-commerce	(i) Does the legal e-commerce circuit presents particular risks for the introduction of falsified medicines, and if so, at what level and to what extent; (ii) is there ia connection between the illegal e-commerce circuit and the legal supply chain, and how the regulatory framework influences this, and (iii) what categories of products are most concerned by this issue?	3 interviews were conducted with representatives from the Belgian NCA, as well as a Spanish industry expert from the wholesaler, broker, distributor sector, and another from the pharmaceutical and hospital sector in Spain	A significant challenge arose in obtaining reliable information concerning the presence of falsified medicinal products within the illegal e-commerce circuit. This area falls beyond the purview of many actors within the pharmaceutical sector and is primarily investigated by law enforcement authorities. To tackle this challenge, part of the data was derived from desk-based sources that assess the prevalence of falsified medicinal products both within and outside the legal supply chain, such as reports by Interpol. Additionally, an interview was conducted with a representative from the Special Investigation Unit at the Belgian NCA to gain further insights.
Alert management system	(i) what are the different modalities of an alert management system; (ii) why did Estonia consider it necessary to adopt one; (iii) what are the best practices in this area?	2 interviews were conducted with, respectively, a representative from the Estonian pharmaceutical industry, and a representative from the Estonian NCA.	One of the primary challenges encountered during this case study was accessing desk-based sources detailing the operation of the Estonian Alert Management System, as this information is not publicly available. To address this challenge comprehensively, an interview with a representative from the pharmaceutical industry in Estonia was conducted, gathering the main insights on the functioning of the system. This interview was complemented by information obtained from the national NCA to ensure a well-rounded understanding of the system's functioning from the perspective of both private stakeholders and public authorities.
Aggregated codes and batch decommissioning	(i) does the EU legislation and its relative guidance document provide a sufficiently clear indication of how aggregation should be implemented? ; (ii) how and why aggregation was developed and implemented; (iii) does aggregation effectively contribute to the objectives of the FMD?	4 interviews were conducted with pharmacists with hands on experience verifying medicine packs and actors involved in the supervision and the implementation of aggregation in France and Ireland: Hospices Civils of Lyon, Hospital Timone of Marseille, Mater Misericordiae University Hospital of Dublin, Mater Private, and Irish MVO	One of the main challenges of this case study was getting in contact with hospital pharmacists twho are often busy and not accustomed to interview request. To address this challenge, we asked already consulted persons to introduce us to the hospital pharmacists, putting the latter in a better position to answer our request. Another challenge we faced was to interview pharmacists with hands on experience verifying medicine packs but eventually this was possible. . Finally, we also made sure to interview the same number of persons both in France and Ireland to ensure here again representativity.
The use of the EMVS data for the purpose of investigation	(i) Can the EMVS alone identify all potential cases of medicine falsification? (ii) How can the EMVS data support national authorities when investigating suspected and confirmed cases of medicine falsification?	5 people through 3 interviews were consulted as actors directly or indirectly utilizing EMVS data: the Bulgarian Drug Agency, France MVO, and OCLAESP	The first challenge encountered for this case study was the access to the EMVS data though the interface of the NCAs, these data being confidential. To mitigate this obstacle, we covered all specific details on individuals and organisations mentioned in the screen shots and pictures illustrating the case studies, only letting appear information necessary to understand the examples presented. A second challenge encountered was the access to details on cases investigated by police forces. Again, to mitigate this obstacle, we made sure not to cite the name of specific persons and organisations involved, and only mentioned past cases already ruled in court
The delayed deployment of the EMVS in French community pharmacies	(i) what were the obstacles to with setting up the verification system in France and were these obstacles specific to French actors or common across Europe? (ii) How did the players overcome these obstacles and what good practices have been put in place? (iii) What is the real impact of the false alarm rate on the verification	7 people through 4 were interviewed at several levels: trade unions (USPO, FSFP), pharmacist order (CNOP) and individual pharmacists.	The main challenge we faced conducting this case study was getting in contact with a sufficiently representative sample of French community pharmacists. To address this issue, we made sure to interview community pharmacists from the two main unions, one being notoriously opposed to the verification (FSFP), system and the other being a strong promoter of the system (USPO). Besides, we have interviewed pharmacists in both rural and urban environments, located in different regions in France.

[109] In addition to these interviews, a documentary review has been systematically conducted.

	system and how can this create risks of non-decommissioning or offending practices?		
A specific case of falsification: Avastin	(i) What is a journey undertaken by the falsified medicines? (ii) how was the falsification detected? (iii) How can preventive measures avoid similar incidents in the future?	3 additional interviews were conducted with one NCA in Bulgaria and one NMVO representative in the Netherlands, and one NCA in the Netherlands. An additional interview with a representative from the NCA in Bulgaria will be conducted on the first week of October. Findings from this interview will be integrated into the revised version of the case study.	One major challenge was finding available desk-based sources. As the case is still currently being processed in the regional courts in Bulgaria, no formal reports or documentation of the case were publicly available. Interviews with stakeholders which investigated the case were able to share vital information, however the sensitivity of the case meant that documentation was not able to be shared. And the information reported are limited to describe the situation as it stands as of October 2023. Therefore, while the case is insightful the findings have to be considered with great attention while waiting for the court ruling.

