Update and status of the Falsified Medicines Directive (FMD)

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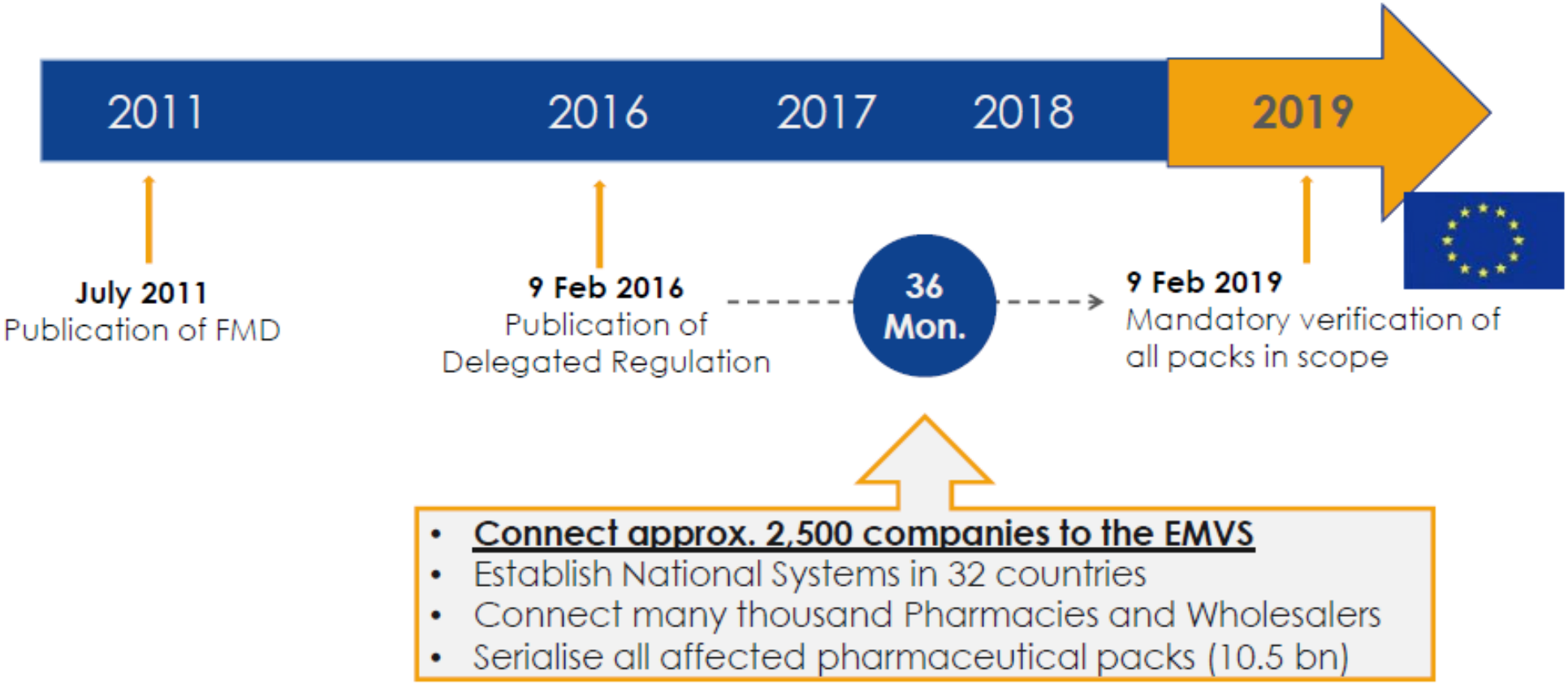
President EIPG

"*New and Emerging Regulations*"
20th February, 2018

Background

FMD LEGISLATION AND DELEGATED ACT



Background

- Safety features (unique identifier, UI) enabling wholesale distributors and persons authorised or entitled to supply medicinal products to the public to
  - verify the authenticity of the medicinal product, and
  - identify individual packs
- Device allowing verification of whether the outer packaging has been tampered with.
- The Qualified Person shall ensure that the safety features have been affixed on the packaging.

Background

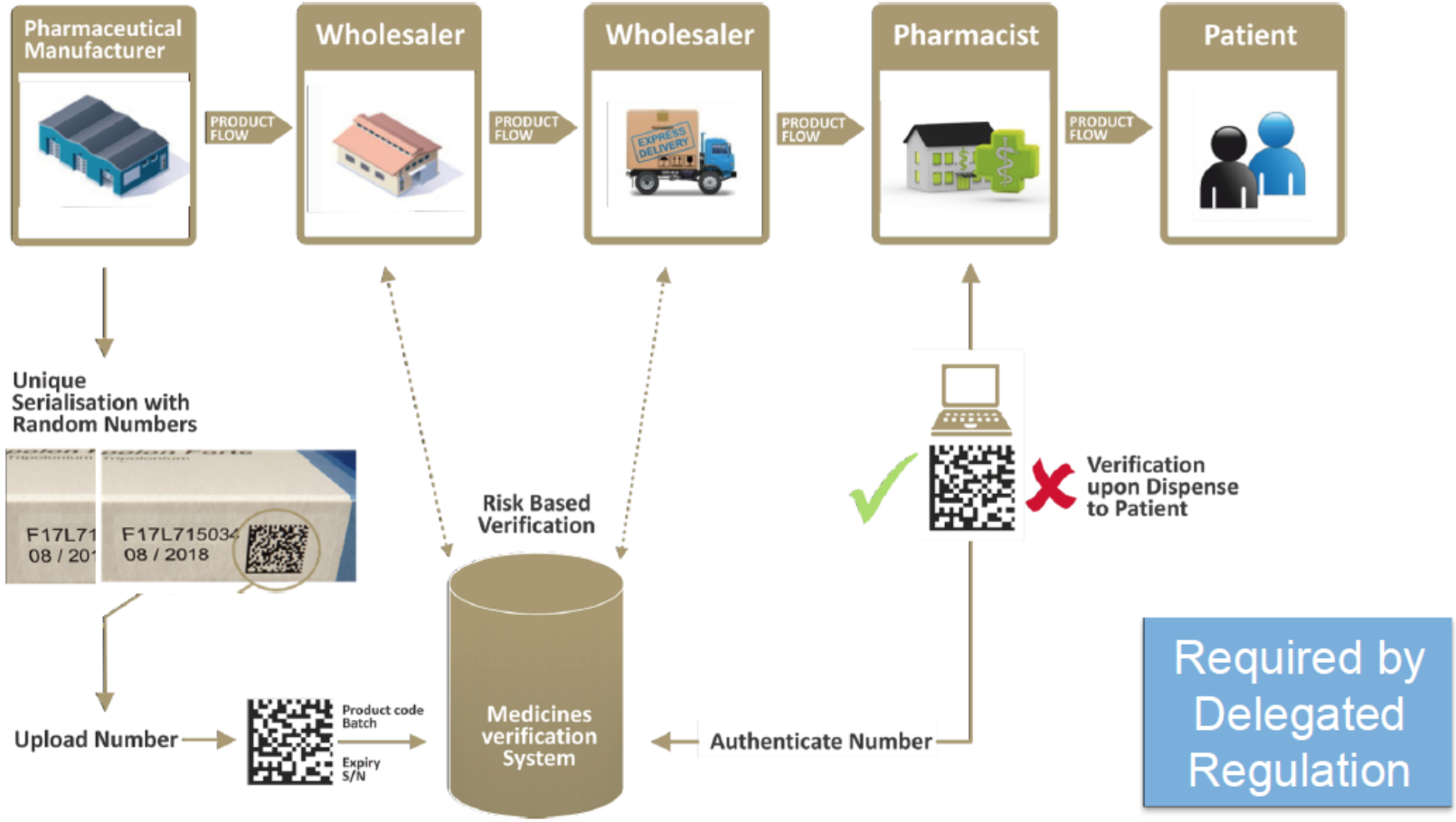
- **Medicinal products**
  - Subject to prescription shall bear the safety features, unless they have been included in the "white list"
  - Not subject to prescription **shall not** bear the safety features, unless they have been included in the "black list"

- **Delegated Regulation** sets out
  - The characteristics and technical specifications of the UI
  - "Black list" and "White list", and procedures for notification
  - Modalities for verification of the safety features
  - Provisions on the establishment, management and accessibility of the repositories system in which information on the safety features shall be contained

Delegated regulation

emvo European Medicines Verification Organisation

Common basic concept: "Point of dispense verification"

