



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Article 57 database of medicinal products



Loris Piccolo – Data Standardisation and Analytics

An agency of the European Union





Topics covered

- Art57 database introduction
- Initial submission and update of product information
- Pharmacovigilance system master file location
- Data quality assurance
- Completeness checks (mapping exercise with NCA databases)

Article 57 database – what is it?

- The Art57 database, also known as eXtended EudraVigilance Medicinal Product Dictionary (XEVMPPD), is a repository of structured information on all medicinal products authorised in the EEA
- The submission of data on medicines by the marketing authorisation holders is a legal requirement introduced by the Article 57(2) of Regulation (EU) No 1235/2010:
 - [...] The **marketing authorisation holders to submit information to the Agency** electronically on all medicinal products for human use authorised or registered in the European Union by 2 July 2012, using this format
 - The **marketing authorisation holders to inform the Agency** of any new or varied marketing authorisations granted in the EU as of 2 July 2012, using this format [...]

Registration with EudraVigilance

- To submit information in the XEVMPD, MAHs have to be registered with EudraVigilance
- Before applying for registration with EV, at least one user from the MAH organisation must complete the [Extended EudraVigilance medicinal product dictionary \(XEVMPD\) training](#) (e-learning or face-to-face)
- As part of the registration with EV process, the MAH must provide a set of documents as per the process described on the [EudraVigilance: how to register webpage](#)
- Once the MAH organisation is successfully registered (i.e. an organisation profile is created, with organisation ID, registered QPPV) -> **XEVMPD production environment**
- Product information is submitted electronically, in so called **Extended EudraVigilance Product Report Message (XEVPRM)** format
- XEVPRMs can be submitted via an internal Gateway or using an on-line tool provided by the Agency called **XEVMPD data-entry tool (EVWEB)**

Initial submission of an Authorised Medicinal Product

- No later than **15 calendar days** from the date of authorisation
- Based on the following main characteristics:
 - a) Name of the medicinal product
 - b) Marketing authorisation holder
 - c) Marketing authorisation number
 - d) Qualitative and quantitative composition (ingredients, strength, pharmaceutical form)
- Whenever any of the characteristics above for a medicinal product are different, a separate medicinal product entity should be submitted in the XEVMPD
- An XEVPRM ACKnowledgement is sent back to the sender, confirming (or not) the successful submission of the information



Initial submission of an Authorised Medicinal Product

Create and Send ICSRs Create and Send AckS WEB Trader ICSRs Create and Send Product Reports Medicinal Products MedDRA

☐ Reset Application Reset Section Clear Replicate Validate Send XML ZIP RTF Duplicate Remove E L R

XEVPRM Message

- Products
 - Insert - Authorised
 - Medicinal Product Types (-)
 - Authorised Pharmaceutical Forms (-)
 - Pharmaceutical Products (1)
 - Pharmaceutical Product**
 - Drug Routes (1)
 - Route of Administration**
 - Drug Ingredients (1)**
 - Drug Ingredient**
 - Old Drug Ingredients (-)
 - Medical Devices (-)
 - Drug ATCs (-)**
 - Drug Indications (1)
 - Drug Indication**
 - Previous EV Codes (-)
 - Product Attachments (-)
 - Substances
 - Sources
 - Organisations
 - ATC Codes
 - Pharmaceutical Forms
 - Routes Of Administration

,,abilify

Description	Name/Value	
Operation Type	Insert (1)	
New Owner ID	MAH	Field is Mandatory
	QPPV	
Master File Location		
PhV enquiry email		
PhV enquiry Phone		
Sender Local Code		
Info Date		
Authorisation Country Code		Field is Mandatory
Authorisation Procedure		Field is Mandatory
Authorisation Status		
Authorisation Number		Field must have a specified value
Authorisation/Renewal Date		
MRP/DCP/EMA Number		
EU Number		
Legal Basis		
Orphan Drug		
Additional Monitoring		
Invalidated Date		Field must have a specified value
Full Presentation Name		Field is Mandatory
Product Short Name		Field is Mandatory Optional

Update of submitted product information

- Information on any **amendments to the terms of marketing authorisations** following variation, transfer, renewal, suspension, revocation or withdrawal must be notified to the EMA no later than **30 calendar days** from the date on which the amendments have been authorised
- Common scenarios requiring updates:
 - Changes of QPPV, PSMF location, name of the product, composition, pharmaceutical form, MAH name, significant variations to section 4 of SmPC
 - If a QPPV is invalidated, the new QPPV has to be registered with EV and the MAH has to update their products referencing the new QPPV, else the EMA will follow-up with the non compliant MAH
 - In case of transfers, company A to invalidate their entries and company B to re-insert them with authorisation status “Valid – Transferred Marketing Authorisation”



Article 57 database – what is it for?