8.5 Annex 5 - Synopsis Report

8.5.1 Introduction

This synopsis report presents the results of the consultation activities conducted to prepare the Study supporting 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. It contains a summary of the consultation activities, reflecting the diversity of the stakeholders' positions, and an analysis of the quality of the information collected – both qualitative and quantitative. This synopsis report is compliant with "Better Regulation Guidelines Toolbox" of the European Commission (November 2021) and summarizes consultation activities and stakeholder views collected so far. This document is a revised version, the draft version having been submitted in July 2023.

8.5.2 Presentation of the consultation strategy

The consultation method defined in the terms of reference for this Study was a targeted consultation. Candidates were pre-selected so only explicitly invited groups/organisations and individuals could participate in the consultation activity and provide feedback and insight on the effectiveness of the measures in place to impede the entry of falsified medicines into the legal supply chain. Spontaneous requests for interviews, when relevant, have been taken into account and their opinions incorporated into the present synopsis report.

The objective of the consultation strategy was twofold: firstly, to obtain information on the trends related to falsification of medicinal products (global trends, suspected / confirmed cases of falsification, risks / challenges, etc.), and secondly to consult Member States and stakeholders of the legal supply chain on their views on the implementation of the measures laid down by the legislative framework.

The consultation used two tools: a survey and targeted interviews. Each tool aimed to collect evidence that complement desk research by providing additional qualitative and quantitative inputs and first-hand experience and knowledge:

- Two surveys were sent respectively to National Competent Authorities (NCAs) and to stakeholders involved in the legal supply chain. Questionnaires were developed to collect as much information as possible to address the issues mentioned in Article 3 of Directive 2011/62/EU (Study focus).
- Targeted interviews aimed to confirm elements from the survey and to foster a more thorough understanding of the subject matter. These interviews were conducted with individuals active both at EU level and national level in 8 Member States (Belgium, Bulgaria, Denmark, Estonia, France, Ireland, Poland and Spain).

Additional consultations/ analyses are currently being undertaken in the context of selected case studies. These studies focus on specific examples and subjects to enable in-depth investigation in certain countries.

As a summary, these three tools aimed to consult the following groups according to the planed consultation strategy:

Type of structures / actors	Surveys	Interviews	Case studies
EU Commission Directorate General for Taxation and Customs Union (DG TAXUD)		✓	
EMA		✓	
EMVO		✓	
International bodies		✓	
Member State national competent authorities (NCA)	✓ (28)	✓ (8)	✓
National Medical Verification Organisations (NMVOs)	✓	✓	✓

Type of structures / actors	Surveys	Interviews	Case studies
Stakeholders involved in the legal supply chain • Manufacturers • Parallel traders and importers • Wholesalers and distributors • Community and hospital Pharmacists	✓		✓
Associations representing stakeholders involved in the supply chain (European and national levels) • Manufacturers • Parallel traders and importers • Wholesalers and distributors • Community and hospital Pharmacists	✓	✓	✓
Law enforcement authorities		✓	✓
Experts and Academia		✓	
Other structures (NGOs and healthcare providers)	✓		

In addition to these data collection tools, specific data requests were sent to NCA in order to collect specific figures (notably number of confirmed cases of falsification). 16 sets of data have been received by the Study team.110

This consultation plan has been established in accordance with the Terms of Reference of the Study with the objective to account for the opinions of all the relevant stakeholders' groups. The information retrieved for the purpose of the study will not be used for other purposes outside this scope.

8.5.3 Description of consultation activities

1.1.1.1 Consultation at Member State level (survey and interviews with NCAs and other actors)

Consultation at national level targeted NCAs and national actors.

NCAs

All EU/EEA NCAs participating to the European Medicines Verification System (EMVS) were consulted through a survey and 8 of them have been interviewed.

- Survey: 52 questions were sent to the 28 NCAs111 (25 EU countries and 3 EEA countries) to gather information and insights on the implementation of the measures set by the EU legislative framework in the Member States. 18 surveys were completed during the dissemination period (26th May to 28th July 2023), during which up to 2 individualized follow-up emails were sent to non-respondents.
- Interviews: 8 interviews were organised with the Member States subject to a specific focus (Belgium, Bulgaria, Denmark, Estonia, France, Ireland, Poland and Spain). 7 were conducted and 1 (with Denmark) remains to be done.

Actors at national level

[110]NCAs from Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, Finland, France, Germany, Hungary, Lithuania, Malta, Portugal, Slovenia, Spain, and Sweden have submitted data on confirmed cases of falsified medicines.
[111] Italy and Greece excluded.

Actors at the national level were also consulted through a survey and interviews were organised from 8 Member States.