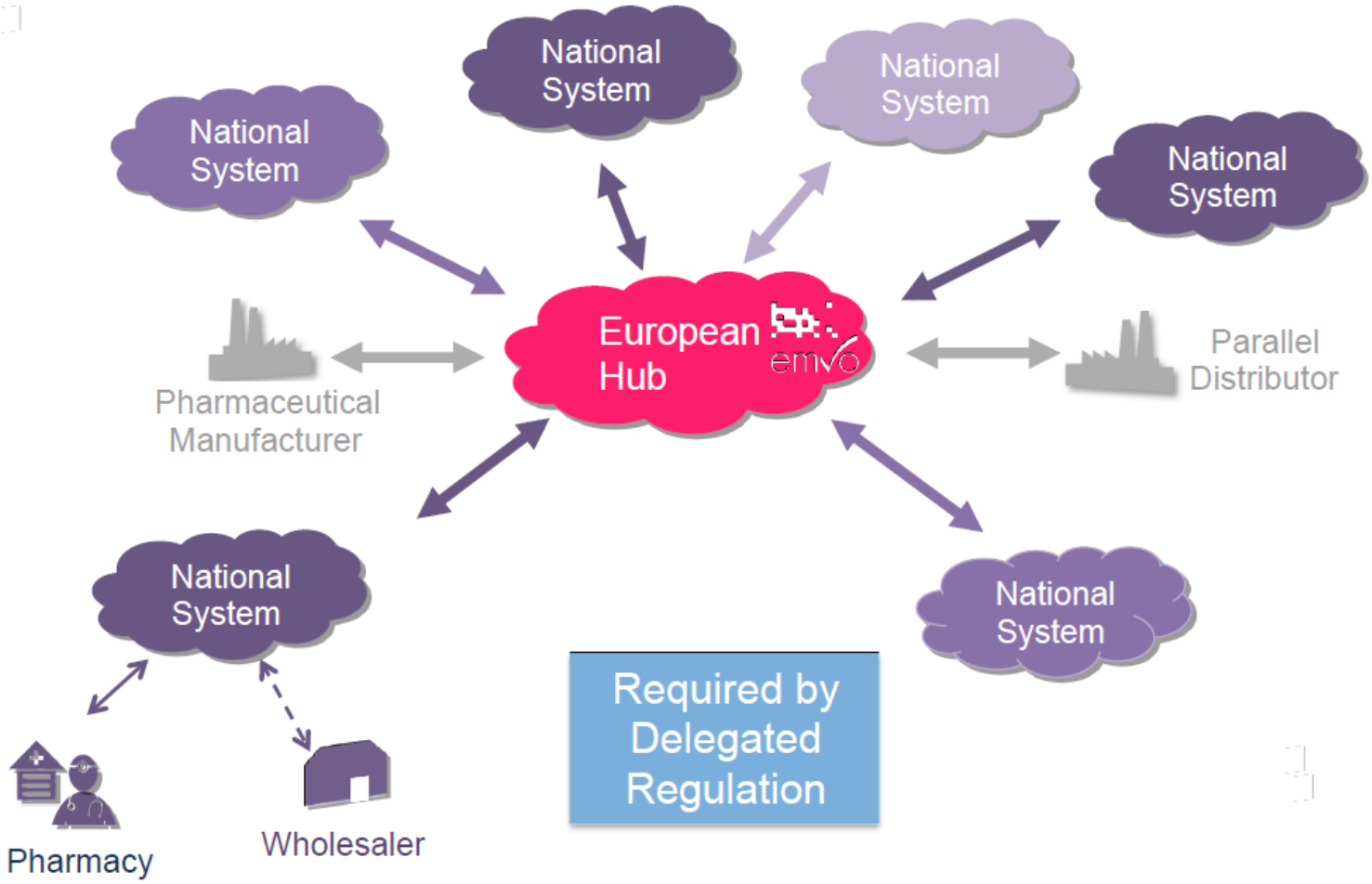


Required by Delegated Regulation

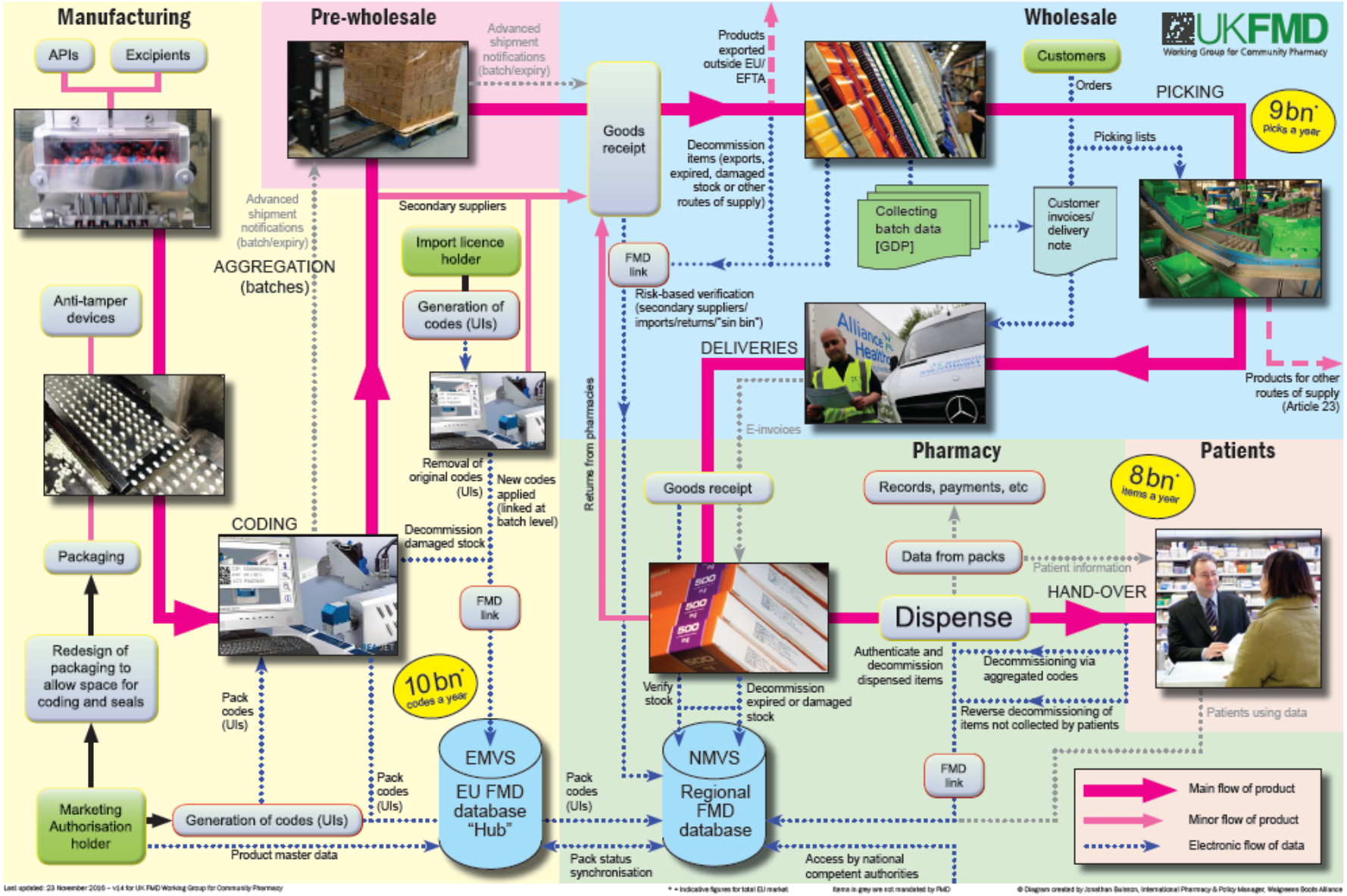
Delegated regulation

emvo European Medicines Verification Organisation

Pan-European Structure



Delegated regulation



The Unique Identifier

- The **Unique Identifier** shall consist of
  - 'product code' (identifying name, common name, form, strength, pack size, pack type, maximum 50 characters, globally unique) [*AI 01*]
  - 'serial number' (numeric/alphanumeric, maximum 20 characters, randomised, less than 1 in 10,000 chance of guessing) [*AI 21*]
  - batch number [*AI 10*]
  - expiry date [*AI 17*]
  - national reimbursement number, if required by MS
- Combination of product code and serial number shall be unique to a given pack until at least one year after expiry or 3 years after QP release, whichever is longer

The Unique Identifier

- The unique identifier shall be encoded in a 2-D barcode
  - Machine-readable datamatrix (ISO/IEC 16022:2006) with internationally recognised coding scheme (ISO/IEC 15418:2009)
  - 'serial number' (numeric/alphanumeric, maximum 20 characters, randomised, less than 1 in 10,000 chance of guessing)
  - Product code, serial number, national reimbursement number shall also be printed in human-readable format as long as sum of two longest dimensions is > 10 cm.
  - Batch number and expiry date are already printed under "Labelling and Package Leaflet" in the Directive.

The Unique Identifier

- **Data-Matrix code, developed to ISO-standards**
- **Key data elements:**
  - Product code (GTIN/NTIN or PPN)
  - Randomised unique serial number
  - Expiry date
  - Batch number
  - National health number (where necessary)

Product #:	09876543210982
Batch:	A1C2E3G4I5
Expiry:	140531
S/N:	12345AZRQF1234567890

ISO 16022

ISO 18004

Role of the manufacturer

- Manufacturers shall:
  - Evaluate the quality of printing of the datamatrix.
  - Establish minimum quality of printing that ensures accurate readability throughout the supply chain till one year after expiry or five years after release, whichever is longer.
  - Verify that the 2-D barcode is compliant, readable and contains correct information.
  - Keep records of every operation with or on the UI for at least one year after expiry or five years after release, whichever is longer.

