ISO IDMP standards implementation. What should MAHs prepare for?

EMA has embraced the challenge of being the first agency to implement the ISO standards for the identification of medicinal products (ISO IDMP). As core component of this process, the Product Management Service (PMS) will become the central database for product information across the European Union. This transition is a significant change to the pharmacovigilance industry and requires thorough preparation from various stakeholders, including major input from the Marketing Authorization Holders (MAHs).

The PMS database will contain certain new PMS identifiers and a new set of data elements. They are described below.

PMS identifiers

A single medicinal product entry in Product Management Service (PMS) is determined by the first regulatory application to the relevant competent authority. This is further defined by a set of characteristics that defines a medicinal product as a single unique entry in the PMS database. Upon successful submission of product data to PMS, the system generates a set of unique identifiers:

- Each medicinal product is assigned a unique **Product Management Service ID (PMS ID)**, created upon the first submission of authorized product data. It's a digit-only identifier, generated automatically and remains unchanged throughout the product's lifecycle. Defining characteristics include regulatory submission number, country, active substance, form, strength, and name.
- The **Medicinal Product Identifier (MPID)** supplements the PMS ID, adhering to ISO standards. It includes a country code, marketing authorization holder code, and medicinal product code. Changes in these codes result in new MPIDs. The identifier ensures uniqueness in the system. Updates unrelated to regulatory submissions don't prompt new MPIDs. Additional defining characteristics may be added later without altering the MPID.
- For each Packaged Medicinal Product, a unique **Packaged Medicinal Product Identifier (PCID)** shall be assigned by the system at the time of the successful submission of the medicinal product data in PMS. This is supplementary to any identifier/existing authorisation/approval number at package level assigned by the relevant competent authority.

PMS data elements

The Product Management Service (PMS) Implementation Guide presents more than 150 data elements that belong to 6 categories by type:

1. Medicinal product;
2. Marketing authorisation information;
3. Therapeutic (product) indication;
4. Packaged medicinal product;
5. Ingredient;
6. Pharmaceutical product.

As seen in figure 1, most of data elements belong to Medicinal product and Packaged medicinal product categories.

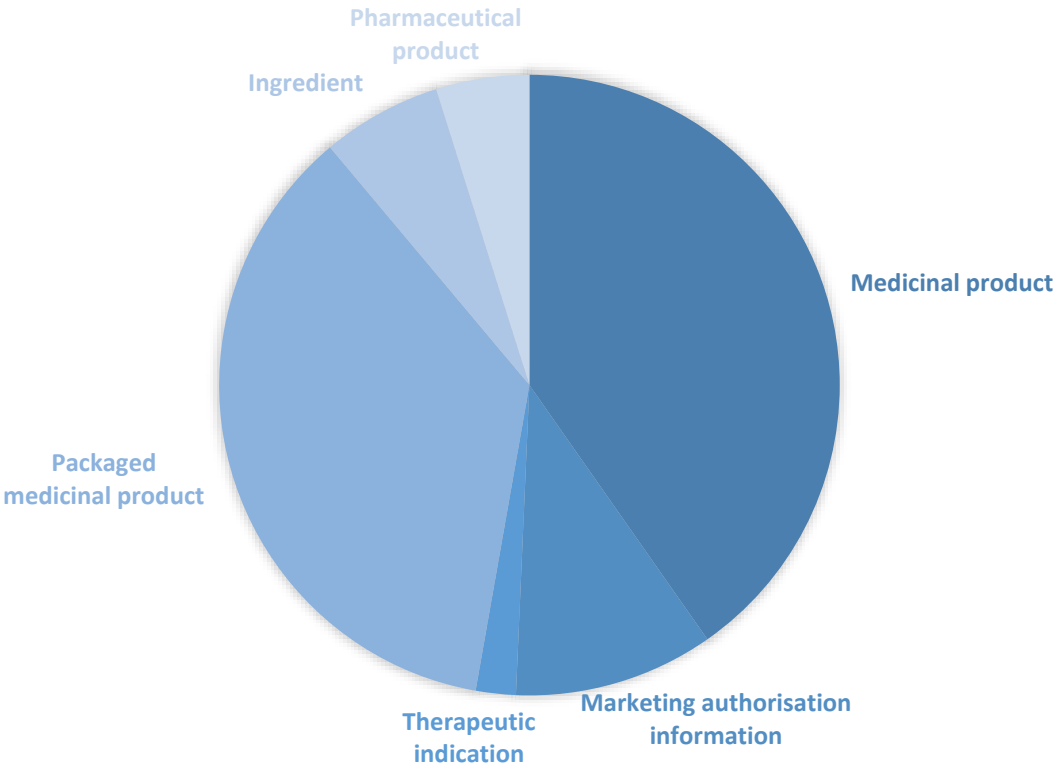

Figure 1. Data elements by type

Each category is described below.