- Survey: 67 questions were distributed to 55 associations and networks working across the medicinal product supply chain as well as to each NMVO across 29 countries. The purpose of this survey was to gather information and insights from stakeholders at national level involved in the legal supply-chain of medicinal products, including manufacturers, distributors, wholesalers, importers, brokers, pharmacists/persons authorized or entitled to supply medicinal products to the public. This survey was conducted between 14th June and 12th July 2023. Following a review of the data provided, the total number of completed survey was 205. Due to the survey being distributed through associations/ networks it is not possible to provide an accurate response rate to the survey.
- Interviews: 34 interviews were organised with the stakeholders of the pharmaceutical supply chain in the 8 Member States selected for in depth studies (same sample as above). The objective was to assess the implementation of the Delegated Regulation at national level by collecting the views of the main local actors using the verification system. Few additional interviews are still conducted in Denmark.

Table 6 Member State involvement in consultation activities (NCA / other national actors)

Member State	Questionnaire to NCA	Replies received to the Questionnaire to Stakeholders	Interviews
Austria	No response	✓ (22)	
Belgium*	✓	✓ (7)	1 NCA 4 actors (Belgium MVO, Pharma.Be, APB, Bapie)
Bulgaria*	✓	✓ (2)	1 NCA 3 actors (ARPharM, BAMPTD, Bg MVO)
Croatia	No response	✓ (2)	
Cyprus	✓	✓ (2)	
Czech Republic	✓	✓ (3)	
Denmark*	No response	✓ (3)	2 actors (Danish MVO, NovoNordisk)
Estonia*	✓	✓ (3)	1 NCA 3 actors (Estonian MVO, EPA, EAPW)
Finland	✓	✓ (2)	
France*	✓	✓ (8)	1 NCA 5 actors (France MVO, CSRP, OCLAESP, SNPHPU, USPO)
Germany	✓	✓ (8)	
Greece	Out of scope	✓ (3)	
Hungary	✓	✓ (7)	
Iceland	No response	✓ (3)	
Ireland*	No response	✓ (71)	1 NCA 3 actors (Irish MVO, IPU, Medicines for Ireland)
Latvia	No response	✓ (1)	
Lichtenstein	No response	No response	
Lithuania	✓	✓ (1)	
Luxembourg	No response	✓ (1)	
Malta	✓	✓ (4)	
Netherlands	✓	✓ (5)	
Norway	Declined	✓ (4)	

Member State	Questionnaire to NCA	Replies received to the Questionnaire to Stakeholders	Interviews
Poland*	✓	✓ (5)	1 NCA 3 actors (INFARMA, PL MVO, PZPPF)
Portugal	✓	✓ (11)	
Romania	No response	✓ (5)	
Slovakia	✓	✓ (3)	
Slovenia	✓	✓ (8)	
Spain*	✓	✓ (1)	1 NCA 4 actors (Spanish MVO, Farmaindustria, Fedifar, General Pharmaceutical Council of Spain)
Sweden	✓	✓ (4)	

*Countries subject to specific interviews

Overall, the participation from the actors at the national level was good, with some differences linked to the specific situation in each Member State:

- Actors were more reactive in countries with a history of legislation related to falsified medicines (i.e., Belgium) and in countries with a limited number of stakeholders in the pharmaceutical supply chain (e.g., Estonia, Ireland).
- Some national calendars have made data collection difficult (especially the holiday periods in June-August) and may explain why some countries are less involved than others. The case of Denmark for instance was challenging (Danish NCA was contacted, but their earliest availability for an interview was scheduled for August, primarily due to the upcoming holiday period). Nonetheless, the Danish MVO was successfully contacted and interviewed. Despite their support in reaching out to stakeholders, only one additional stakeholder (Marketing Authorization Holder) was able to be interviewed. Further efforts are ongoing to secure further interviews.

1.1.1.2 Consultation at EU and international level (interviews with other actors)

13 interviews were also conducted with actors at the European level to collect qualitative information on the implementation of the EU legal framework at the EU/ EEA level.

- Associations representing stakeholders at the European level were, in their vast majority, highly cooperative and willing to contribute to the study. Some organisations, not initially contacted, got in touch with the study team through DG SANTE to express their willingness to participate. Some other associations were also very active in circulating the survey to stakeholders among their members in the Member States.
- The organisations targeted for the interviews represent the main stakeholders involved with the implementation and the governance of the European Medicines Verification System, namely, associations representing manufacturers, parallel traders, wholesalers and pharmacists.
- Other EU and international institutions (namely, DG TAXUD, EMA, EMVO and WHO), concerned by the issue of falsified medicines were also consulted to obtain contextual information and data[112].
- Still, some European actors were more difficult to interview. This is particularly the case for patients' associations, who declined invitations for interview as they consider themselves as not relevant/ not sufficiently involved in the subject of medicines verification.

Also, 2 interviews were conducted with international experts and researchers on the topic of falsified medicinal products.

- They provided useful elements of context on the issue of falsified medicines at the international level (e.g., global risks and trends of medicine falsification).

[112] Information collected during these interviews, conducted at the beginning of the study, were broad overviews on the situation of medicine falsification in the EEA/Europe and elsewhere. They are not specifically referenced in the present report.

- It is to be noted that most research on the issue of falsified medicine focus on South-East Asia and Sub-Saharan Africa. It was thus difficult to collect data and qualitative insights specifically on the subject of this Study.