Some new Q&A's

- **2.17 Do human-readable headers (PC, SN, Lot, EXP, NN) have to be placed adjacent to the respective data elements, on the same line, or is some flexibility possible?**

- Human-readable headers are not required to be placed adjacent/on the same line as the respective data element. Headers can be placed in any position which allows the unequivocal identification of the human-readable data element.

Some new Q&A's

- **2.18 Is it acceptable to place data elements in multiple locations across the packaging?**

- It depends on the data elements. The product code and serial number should always be placed on the same surface so to facilitate manual decommissioning of the unique identifier. Concerning the other data elements, an effort should be made to place them on the same surface as the product code and serial number. Should the packaging dimensions not allow it, however, it is acceptable to place the other data elements elsewhere on the packaging.

Some new Q&A's

- **2.19 Is it acceptable to use a 2D Data Matrix which is rectangular (rather than square) or printed white on black (rather than black on white)?**

- Yes. Manufactures can chose to encode the unique identifier in a 2D Data Matrix which is rectangular and/or printed white on black, provided that it fulfils the technical requirement laid down in Article 5 of Regulation (EU) No 2016/161.

Some new Q&A's

- **2.20 Is it mandatory to include Application/Data Identifiers as part of the human-readable headers or data elements?**

- No. Manufacturers can choose whether to include the Application/Data Identifiers as part of the human-readable headers/data elements.

Some new Q&A's

- **4.4 Can a manufacturer use an outer packaging carrying a unique identifier which has been placed by another (contracted) manufacturer?**

- Yes. Art. 14 of Regulation (EU) No 2016/161 requires that the manufacturer placing the safety features on the medicinal product verifies that the two-dimensional barcode carrying the unique identifier complies with Articles 5 and 6 of the said Regulation, is readable and contains the correct information. Where pre-printed cartons are used, the manufacturer using the pre-printed carton has the obligation to verify the 2D barcode complies with Articles 5 and 6 of the above Regulation, is readable and contains the correct information before releasing the medicinal product for sale and distribution.

Some new Q&A's

- **2.21 Is it acceptable to use stickers to place the unique identifier on the outer/immediate packaging?**

- As a general rule, the unique identifier should be printed on the packaging, in accordance with Article 5(3) of delegated Regulation (EU) No 2016/161.
- Placing the unique identifier by means of stickers can only be accepted in exceptional, justified circumstances .
  - No legal and/or technically feasible alternative exists
  - Competent national authorities authorise it to safeguard public health and ensure continued supply

Some new Q&A's

- **2.21 Is it acceptable to use stickers to place the unique identifier on the outer/immediate packaging?**

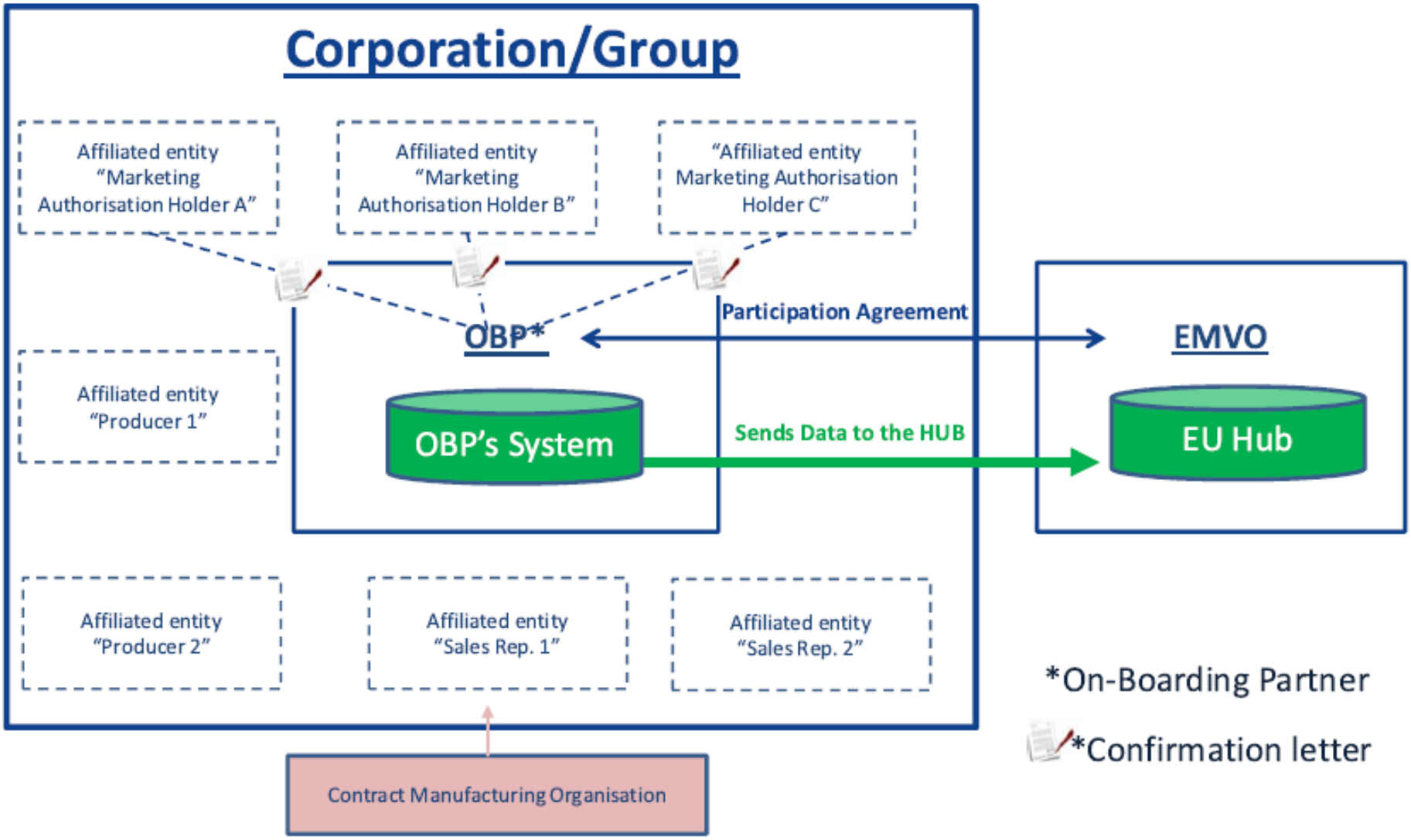
- In cases where placing the unique identifier by means of stickers is exceptionally authorised
  - The sticker on which the unique identifier is printed should become one with the outer packaging/immediate packaging, i.e. the sticker should be tamper-evident and it should not be possible to remove it without damaging the packaging or the sticker itself or leaving visible signs
  - The sticker on which the unique identifier is printed should be placed by a manufacturer under GMP conditions

Some new Q&A's

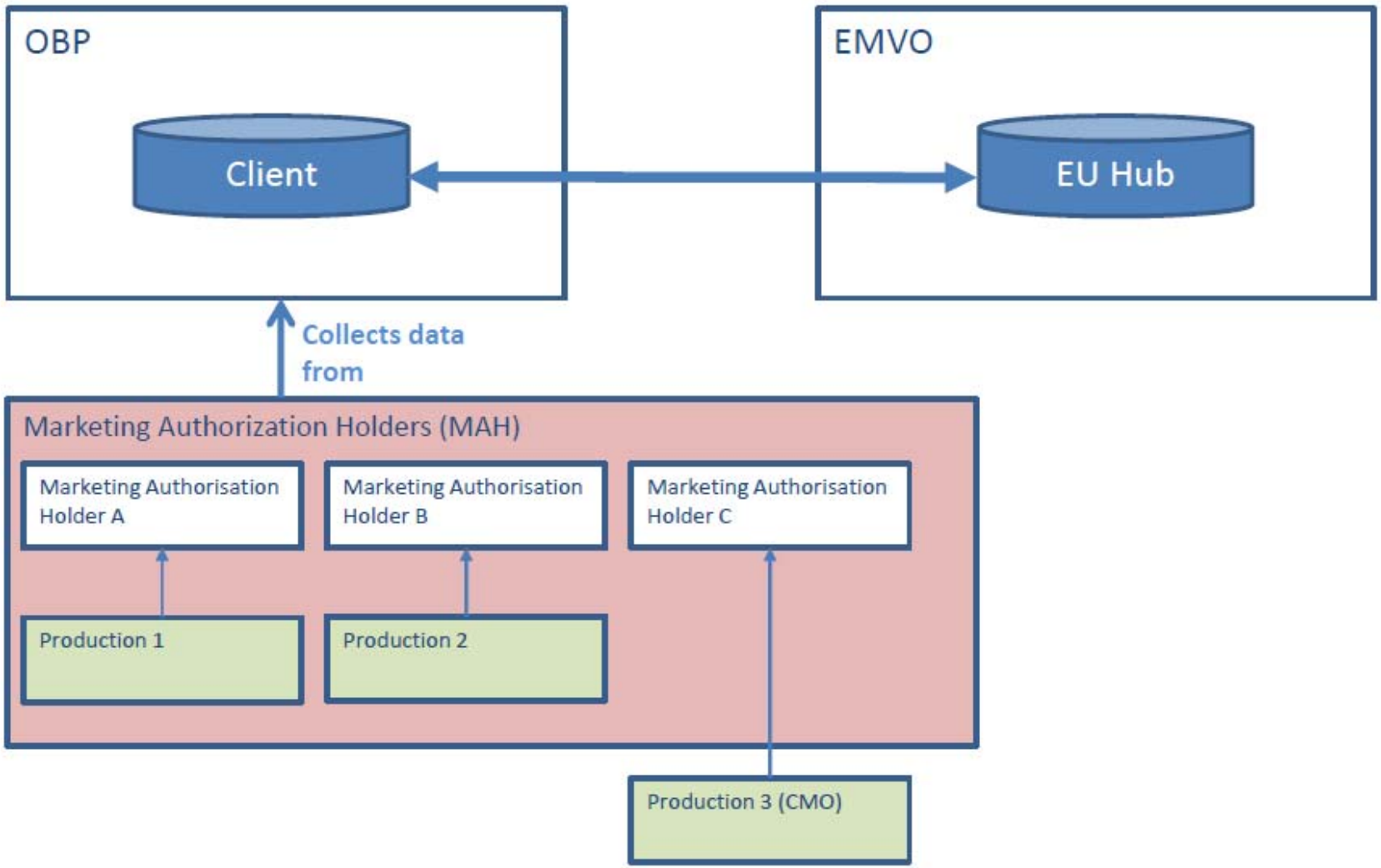
- **2.21 Is it acceptable to use stickers to place the unique identifier on the outer/immediate packaging?**