Performance of pharmacovigilance data analysis

Aggregated data analysis and signal detection in the EudraVigilance Data Analysis System (EVDAS) by establishing a repository of medicinal product and active substance information to support the coding of reported Individual Case Safety Reports (ICSRs)

Facilitate the coordination of regulatory decisions and fulfil legal obligations

Supporting referral procedures

Establishing a repository of Periodic Safety Update Reports (PSURs)

Medical Literature Monitoring

Calculation of pharmacovigilance fees

Communicate effectively with EMA's stakeholders

Exchanging data within EU and internationally

Facilitating the identification of alternatives in case of drug shortages

Enabling targeted communication between EMA committees (e.g. PRAC) and MAHs

Name of the medicinal product

- Product names in Art57 database:

Num	EV Code	Full Presentation Name	Product Short Name
✓ 0001	PRD616412	Nurofen 400 mg überzogene Tabletten	Nurofen
✓ 0002	PRD2899373	NUROFEN 200 mg, comprimé orodispersible	NUROFEN
✓ 0003	PRD3337627	NUROFEN GEL, gel 5%	NUROFEN
✓ 0004	PRD620594	NUROFEN 200 mg drajeuri	NUROFEN
✓ 0005	PRD636255	Nurofen, 200 mg, tabletki powlekane	Nurofen
✓ 0006	PRD701281	Nurofen 40 mg/ml Suspension zum Einnehmen	Nurofen
✓ 0007	PRD642987	Nurofen for Children Sachets 100mg/5ml Oral Suspension	Nurofen for Children
✓ 0008	PRD640453	Nurofen for Children Orange 200 mg/5 ml suspensija iekšķigai lietošanai	Nurofen for Children Orange
✓ 0009	PRD640872	Nurofen for Children Strawberry 200 mg/5 ml suspensija iekšķigai lietošanai	Nurofen for Children Strawberry
✓ 0010	PRD640816	Nurofen for Children Six Plus Strawberry 200mg/5ml Oral Suspension	Nurofen for Children Six Plus Strawberry
✓ 0011	PRD639050	Nurofen für Kinder Zuckerfrei 4% Suspension zum Einnehmen	Nurofen für Kinder Zuckerfrei
✓ 0012	PRD616416	Nurofen für Kinder suppo 125 mg, Zäpfchen	Nurofen für Kinder
✓ 0013	PRD616417	NUROFEN VOOR KINDEREN 200 mg omhulde tabletten	NUROFEN VOOR KINDEREN
✓ 0014	PRD627875	Nurofen voor Kinderen suikervrije suspensie	Nurofen voor Kinderen suikervrije



- Full presentation name as per section 1, in the local language of authorisation -> particularly useful as it provides the system with a large amount of information on how a product is potentially reported in ICSR
- [Guidance on the splitting of the medicinal product name](#)

Submission of PhV System Master File Location

- In accordance with Article 3 of Regulation (EU) No 1235/2010 (the pharmacovigilance legislation), **from 2 July 2015 MAHs are required to submit the Pharmacovigilance System Master File Location (PSMFL) information to the Article 57 database**
- To request an EV code for a PSMF, the following three characteristics need to be considered:
 - 1) Marketing authorisation holder
 - 2) Location of the PSMF
 - 3) Pharmacovigilance system
- The PSMFL EV code is given based on the relation between the three variables above and **does not solely identify the pharmacovigilance system master file**

Submission of PhV System Master File Location

- The PSMFL EV code is assigned at organisation level and will have to be referenced in each product entry owned by the MAH in the database (similar logic to QPPV)

Where the PSMFL details must first be submitted

XEVPRM Message

- Products
- Substances
- Sources
- Organisations
- ATC Codes
- Pharmaceutical Forms
- Routes Of Administration
- Attachments
- Master File Locations
 - Insert