1.1.1.3 Case Studies

To complement the previously described consultation activities, 6 case studies are currently conducted, focusing on the sample of 7 countries. These case studies will enable the study team to delve deeper into the functioning and the effects of the measures introduced by the Delegated Regulation and hence to respond to the evaluation questions concerning the effectiveness and relevance of such measures and their impact on national systems. They will make it possible to study both specific cases of falsification and/or major issues affecting several countries.

The case studies will be based on detailed actor interviews and in-depth research. This selection has been proposed:

Country	Product / Topic	Rationale
Belgium and Spain	E-commerce	Legislative blind spot regarding illegal e-commerce. E-commerce is an important issue mentioned by many actors. The case study also investigates instances of falsification of medicinal products supplied through legal e-commerce circuits, that is to say e-commerce circuits that display the EU Common Logo for online medicine retailers adopted through Directive 2011/62/EU and updated with Implementing Regulation 699/2014.
France and Ireland	Decommissioning of large batches in Hospitals	One of the main challenges of the implementation of the legislation. This will allow investigation of consolidated / aggregated code solutions.
Bulgaria – Netherlands	Specific case of falsification	This will help to see what a possible journey of a falsified medicinal product can be, and how can this type of cases be prevented in the future.
Bulgaria and France	The use of the EMVS data for investigation purposes	This case will illustrate with practical examples how the data contained in the EMVS can be used by the competent authorities to investigate suspected and confirmed cases of falsification. The Bulgarian case will focus on investigations conducted by the NCA. The French case will elaborate on the cooperation between France MVO and law enforcement authorities on criminal investigation involving falsified medicines.
Estonia	Alert management system	Assessment of the effectiveness of a national alert management system: implementation, added value, results
France	Specific situations of pharmacists in France	Specific difficulties were encountered in France regarding the connexion of pharmacists to the system. This case study will allow to look at the reasons and consequences.

The case studies have been launched between end of July and end of August 2023. Due to the holiday period, their deployment is currently taking place (in September 2023). Their results will be presented in the case studies reports.

8.5.4 Results of the contribution

The results from the consultation activities are used as a base for the Study. The surveys and interviews made it possible to cover all the questions of the study, with a particular focus on the legislative framework and implementation at national level. Overall, regarding trends and risks of falsification in the supply chain, we found that data were generally lacking and/or inconsistently reported, that the perception of risks varies importantly across actors, but most respondents agree that the online and illegal markets are the most concerned about falsification. On the implementation of the Delegated Regulation, we found that actors were more satisfied by the governance of the NMVOs than the EMVO, that the safety features and the verifications requirement were overall considered adequate, and that the persisting high number of alerts was considered a major issue by most.

1.1.1.4 Trends and developments in the market of falsified medicinal products, and risk associated with the introduction of falsified medicinal products

This section describes (i) how the trend of falsified medicines has changed over time and in particular after the Delegated Regulation became applicable in the EU/EEA, (2) the divergent views of stakeholders with regards to

the risks of falsification of medicinal products, and (3) the aspects where the perspectives of stakeholders converge.

Firstly, quantitative analysis of the trends of medicine falsification proved difficult to be assessed due to a lack of available data and differences with the definitions.

- In many instances, the European and National actors contacted struggled to provide data regarding the number of confirmed cases of falsified medicinal products. Several reasons were raised to justify these gaps. Whilst NMVOs have no authority to qualify a case as a confirmed case of falsification (which is usually the responsibility of the NCA) and do not keep any records, some NCAs rely on other authorities to monitor the number of confirmed cases (such as the customs or the judicial authorities, which deal with medicines thefts and trade of illegal drugs altogether). Most NCAs simply did not respond to our request.
- When figures were provided, the quality of the data was sometimes put into question: some respondents only submitted estimations and inconstancies were detected between different sources. The main explanation raised was the differences in definition of a confirmed case of falsified medicinal products between countries and between authorities. For example, a case considered as confirmed by an NCA may need validation by a court ruling to be officially treated as such, generating "pending" confirmed cases. The treatment of falsified medicinal products intended for the export market also causes problems as to where the case should be recorded (i.e., the country of origin or destination or transiting country). Some NCAs also pointed out that the cases of falsification in the legal supply chain, the cases of falsifications in the illegal supply chain and cases of stolen medicinal packs were recorded in the same database, as they were often difficult to differentiate. Finally, inconstancies were detected between European and National reports, partly because of the different scope of the products considered (e.g., the EMA focuses on medicinal products with a European marketing authorization, while national authorities treat all products with a marketing authorisation).

Secondly, discussions on the risks of medicine falsification gave rise to various positions among those interviewed, both on specific and general matters.