- Placing the unique identifier by means of stickers should never be allowed when
  - It impairs readability
  - The sticker on which the unique identifier is printed can be detached from the packaging without damaging the packaging or the sticker itself or leaving visible signs
  - The sticker on which the unique identifier is printed is intended to be placed on a cellophane foil or a similarly soft wrap, as this could lead to the loss of the unique identifier information
  - The sticker on which the unique identifier is printed is intended to be placed on top of an existing sticker, as this could engender confusion and suspicions of tampering

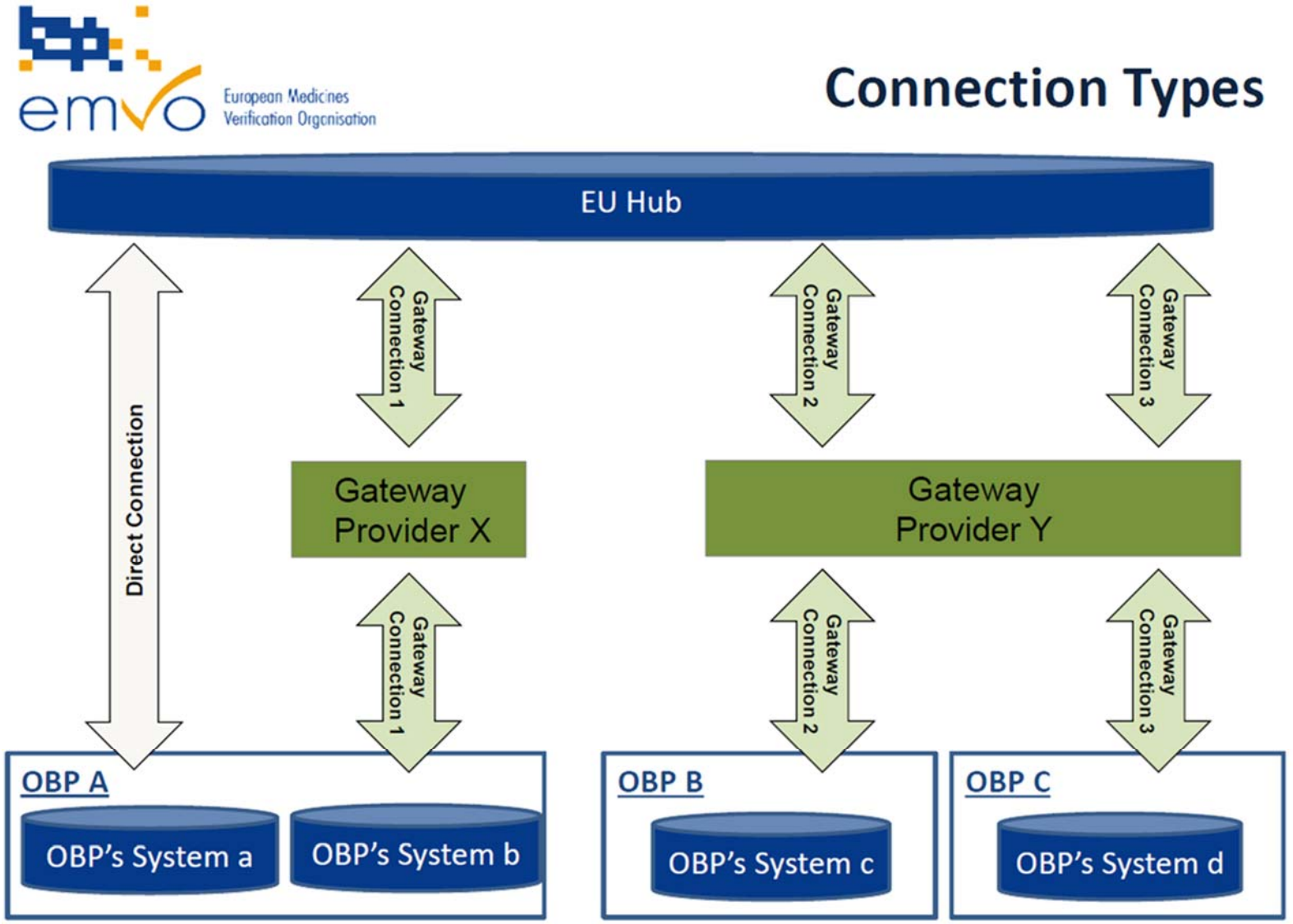
Uploading the data



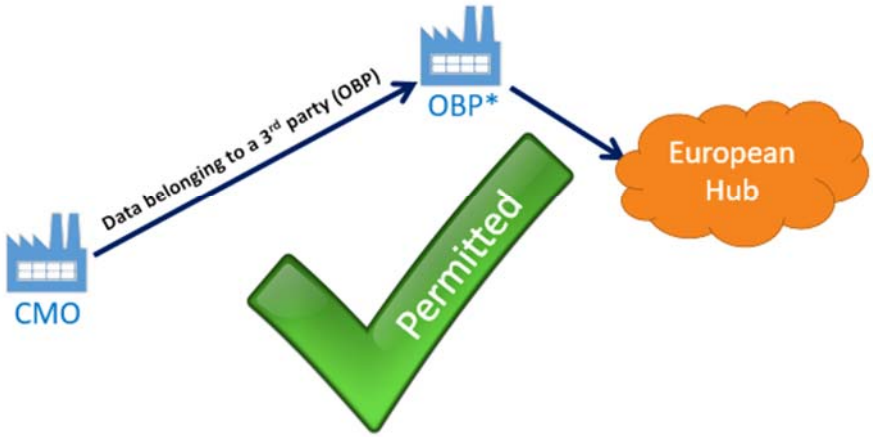
Uploading the data



Uploading the data

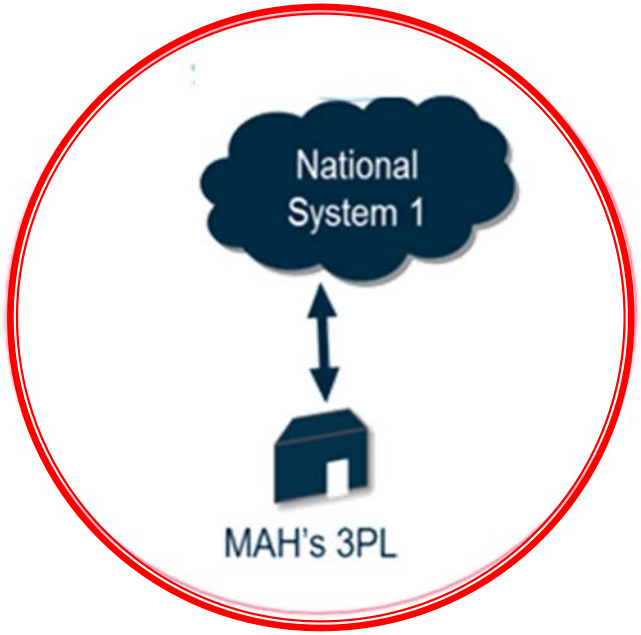


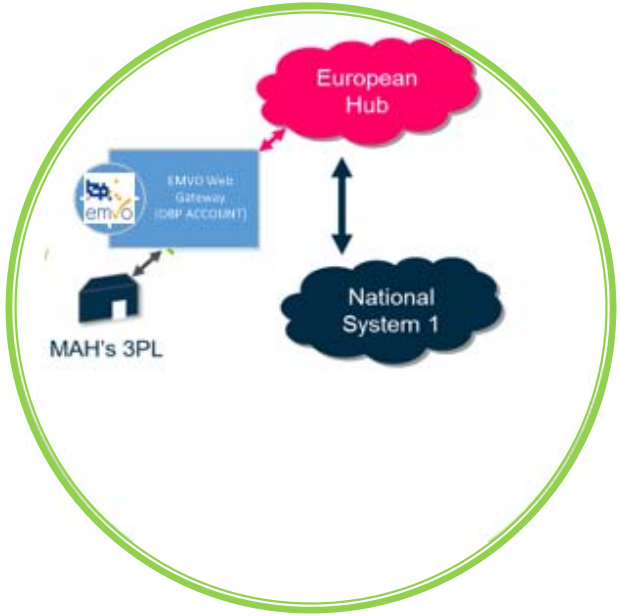
Uploading solutions

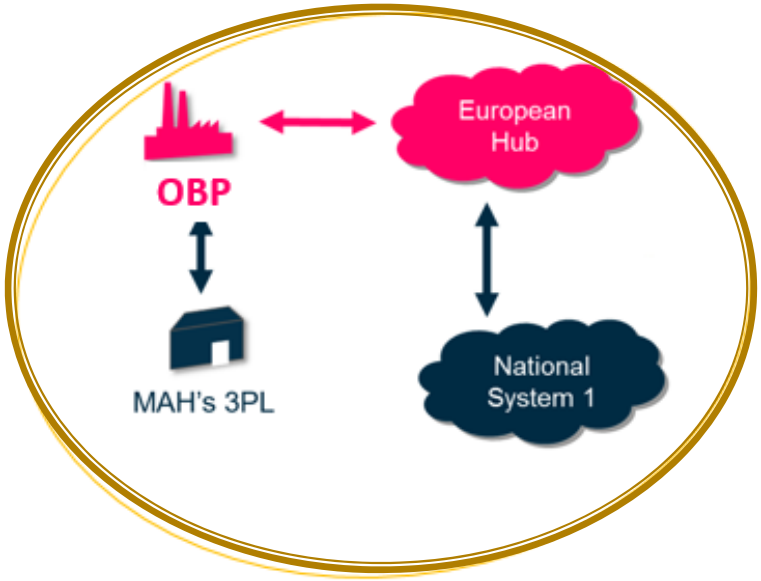


*OBP: On-boarding Partner

Uploading solutions







So what about the QP?

- The Qualified Person shall in the case of medicinal products intended to be placed on the market in the Union, ensure that the safety features….have been affixed on the packaging. [*Article 51*]

- The marketing authorisation holder….shall ensure that the information referred to in paragraph 2 is uploaded to the repositories system before the medicinal product is released for sale or distribution by the manufacturer, and that it is kept up to date thereafter. [*Article 33(1)*]

Remember

- In the case of multi-market packs, the data needs to be distributed to multiple national systems.
- Multi-market packs may not be uploaded to one local system for all markets.
- The EMVS access principles foresee that only those entities holding marketing authorisations can establish a legitimate connection to the EU Hub for the uploading of product data.
- It will be each manufacturer's responsibility to upload product pack data to the European Hub. This task cannot be transferred to another party, e.g. a contract manufacturer

Source: European Medicines Verification Organisation: Requirements for the European Medicines Verification System – URS Lite

Some new Q&A's

- **7.16 In accordance with Article 33(1), the information laid down in Article 33(2) must be uploaded in the repositories system before the product is released for sale and distribution. Does this mean that the upload needs to take place before the Qualified Person (QP) performs the batch certification and thus the safety feature information relative to any manufacturing waste should also be uploaded in the system?**