Description	Name/Value	
Operation Type	Insert (1)	
EV Code		
Company		
Department		
Building		
Street		Field is Mandatory
City		Field is Mandatory
Region		
Post Code		Field is Mandatory
Country		Field is Mandatory
Comment		

Where the PSMFL EV code received must be referenced

XEVPRM Message

- Products
 - Insert - Authorised
- Substances
- Sources
- Organisations
- ATC Codes
- Pharmaceutical Forms
- Routes Of Administration
- Attachments
- Master File Locations

Description	Name/Value
EV Code	
Type	Authorised (2)
Is EMA Owned	
Operation Type	Insert (1)
New Owner ID	
MAH	
QPPV	
Master File Location	
PhV enquiry email	
PhV enquiry Phone	
Sender Local Code	
Info Date	
Authorisation Coun...	
Authorisation Proc...	
Master File Location	
Query Mode	Begins

Submission of PhV System Master File Location

- Changes in the location of the PSMF require update of PSMF details in PSMF section of XEVMPD
- Two MAHs using the same PSMF: each MAH request their own MFL code (as there is no visibility on other MAHs' codes) and list the code assigned to the PSMF of the other MAH in the PSMF Comment field

EV code	MFL10	MFL20
MAH	Company A	Company B
Location	Roma	Roma
Comment field	MFL20	MFL10














Documents

- [Article 57 leaflet in italiano](#)
- [Article 57 submission related documents webpage](#)
- Guidance on product information submission:
 - [Chapter 3.II: Extended EudraVigilance product report message \(XEVPRM\) user guidance](#)
 - [XEVMPD Data-Entry Tool \(EVWEB\) User Manual](#)
- [Guidance on the splitting of the medicinal product name](#)
- [Frequently asked questions](#)
- [XEVMPD training webpage](#)
- [EudraVigilance: how to register webpage](#)



Article 57 submission statistics

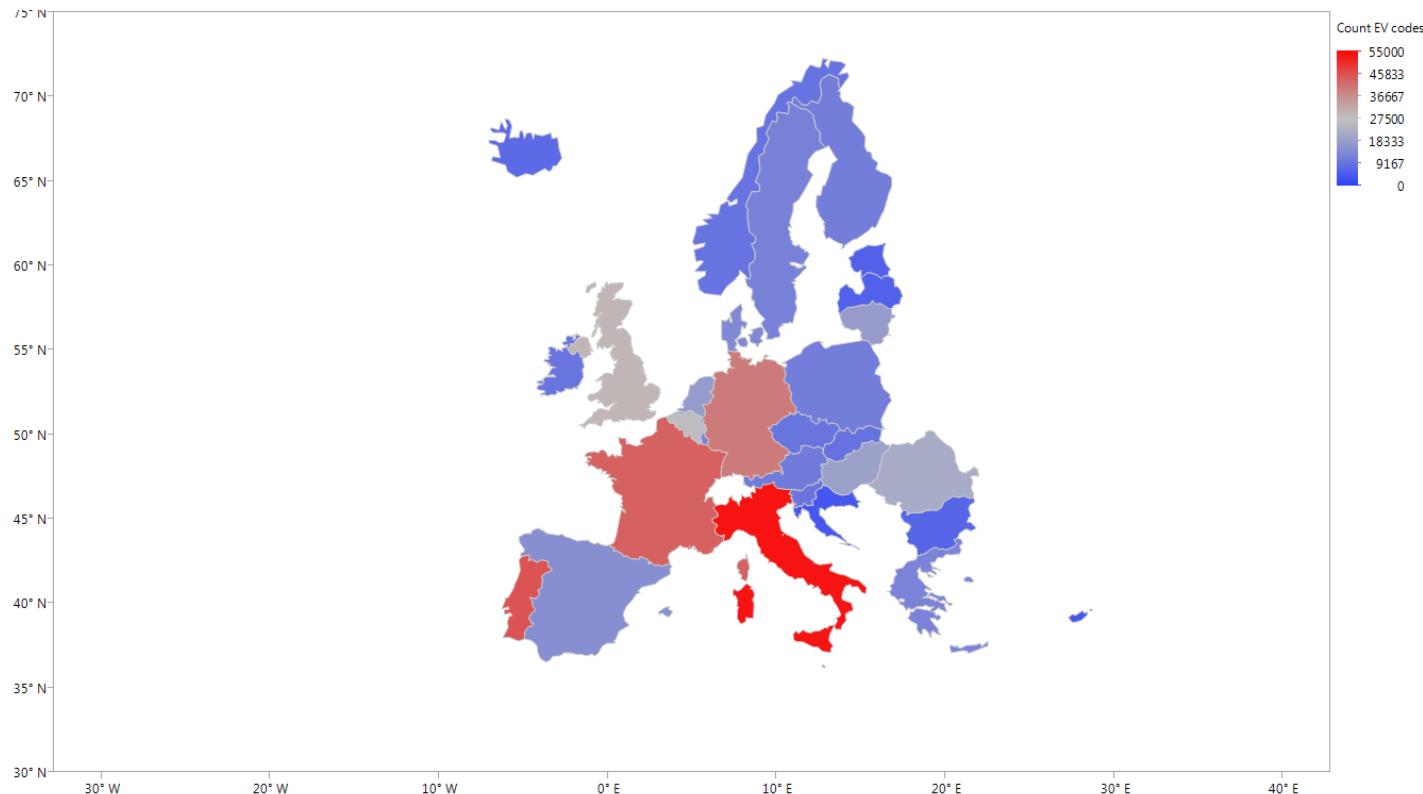
Count of product EV codes per authorisation status