- Certain topics, such as the risks of falsification linked with parallel trade and medicinal products imported from outside the EU/ EEA, generated various opinions. Some argued that parallel trade adds extra steps to the pharmaceutical supply chain, and thus increases the risks of falsified medicinal products being introduced into the legal supply chain. Overall, 30% of the respondents (64 out of the 205 respondents to the survey to stakeholders) believe that globalisation of the pharmaceutical supply chain constitutes an emerging risk in terms of medicine falsification. Supporters of parallel trade argued that their operations were subject to extra verifications procedures, in addition to those required by the legislation, guaranteeing the safety of the supply chain. The latter also argued that falsifiers are more incentivised to divert medicinal products outside of the EEA/EU, where prices are high and control is low, rather than reintroducing the products into the legal supply chain in another EEA Member States where controls are significant.
- Opinions on the verification system as it is currently in place, vary greatly between stakeholders. On the one hand, all the NCAs contacted reported little or no cases of falsification in their country when data were available. France, Belgium, Ireland, Estonia, and Spain for instance, described their supply chain as secure. Traditionally, in France, the supply chain from the manufacturers of packs of medicines and the end suppliers is very localised; in Belgium, the outer packaging and the documentation needs to show information in the three official languages, which can be a major obstacle for falsifiers, notably in terms of translation; in Estonia and Ireland, the market is relatively small and thus easily controllable; in Spain, finally, the supply chain is perceived to be so highly regulated, (for instance with a view to safety and security of medicinal products), as to eliminate virtually most risks of falsification. These conclusions were also drawn by European and national stakeholders towards the middle and the end of the supply chain (i.e., mainly wholesalers and pharmacists), leading some stakeholders to question the utility/ relevance of the verification system. Pharmacy hospitals, for example, who are almost exclusively supplied by directly by manufacturers, tend to see the verification requirements as an "unnecessary source of extra work". On the other hand, stakeholders at the beginning of the supply chain (i.e., mainly manufacturers), see the introduction of falsified medicinal products in the legal supply chain as a real threat for patient safety. They are joined by most NCAs in the opinion that, whilst the European verification system does not detect many cases of falsified medicinal products, it constitutes a deterrent against falsification attempts.
- Despite this, experts and academia that were consulted agreed that traceability and regulation on medicinal products remain fundamental factors against medicine falsification. In their view, and in

accordance with Crime opportunity theory[113], falsification tend to increase (1) for those medicinal products with high prices, (2) when medicinal products (expensive or not) are in shortage, (3) and when the inspections on the production of medicinal products are marginal.

Thirdly, despite the challenges mentioned above, the consultation phase allowed the Study team to identify some consensus among stakeholders, and notably on the threats posed by the illegal online market (or the illegal market in general), and the categories of medicines the most subject to falsification.

- Illegal online trade is the first emerging risk identified by the stakeholders consulted. More than 50% (110 out of 205) of the stakeholders that replied to the survey identified the increase of online sales as an emerging risk of medicine falsification. This risk is fostered by (1) the ease of ordering online, (2) the challenge for customs to control large volume of parcels, and (3) the low public awareness regarding the health risks posed by falsified medicinal products[114]. Stakeholder views on e-commerce also varied, however. For example, several stakeholders expressed concerns about its potential to increase the risk of introducing falsified medicinal products into the market, especially through illegal online platforms. Others[115], however, saw e-commerce as an opportunity for safe and legitimate sales when properly regulated and tied to licensed pharmacies. Collaboration with physical pharmacies (i.e., implying for example that online pharmacies must operate physical points of dispense or enter a partnership with community pharmacies) was thus deemed essential by some respondents to reduce risks. Others emphasised the importance of effective regulations and information dissemination to prevent e-commerce from becoming a gateway for falsified medicinal products.
- The registered online pharmacies interviewed also acknowledged this problem, although they noted that the EU common logo, required to be displayed on the front page of all registered online pharmacies, helps in fighting this emerging risk. This is notably evident in Spain, where all interviewed representatives of the online pharmacy sector emphasised that pharmaceuticals are exclusively allowed to be sold online through registered pharmacies with a physical presence. This stringent regulation[116] serves as a robust assurance for the safe dispensing of products and the provision of tailored advice to ensure utmost consumer safety.
- More generally, the illegal supply chain was identified as an important source for the trade of falsified medicinal products. In Bulgaria and Poland, NCAs and most stakeholders of the supply chain were particularly concerned about the diversion of medicinal products into the illegal market. Law enforcement authorities in France also mentioned many cases of safe products being supplied by community pharmacies on the basis of false prescriptions, or stollen from hospital pharmacies, to be latter sold illegally in third countries. Spanish authorities have raised concerns regarding recent incidents of theft or loss of medicinal products within the wholesale supply chain, indicating that such occurrences may potentially lead to an upsurge in the circulation of pharmaceuticals through the illegal supply chain.
- Finally, data collected from public authorities (NCAs, customs) and interviews indicate that expensive medicines[117] and lifestyle medicines are the products most at risk of falsification. This tendency is supported by the fact that these products are the most desired. On the one hand, the falsification or diversion of expensive medicines provide the most economic incentives for criminals. On the other hand, lifestyle medicines for which customers demand discretion and do not require prescriptions (e.g., sexual and muscular enhancers, weight loss medications), are particularly suited for online purchases. In that regard, more than 60% (127 out of 205) of the stakeholders identified lifestyle drugs as particularly concerned by falsification.

[113] Crime opportunity theory claims that criminals act rationally and thus choose targets offering high reward with little effort and risk. The occurrence of crimes depends on the existence of a motivated offender and a favourable environment to commit that crime (source: Hindelang, Michael (1978), *Victims of personal crime: an empirical foundation for a theory of personal victimization*).