- No. The information…needs to be present in the system at the time the batch is released for sale and distribution. It is acceptable to upload that information at such a time that the system is not burdened with information relative to manufacturing waste,.. provided that the upload takes place before the medicinal product is transferred to saleable stock.

Import/export

- **Scenario:** Products, manufactured and released for the sale in the EU, are sold to a party established outside the EU, but physically remain in the EU. The product is subsequently sold back to a party in the EU (*separation of physical and financial flow*).

- **Regulatory interpretation:** The sale of products from outside the EU to a party inside the EU constitutes importation, and requires a manufacturing and import authorisation, and checking of the manufacture and testing of the batch, QP certification of the finished product batch, prior to release for sale.

The Swiss scenario

- In the case of Switzerland, since appropriate arrangements have been made to ensure that the manufacturers in Switzerland apply standards of GMP equivalent to those laid down in the EU the QP is relieved of the responsibility for carrying out the controls in Article 51(1)(b) if they have been carried out in Switzerland. (*Article 51(2)*)

- The provisions of Article 51(2) do not appear to extend to the responsibilities of the Qualified Person with regards to ensuring that the safety features have been affixed on the packaging.

- Therefore the provisions of Annex 16 should be taken as the guiding principle.

Some new Q&A's

- **3.5 Is it possible to reverse the decommissioned status of a medicinal product which has been exported to third countries, when such product is brought back into the EU?**

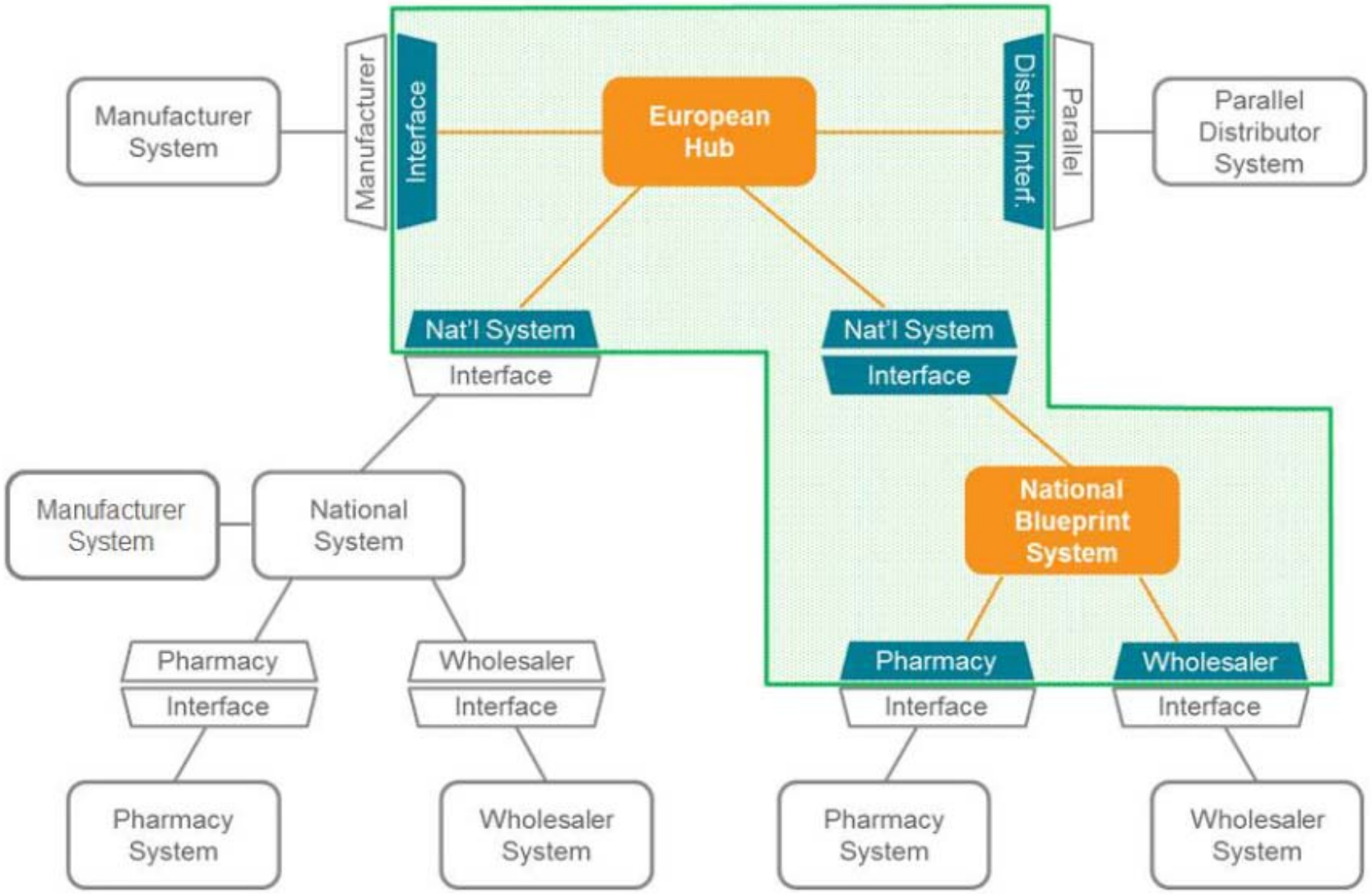
- No. A medicinal product which has been exported outside of the EU and is then reintroduced on the EU territory should be considered an "import". Such product therefore needs to be imported by a MIA holder (not a wholesaler) and is subject to the import requirements laid down in Article 51 of DIR 2001/83/EC (batch testing, batch release, etc). The imported medicinal product needs to be given a new unique identifier containing a new batch number and expiry date before it is released for sale and distribution.