Valid - Transferred Marketing Authorisation	 18,716	502,329
Valid - Suspended	 735	
Valid - Renewed/Varied Marketing Authorisation	 9,712	
Valid	 472,016	
Not Valid - Revoked by Competent Authority	 1,150	165,173
Not Valid - Not Submitted for Renewal by Marketing Authorisation Holder	 2,440	
Not Valid - Not Renewed by Competent Authority	 197	
Not Valid - Expired due to Sunset Clause	 9,799	
Not Valid - Superseded by Marketing Authorisation Transfer	 32,048	
Not Valid - Superseded by Marketing Authorisation Renewal/Variation	 7,631	
Not Valid - Withdrawn by Marketing Authorisation Holder	 113,058	



Article 57 submission statistics

Count of product EV codes per authorisation country



Quality assurance – how we manage it

- Since June 2014 a systematic assessment of the latest version of the received medicinal product data is performed by checking each data element against the information stated in the provided SmPC or equivalent document
- A product versioning system is set in place to handle the validation process:
 - Each version of the product is identified by the “owner” and a validity flag
 - Versions sent by EMA are marked as “valid”, subsequent updates by MAH as “pending”
 - All versions are kept in the system and can be used for future maintenance submission and reference

Version 1 (sender:
MAH)

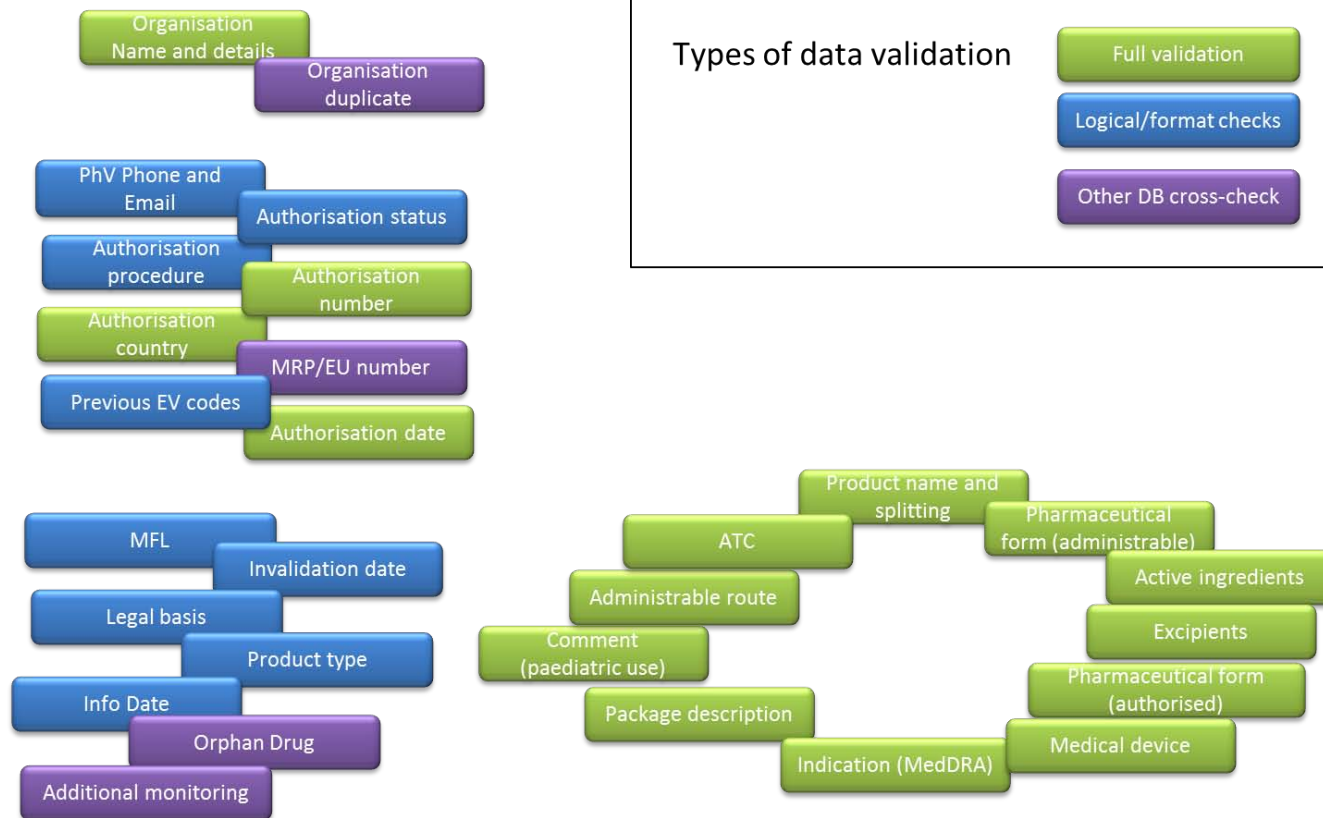
Version 2 (sender:
MAH)

Version 3 (sender:
EMA)

Version 4 (sender:
MAH)

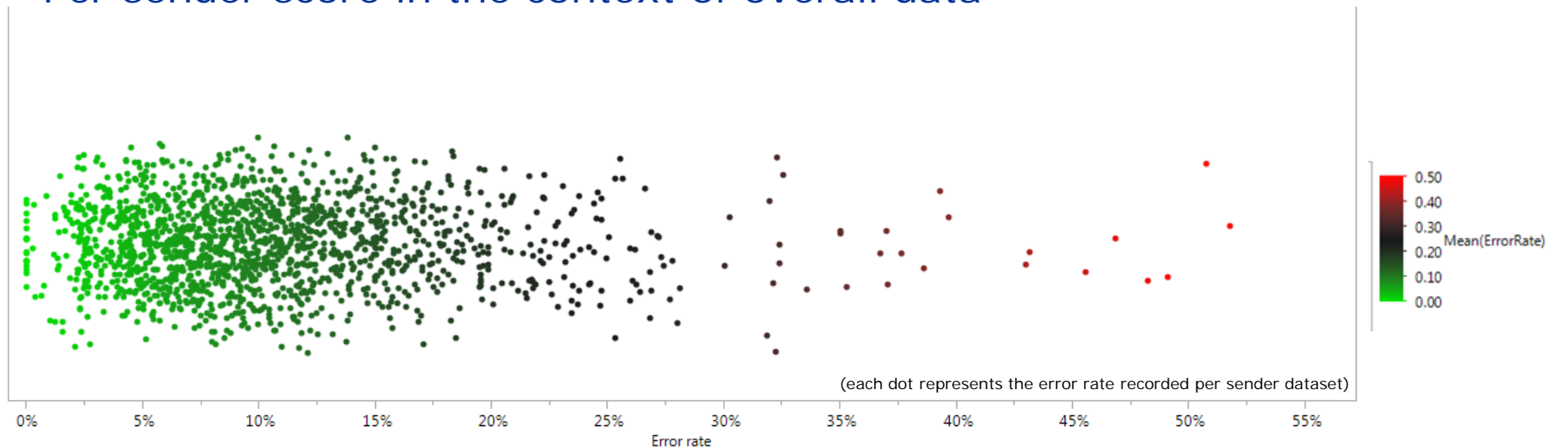


Quality assurance – how we manage it



Quality assurance visualisation

Per sender score in the context of overall data



- 11% average error rate found in MAH submissions
- 2% estimated error rate in entire database post EMA validation