[114] In relation to this element, the community pharmacists also noticed little to no awareness of the patients regarding the existence of the EMVS. Confirming this observation, the patients and consumers association that was contacted refused to take part in the study, arguing that it was not working on the topic of the EU legislation regarding falsified medicinal products.

[115] Primarily business associations, designated wholesalers, distributors, and pharmacies/persons authorized to supply medicinal products.

[116] Spanish Ministry of Health, Royal Decree 870/2013 regulating the sale at a distance to the public, through websites, of medicinal products.

[117] Preliminary data submitted by NCAs show that prescribed anti-cancer drugs (e.g., Herceptin, Keytruda), which price per dose can reach several thousand depending on the country, are particularly targeted by falsifiers.

1.1.1.5 Implementation of the safety features and medicine verification system

This section describes the views of the different actors contacted regarding: (1) the governance model of the system; (2) the safety features and the verification modalities; (3) the alert management system and repositories system; (4) eventual amendments of the system.

Firstly, while the stakeholder-led governance system is deemed overall adequate, the governance system at the European level is currently encountering major challenges due to conflicting interests between parties.

- The stakeholder-led governance at the national level is reported as adequate and well-functioning by most of the actors interviewed. Many stakeholders and public authorities recognized that the participation of the private parties directly concerned by the EU legislation accelerated the implementation of the verification system. That being said, some concerns were raised, notably regarding the lack of authority of both the NMVOs and the NCAs over software providers, who can be reluctant to address IT issues on a timely and specific manner. Some actors also mentioned issues regarding the fees for participating in the EMVS, which can deter small manufacturers and MAH. In this context, interviewees pointed out that numerous pharmaceutical companies are required to register and pay fees to each NMVOs and EMVO. This situation leads to duplicated costs, whereas streamlining processes and sharing information across NMVOs could significantly reduce expenses for companies. Several interviewees (both NCA and stakeholders) also mentioned the occasional conflicts arising at the NMVO boards, resulting from diverging interest between stakeholders, particularly in relation to data protection.
- Conflicting interests between stakeholders are unequivocal at the European level, which may affect the EMVO's ability to steer the system effectively in the long term. Indeed, all the participants of the EMVO board highlighted the current climate of tension between them; the main subject of conflict is around data protection. On the one hand, manufacturers/MAH support transparency over the data contained in the EMVS, which can help to better trace the movement of medicinal packs across the EEA. On the other hand, wholesalers and pharmacists are particularly concerned about the protection of the data they share in the system. This conflict seems to be impeding progress on other potential areas of cooperation, such as the issue of aggregated codes and bulk verification118.

Secondly, most stakeholders recognised the adequacy of the safety features and the verification system, while identifying some areas for improvements regarding the Anti Tampering Device, the costs of the verifications and the scanning of large volumes of medicinal packs.

- The majority of the actors consulted were satisfied with the current design of the safety features and the verification modalities. More than 85% (137 out of 157) of the respondents to the survey to stakeholders considered the Unique Identifier (UI) to be adequate or fully adequate. Indeed, more than 70% (112 out of 157) reported the same opinion regarding the Anti Tampering Device (ATD). As for the NCA, all the answers received were positive in this respect. In addition, 61% (95 out of 157) of the respondents to the survey to stakeholders also believed that it is not necessary to extend verifications requirements, as both UI and ATD are deemed sufficient. Various stakeholders that responded to the survey, such as Manufacturers, Distributors, Pharmacies/Persons authorised to supply medicinal products, and Healthcare providers, agreed that ensuring the authenticity of medicines is of utmost importance and acknowledged the significance of verifying both the UI and ATD together.
- Despite this, some critiques regarding the verification system were raised, primarily from pharmacists. Firstly, the quality of the ATD differs greatly between single medicinal packs (depending on the manufacturer in charge), which means that some medicinal boxes can be more easily falsified. Secondly, most pharmacists raised concerns about the cost of the equipment (scanners, software, etc.) and the cost of additional staff required to verify the boxes (in hospitals notably). Hospital pharmacists also reported the extensive time that is needed to decommission larges batches of products, scanning packs one by one. These criticisms, often relayed by the NCAs[119], generated delays in countries such as France in the implementation of the DR. Pharmacies/persons authorised to supply medicinal products expressed dissatisfaction with the impact of the verification system on their workflow. Indeed, it was often cited that the verification

[118] Aggregating the UI of multiple boxes of medicines into one unique barcode allows the decommissioning of an entire delivery of medicines in on single operation. Hospital pharmacies, who handle large volume of medicines each day, have been supporting this process since the elaboration of the DR. Practically speaking, the generalisation of aggregation would require medicine suppliers to adapt their sorting and distribution practices. A case study specifically addresses this subject.