Some new Q&A's

- **5.5 Question: Article 22(a) requires a wholesaler to verify the authenticity of and decommission the unique identifier of all medicinal products he intends to distribute outside of the Union. Is it necessary to decommission the unique identifier if the medicinal product is sold to a party established outside the EU but that product does not physically leave the wholesaler's premises in the EU?**

- No. The purpose of Article 22(a) is to ensure the decommissioning of unique identifiers on packs which leave the EU territory, in order to avoid that those active codes may be harvested by traffickers. In case the medicinal product is sold to a party established outside the EU but physically remains in the wholesaler's premises in the EU, the unique identifier on the product should not be decommissioned. If that medicinal product is subsequently imported (while physically remaining in the EU) by a holder of a manufacturing and import authorisation (a wholesaler cannot import medicinal products), no action is required with regard to the safety features.

Who's going to pay?



Who's going to pay?

- The costs of the repositories system shall be borne by the manufacturers of medicinal products bearing the safety features, in accordance with Article 54a(2)(e) of Directive 2001/83/EC. (*Article 31*)
- To finance the system, the stakeholders representing the manufacturers….have agreed upon a model that will charge annual upfront usage fees based on a single flat fee per Marketing Authorisation Holder or parallel distributor.
- Where the Marketing Authorisation Holder for any given product is not the same legal entity as the Manufacturing Authorisation Holder, both parties shall be required to contractually agree how to attribute the usage fees between them in compliance with the FMD.

Source: European Medicines Verification Organisation: Requirements for the European Medicines Verification System – URS Lite

Harmonisation: GTIN – NTIN

- **Data-Matrix code, developed to ISO-standards**
- **Key data elements:**
  - Product code (GTIN/NTIN or PPN)
  - Randomised unique serial number
  - Expiry date
  - Batch number
  - National health number (where necessary)

Product #: 09876543210982
Batch: A1C2E3G4I5
Expiry: 140531
S/N: 12345AZRQF1234567890

ISO 16022

ISO 18004

Coding harmonisation

GTIN Data Structures

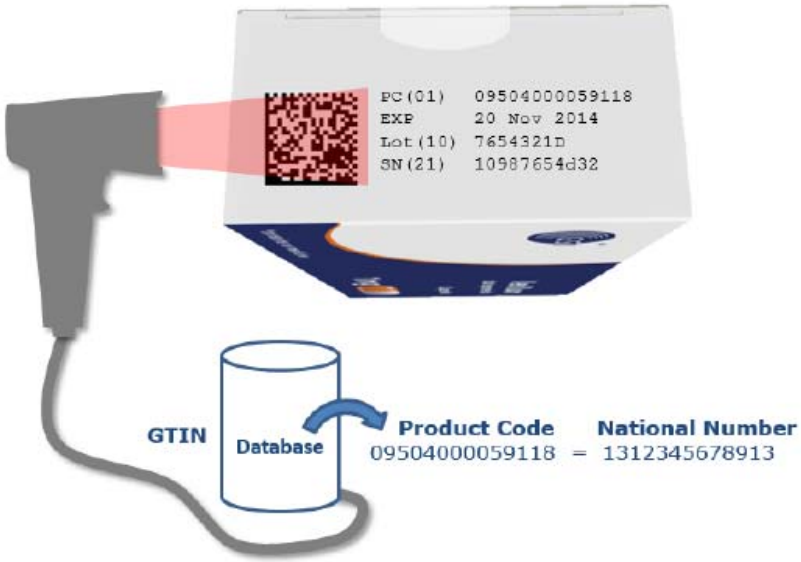
Application Identifier		Digit Positions 1	2	3	4	5	6	7	8	9	10	11	12	13	14	
	(0 1)	0	0	0	0	0	0	N	N	N	N	N	N	N	C	GTIN-8
	(0 1)	0	0	N	N	N	N	N	N	N	N	N	N	N	C	GTIN-12
	(0 1)	0	N	N	N	N	N	N	N	N	N	N	N	N	C	GTIN-13
	(0 1)	N	N	N	N	N	N	N	N	N	N	N	N	N	C	GTIN-14

Coding harmonisation

GTIN Data Structures

<---------- Digit Positions ---------->

Application Identifier	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
(0 1)	0	0	0	0	0	0	N	N	N	N	N	N	N	C	GTIN-8
(0 1)	0	0	N	N	N	N	N	N	N	N	N	N	N	C	GTIN-12
(0 1)	0	N	N	N	N	N	N	N	N	N	N	N	N	C	GTIN-13
(0 1)	N	N	N	N	N	N	N	N	N	N	N	N	N	C	GTIN-14

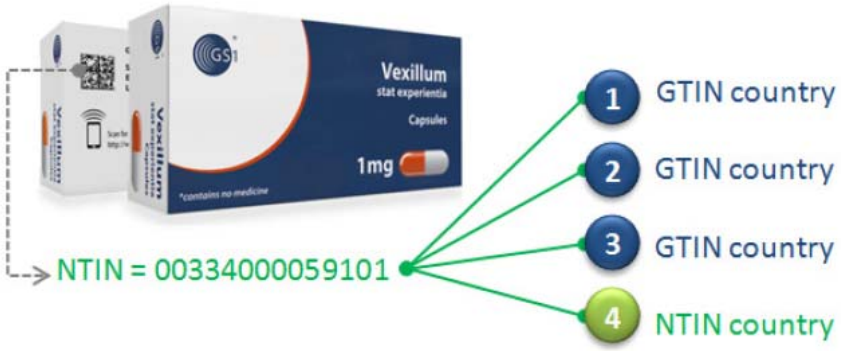


Coding harmonisation

"NTIN" Data Structures

		<---------- Digit Positions ---------->													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
Application Identifier	(0 1)	0	0	3	N	N	N	N	N	N	N	N	N	N	C
	(0 1)	0	Np	Np	Np	Nn	Nn	Nn	Nn	Nn	Nn	Nn	Nn	Nn	C

NTIN-12
NTIN-13



Fields in GS1 DataMatrix			Market types which can take this pack		
Primary key	Other fields				
(01) Containing a GTIN			GTIN countries		
(01) Containing a GTIN	NHRN 1		GTIN countries	NHRN 1 country	
(01) Containing a GTIN	NHRN 1	NHRN n	GTIN countries	NHRN 1 country	NHRN n country
(01) Containing an NTIN			NTIN country		
(01) Containing an NTIN			GTIN countries	NTIN country	