Quality assurance - communication

- Open channel of communication: Art57-QC@ema.europa.eu
- Communications sent out proactively by EMA (most common reasons):
 - Product attachment needs updating (e.g.: SmPC missing, format unreadable)
 - Duplicate products are identified
 - Missing products are identified
 - Update of invalid QPPV information in product EV codes
- Summarised data quality reports were sent out routinely in 2015 (approx. 970 manually created reports) and currently they are sent on request
- Since November 2015 an automatic communication (3rd Acknowledgement) is sent via XEVMPD system (automated XML file in system, not an e-mail) when a product EV code is validated by EMA



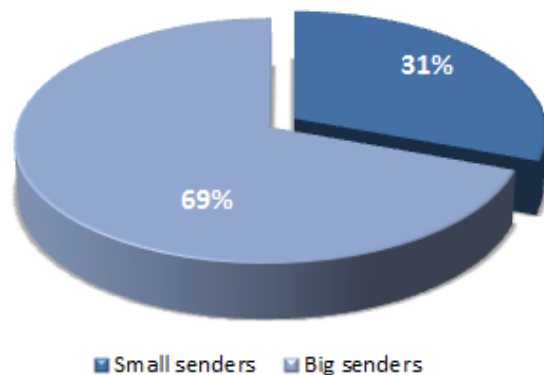
Completeness checks – comparison with NCA databases

- May 2015: EMA conducted a comparison of the data held in the Article 57 database against the data available in selected NCA (national competent authority) databases – Croatia, Ireland, Italy, Netherlands, Sweden
 - Results estimated 91% completeness of Art57 database
- Ongoing: EMA is currently running an extension of this initial mapping with 9 additional NCA databases – Austria, Belgium, Czech Republic, Denmark, Estonia, France, Iceland, Spain
 - Work in progress, the mapping for five of the above databases shows completeness around 97% (to be confirmed)
- To perform the mapping exercise, products are defined primarily by their authorisation number, secondary by the concatenation of “invented name” and authorisation country

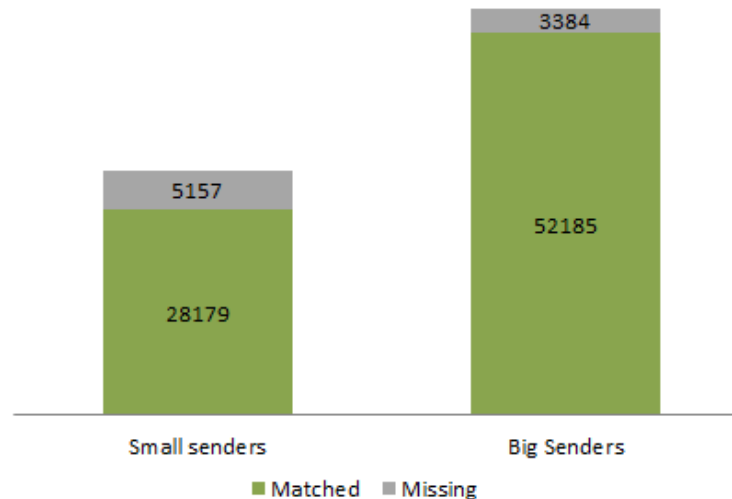
Completeness checks – comparison with NCA databases

- The results have shown a pattern of compliance related to the sender type, with a tendency for data to be missing for senders with a small numbers of products