[119] NCAs of Bulgaria, Cyprus, Finland, France, Lithuania, Hungary, and Spain have explicitly identified the verification and decommissioning of large volumes of medicine boxes to be a challenge for actors such as wholesalers and hospital pharmacies. NCAs of Belgium, France and Sweden also explicitly indicate supporting aggregation/bulk verification to help stakeholders handling high volumes of medicines.

process should occur either at the wholesaler level or upon receipt in the pharmacy, as the current system complicates their roles and causes difficulties in day-to-day pharmacy operations. In this case (decommission at the entry of products into the pharmacy), the effectiveness of the system may be reduced, since the risk of falsification exists when the product remains in stock in the pharmacy.

Thirdly, progress has been made regarding the functioning of the repositories system and the management of alerts. Despite this, critics tend to focus on the persisting high alert rate, the role of software providers and the financial implications of the alerts for pharmacists.

- Overall, the repositories system is seen as functioning and relatively easy to operate. Some actors, especially NCAs, have nonetheless expressed issues extracting reports[120] and accessing data contained in the National Medicines Verification System.
- The persisting high alert rate is one of the main challenges for most of the actors contacted, especially for end-users who are most affected by verification processes. Manufacturers are concerned more marginally when uploading their data, wholesalers from time to time during their checks. The alerts raised by the system were very numerous in the first months of the implementation of the Delegated Regulation, leading to the introduction of "stabilisation periods", during which pharmacists were allowed to dispense medication despite alerts being triggered. The vast majority of the alerts were linked to human and technical errors (e.g., double decommissioning, lack of uploaded UI in the European Medicines Verification System, etc.). For example, results from the survey to stakeholders found that the top three reasons for alerts originated from a batch number mismatch, batch not being found or a pack already being in a requested state121. Although the alert rate has decreased over the years with the organisation of end users' trainings sessions and with the intervention of the software providers, the number of alerts remains too high for many actors interviewed, which prevents the system from functioning correctly. More than four years after the entry into force of the Delegated Regulation, seven countries out of the 29 participants are still in a stabilisation period122.
- At the European level, the lack of competition over the software market was also raised as a challenge by end users. The situation of duopoly on the market for the EU Hub increases the bargaining power of the suppliers and reduces the ability of the end users to require software providers to solve IT issues quickly. This asymmetric relation is exacerbated by the lack of authority of the NMVOs/ EMVO and the NCAs over the software providers, at both the national and European level.
- Finally, the costs involved with products suspended because of an alert was mentioned as an important issue for community pharmacists. In countries where the stabilization period has ended, community pharmacists are concerned about the financial responsibility of a product suspended because of an alert (especially for expensive medicines with a short expiration date), an element omitted by the current legislation.

Finally, different, and sometimes contradictory recommendations have been formulated by the actors interviewed to amend the EU legislation. The two main areas concern the scope and purpose of the DR, and the verification modalities.

- The "track and trace" system: Manufacturers support the convergence of the current verification system into a "track and trace system" to better monitor the movement of medicinal products across the EU/EEA. This proposition has received the support of some NCAs[123], who believe that such the modified a system could be used to monitor shortages of medicines across Europe. Most of the other stakeholders do not share the same opinion. Indeed, the survey to stakeholders found that 60% of respondents (95 out 157) believed that the system should "not at all" or "not really" evolve from an

[120] For the purposes listed in the DR, NCAs can extract reports with a selection of data from the EMVS. Reports can show many kind of information, such as audit trails, number of alerts per type, information on boxes of medicines produced in another EEA/EU country, etc.

[121] "Pack already in requested state" refers to a situation in which an action related to a pharmaceutical product pack is requested, typically during the verification or authentication process, but the pack is already in the desired state. This means that the requested action is redundant or unnecessary because the pack has already been through that particular process or met the required criteria. For example, this could occur when attempting to decommission a pack that has already been marked as decommissioned, making the request to change its state irrelevant (source: EMVO (2020), *EMVS Alerts and Notification*).