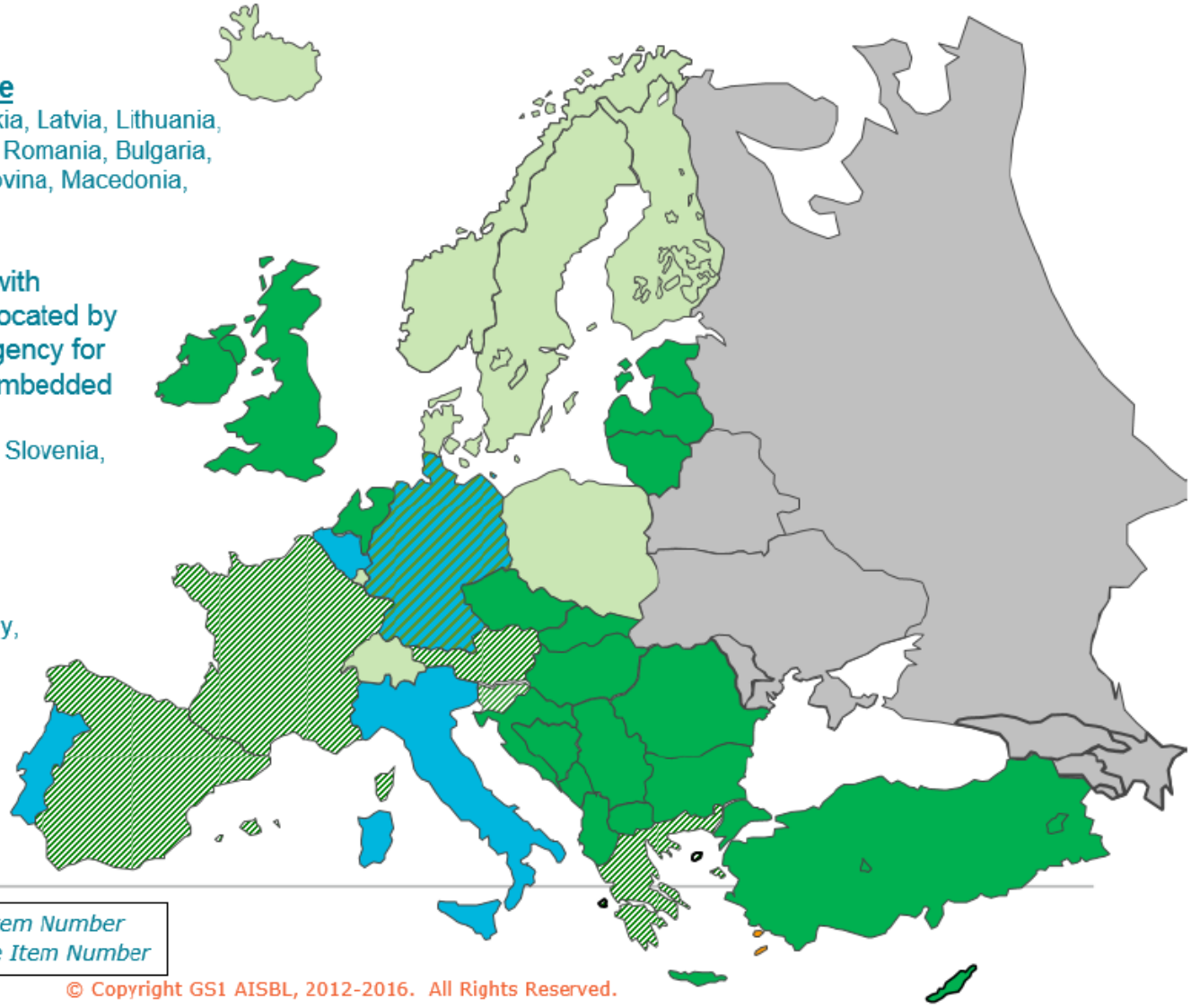
Coding harmonisation

19 countries have a **full GS1 GTIN (1) code structure**
(UK, Ireland, Czech Republic, Slovakia, Latvia, Lithuania, Estonia, Malta, Netherlands, Turkey, Romania, Bulgaria, Serbia, Albania, Bosnia and Herzegovina, Macedonia, Croatia, Cyprus, Hungary)

6 countries use **a GS1 NTIN (2)** with product identification number allocated by a number bank or an external agency for the coding of pharmaceuticals embedded in GS1 data structure
(Austria , France, Germany, Greece, Slovenia, Spain)

7 countries allow GS1 GTIN **AND** GS1 NTIN
(Denmark, Finland, Iceland, Norway, Poland, Sweden, Switzerland)

4 countries use their own **non-GS1 compatible solution**
(Belgium, Germany, Italy, Portugal)



(1) GTIN: Global Trade Item Number
(2) NTIN: National Trade Item Number

Extension of scope

	Prescription-only	OTC
Unique identifier	Present	Default: No
		MS: Yes (reimbursement or pharmacovigilance)
Anti-tampering device	Present	Default: No
		MS: Yes(patient safety)
28 Member States Product may have different legal status in different MS		

Extension of scope

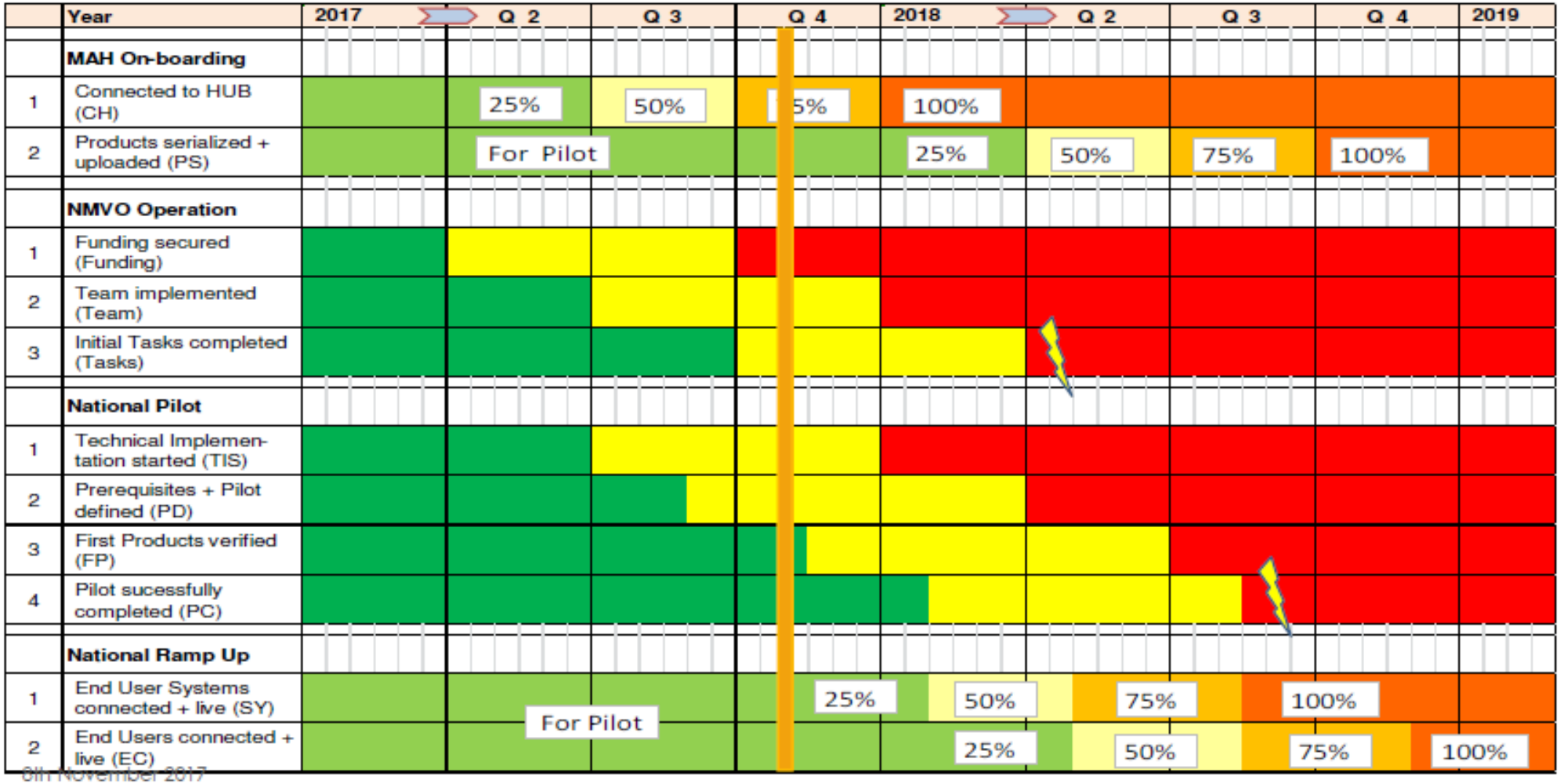
	Prescription-only	OTC
Unique identifier	Present	Default: No
	MS: Extension to white list (*Yes if reimbursed* / ***No**** / *Under discussion*)	MS: Extension to reimbursed products (***Yes**** / *No* / *Under discussion*)
Anti-tampering device	Present	Default: No
	MS: Extension to white list (*Yes* / *No* / ***Voluntary**** / *Under discussion*)	MS: Application on products (*Yes* / *No* / ***Voluntary**** / *Under discussion*)
		MS: Retention on products (***Yes**** / *No* / *Under discussion*)

**** Belgian position***

Points to ponder

- What happens if countries currently supplied by a multimarket pack decide on different extents of extension of scope?
- What happens if countries from which product was purchased under normal circumstances no longer represent a feasible source of product?
- What happens if markets that could originally be relied upon in an emergency as a source of product to help mitigate a shortage are (at least temporarily) not compliant with the provisions of the Delegated Regulation (*Italy and Greece have a derogation till 2025*) or have different extensions of scope?

Implementation schedule



Is Europe on track?

- Alarm 1: MAH On-Boarding*
  - If a country falls behind one of the targets "Connected to the HUB" or "Products serialized and uploaded" it is counted as "late"
- Alarm 2: NMVS Readiness
  - Every country is counted according to its worst placement in relation to the Reference Schedule
- Alarm 3: End User Readiness*
  - If a country falls behind one of the targets for "End User Systems" or "End Users Connected" it will be counted as "late"

Is Europe on track?