Art57 structure by type of sender

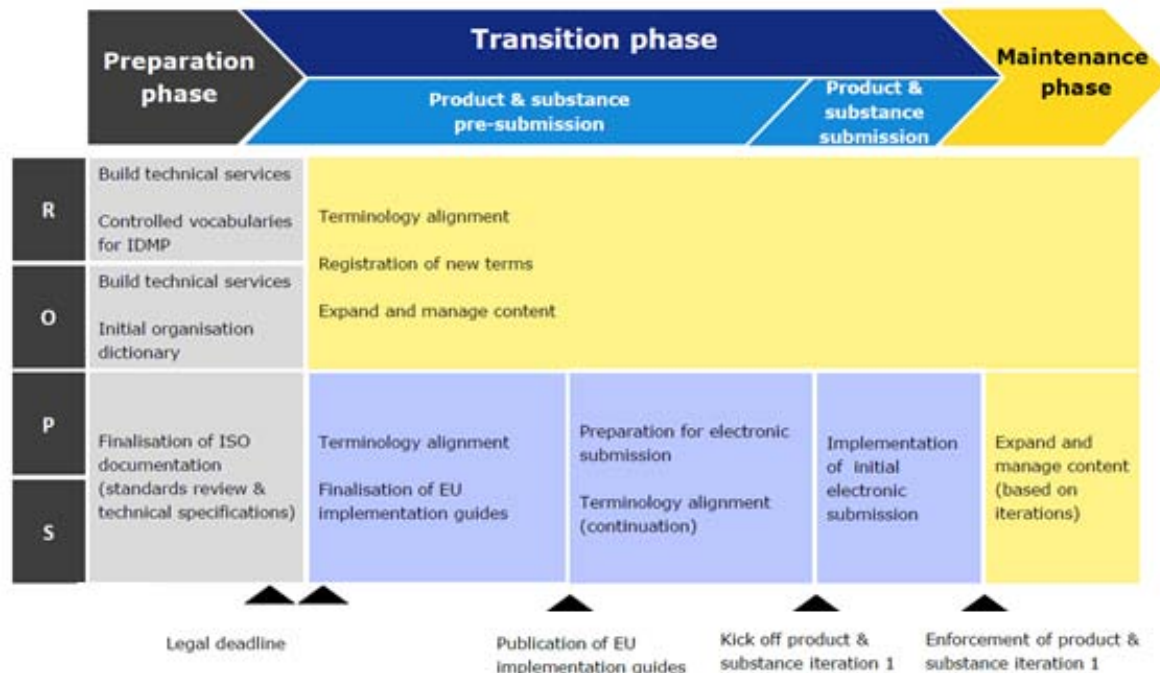


Proportion of missing data identified in NCA data



Article 57 database and transition to ISO IDMP

- A phased approach is planned for the transition to SPOR and compliance with the ISO IDMP format
- The current Article 57 structure will be expanded gradually in successive iterations
- Iteration 1 will expand to approx. 80 fields (discussions are still ongoing in the relevant forums)



Article 57 database and transition to ISO IDMP

- Information published on the [EMA website](https://www.ema.europa.eu/): implementation phases, timelines, minutes and agendas of the ISO IDMP Task Force



The screenshot shows the EMA website interface. At the top, there is the EMA logo and the text 'EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH'. To the right, it says 'An agency of the European Union' with the EU flag. Below this is a search bar with 'Text size: A A A' and 'Site-wide search' with a 'GO' button. There is also a 'Search document library' link and social media icons for Twitter, RSS, and YouTube. A navigation bar contains links: Home, Find medicine, Human regulatory (highlighted), Veterinary regulatory, Committees, News & events, Partners & networks, and About us. On the left, a sidebar lists: Pre-authorisation, Post-opinion, Post-authorisation, What we publish, Product information, and Scientific advice and. The main content area has a breadcrumb trail: Home > Human regulatory > Data submission on medicines > Implementation of ISO IDMP standards. The title 'Implementation of the ISO IDMP standards' is displayed with links for Email, Print, Help, and Share. The text states: 'The European Medicines Agency (EMA) is in the process of implementing the standards developed by the International Organization for Standardization (ISO) for the identification of medicinal products (IDMP). These are a set of common global standards for data elements, formats and terminologies for the unique identification of and the exchange of information on medicines. Following a phased implementation process, pharmaceutical companies will be required to submit data on medicines to EMA in accordance with these formats and terminologies.' To the right, under 'Related content', there are links: 'Data submission on medicines' and 'Implementing ISO IDMP: introduction to SPOR data services (4/8/2016)'.



Thank you for your attention

Further information

Contact us at:

Art57-QC@ema.europa.eu for data related queries

<https://servicedesk.ema.europa.eu> for guidance on submissions to Art57

European Medicines Agency

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom

Send a question via our website www.ema.europa.eu/contact

Follow us on  **@EMA_News**