[122] EMVO (2023), *Monitoring Report – January 2023.*

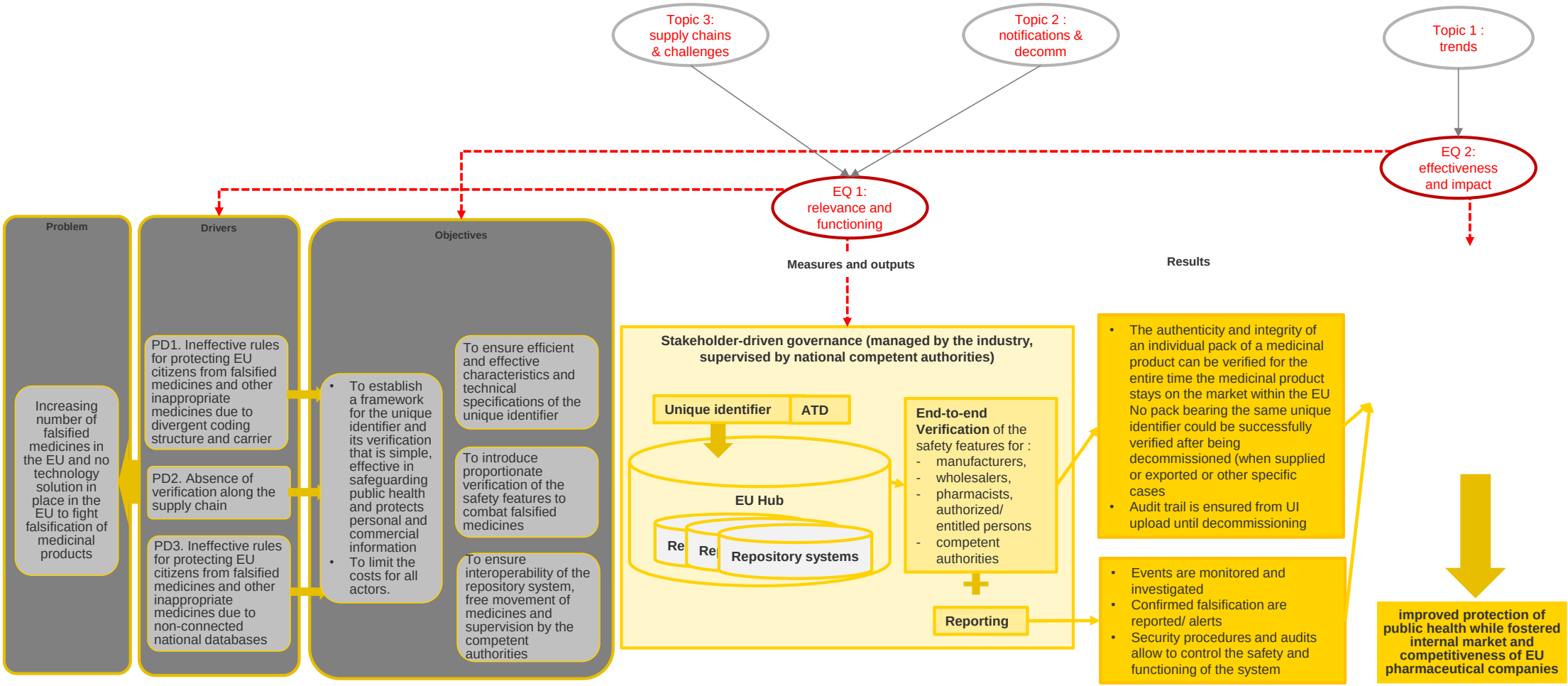
[123] 9 out of the 18 NCAs consulted are explicitly in favour of using the EMVS to monitor shortages: Belgium, Bulgaria, Estonia, Lithuania, Malta, Portugal, Slovenia, Spain, Sweden. 1 is explicitly against: France. The other did not mention monitoring shortages explicitly.

end-to-end system to a track and tracing system. Wholesalers argue that this system would require them to scan all the medicinal packs they handle, an operation deemed highly impractical and too costly for a low margin industry. They also join pharmacists in their concerns about the protection and use of the data that would be collected in the European Medicines Verification System.

- Aggregated codes and bulk verification: Hospital pharmacists have been strong advocates of the development of "aggregated codes" supporting the verification of large batches of medicinal packs in a few scanning operations. This would ease the handling the large deliveries they receive regularly, and thus improve the participation of hospital pharmacies in the system according to the actors interviewed. However, concerns can be raised regarding the impact of such a procedure on the safety of the medicinal packs handled by hospitals, as individual packs would not be verified anymore. This subject have been further investigated in the case study dedicated to this topic.

All the elements used in the above analyses are presented in more details in the various documents appended to this synopsis report: the interviews report, the survey summary, and the country fiches.

8.6 Annex 6 - Intervention Logic


Topic 3: supply chains & challenges
Topic 2 : notifications & decomm
Topic 1 : trends
EQ 2: effectiveness and impact
EQ 1: relevance and functioning
Problem
Drivers
Objectives
Measures and outputs
Results
Increasing number of falsified medicines in the EU and no technology solution in place in the EU to fight falsification of medicinal products
PD1. Ineffective rules for protecting EU citizens from falsified medicines and other inappropriate medicines due to divergent coding structure and carrier
PD2. Absence of verification along the supply chain
PD3. Ineffective rules for protecting EU citizens from falsified medicines and other inappropriate medicines due to non-connected national databases
• To establish a framework for the unique identifier and its verification that is simple, effective in safeguarding public health and protects personal and commercial information
• To limit the costs for all actors.
To ensure efficient and effective characteristics and technical specifications of the unique identifier
To introduce proportionate verification of the safety features to combat falsified medicines
To ensure interoperability of the repository system, free movement of medicines and supervision by the competent authorities
Stakeholder-driven governance (managed by the industry, supervised by national competent authorities)
Unique identifier
ATD
EU Hub
Re
Re
Repository systems
End-to-end Verification of the safety features for :
- manufacturers,
- wholesalers,
- pharmacists, authorized/ entitled persons
- competent authorities
Reporting
• The authenticity and integrity of an individual pack of a medicinal product can be verified for the entire time the medicinal product stays on the market within the EU No pack bearing the same unique identifier could be successfully verified after being decommissioned (when supplied or exported or other specific cases
• Audit trail is ensured from UI upload until decommissioning
• Events are monitored and investigated
• Confirmed falsification are reported/ alerts
• Security procedures and audits allow to control the safety and functioning of the system
improved protection of public health while fostered internal market and competitiveness of EU pharmaceutical companies

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