EXECUTIVE SUMMARY
A1: MAH ON-BOARDING

Above Target

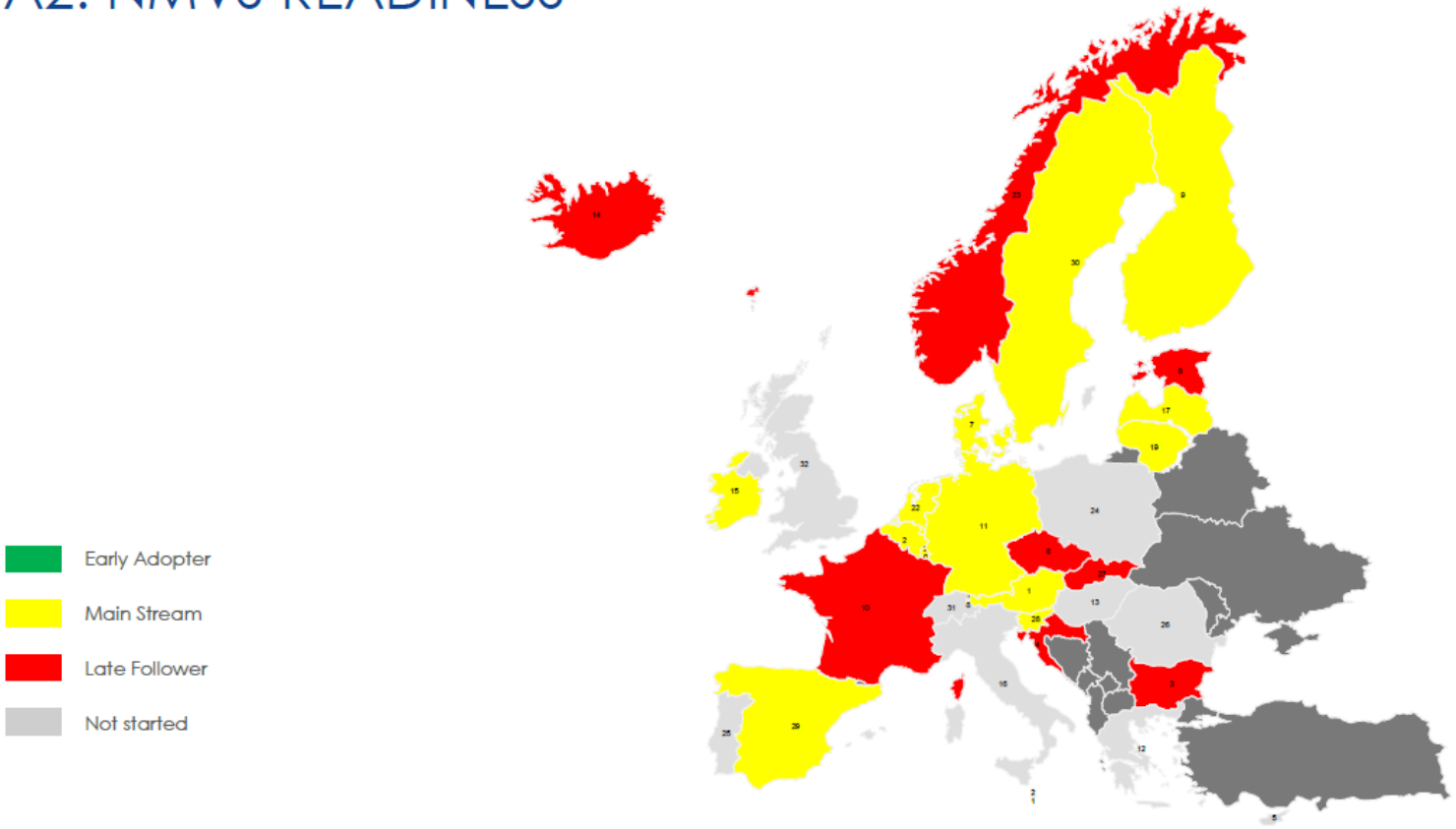
Below Target

Actual Target 100%

	OBP (Status July 17)		NMVO			NMVS Pilot				User		Alarms		
	CH %	PS %	Fund	Team	Tasks	TIS	PD	FP	PC	SY %	EC %	A1	A2	A3
2 Belgium	5													

Is Europe on track?

EXECUTIVE SUMMARY
A2: NMVS READINESS

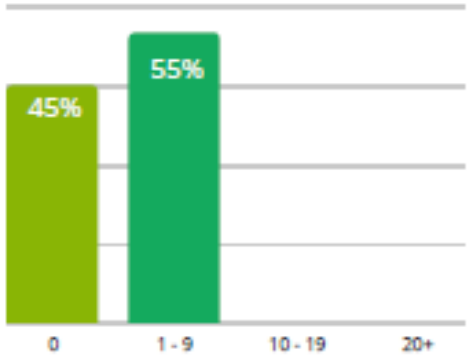


	OBP Status July 17		NMVO			NMVS Pilot				User		Alarms		
	CH %	PS %	Fund	Team	Tasks	TIS	PD	FP	PC	SY %	EC %	A1	A2	A3
2 Belgium	5													

Is the industry prepared?

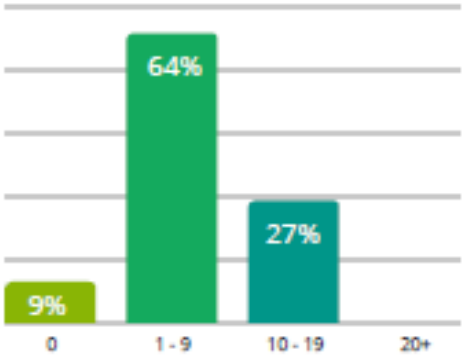
7. How Many Packaging Lines Are Ready To Serialise Product For The EU Market?

Of those who had 1 - 9 lines to serialise, 55% have 1 - 9 lines completed



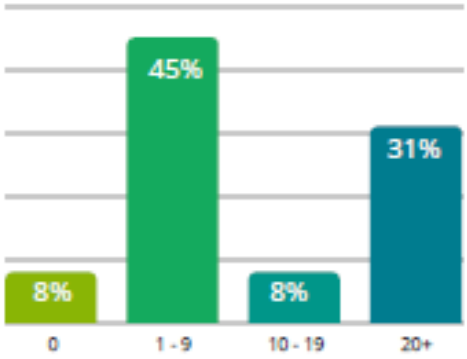
1 - 9 Lines To Serialise

Of those who had 10 - 19 lines to serialise, 64% have only 1 - 9 lines completed



10 - 19 Lines To Serialise

Of those who had greater than 20 lines to serialise, only 31% have more than 20 lines completed



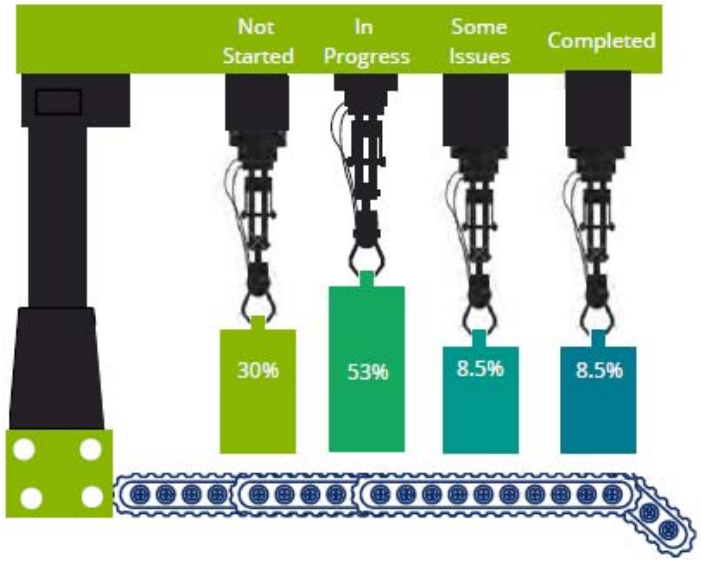
20+ Lines To Serialise

*one respondent left field blank

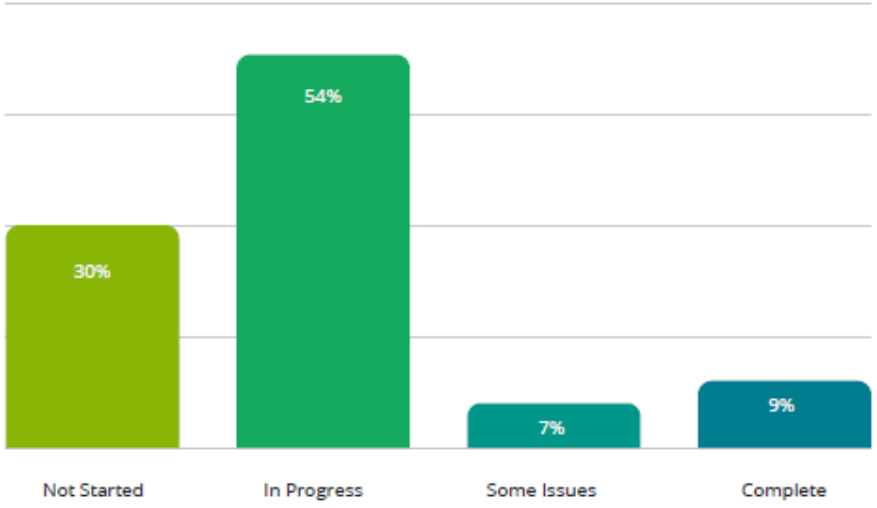
Serialisation Industry Readiness Report 2017, GS1 Ireland, October 2017

Is the industry prepared?

11. Are Your Warehouse Processes Ready For EU FMD?



12. Have You Mapped Your Downstream Processes To Meet The EU FMD Requirements?



Serialisation Industry Readiness Report 2017, GS1 Ireland, October 2017

Conclusions

- It is a tremendous challenge is to connect all manufacturing companies to the EMVS, establish national systems, connect thousands of pharmacies and wholesalers, and serialise all appropriate pharmaceutical packs.
- The impact of the EMVS on medicines availability is difficult to assess. The application of the safety features has the potential to exacerbate shortage situations unless a risk assessment and management process is applied *a priori* to identify and prepare for changes.
- Member States need to prepare legislation for matters related to FMD.
- Europe can only be ready to implement the safety features if all stakeholders make a strong commitment and effort.