Pharmaceutical product

This is a category comprising of 58 data elements. Each authorized medicinal product must contain at least one pharmaceutical product, representing its composition approved for patient administration. Pharmaceutical products may consist of multiple components, including active ingredients, excipients, and adjuvants.

Marketing authorisation information

In this section comprising of 15 data elements, details about marketing authorisation are provided. Marketing authorisation is granted by a competent authority within a specific region to an organization that has applied for it. This process, known as the marketing authorisation procedure, allows the organization to place a medicinal product on the market in that region. In the European Union (EU) and the European Economic Area (EEA), national competent authorities (NCAs) grant marketing authorisation for human medicines within their respective territories. The European Commission grants marketing authorisation for applications submitted through the centralised procedure, covering the entire EU.

Products authorised in Iceland, Liechtenstein, and Norway, following EU procedures, require separate entries. Medicines approved in Northern Ireland, under the UK, need registration referencing "United Kingdom (Northern Ireland)". Liechtenstein recognizes Austrian and Swiss marketing authorizations, but only those from Austria fall under EU regulations. Swiss approvals recognized by Liechtenstein are outside EU legislation and exempt from submission.

Therapeutic (product) indication

This section introduces 3 data elements, 2 of them mandatory, and the quidance on how therapeutic indications will be managed. In Iteration 1 of the PMS implementation, certain elements highlighted in a red rectangle are within scope and must be provided following the rules and guidance outlined here. The Therapeutic Indication class is mandatory and repeatable, while other attributes must be filled out where applicable but cannot be repeated (except for the Co-morbidity data element). The details provided specify how diseases, symptoms, or procedures authorized for treatment should be coded using MedDRA terms. Additionally, guidance is given on specifying co-existing conditions and the intended effects of treatment, all following specific data coding conventions and standards. Examples are provided to illustrate the application of these rules in different scenarios.

Packaged medicinal product

This section outlines the information required for describing ingredients of a manufactured item and pharmaceutical, consisting of 52 data elements.

Ingredients of manufactured items and pharmaceutical products should be selected from the list of relevant ingredients.

Key points to consider:

- Attributes such as Ingredient Role, Origin of the Substance, Composition Grouping Description, Manufacturer, and Substance are specified.
- The manufacturer of active substances and adjuvants should be selected from a list of manufacturers based on manufacturing business operations.
- Information about substances, including their strength (quantitative composition), should be provided based on a numerator and denominator value and unit. Strength should be specified based on regulated product information without performing any calculations or conversions.

- Specific requirements exist for substances like esters or pro-drugs.

Pharmaceutical product

Each authorized medicinal product must contain at least one pharmaceutical product, as per ISO standards for medicinal product identification in Europe. A pharmaceutical product includes the qualitative and quantitative composition of a medicinal product in its approved form for patient use. It may consist of one or more components, including active ingredients, excipients, and adjuvants. The administrable pharmaceutical form is the final form for patient administration after manufacturing transformations. Only the final forms given to the patient are included in data records. Detailed information on active ingredients, excipients, and adjuvants should be provided based on standardized documentation, ensuring data alignment across regulatory documents. Alignment between supporting documentation enhances data quality in the Product Management Service (PMS). The Summary of Product Characteristics serves as the main reference document for data entry of the fields of this data category, this shall ensure consistency in pharmaceutical product data.

PMS data without migrated information

Among the must-fill fields, a total of 38 remain without migrated information and thereby will not transition from SIAMED or XEVMPD. While some of these fields, such as specific identifiers, are system-generated, the majority of them need to be extracted from alternative sources. This is the summary of guidance related to these mandatory fields, provided by EMA:

1.2. Medicinal product identifier (MPID) – This attribute is automatically generated and maintained by the PMS system.

1.9.5. Market Exclusivity start date – The date when the market exclusivity of the orphan medicinal product starts shall be specified where applicable and shall reflect the date of the authorisation of the first indication. The date of start of the market Product Management Service (PMS) - Implementation of International Organization for Standardization (ISO) standards for the identification of medicinal products (IDMP) in Europe EMA/285848/2020 Page 46/231 Tag Description exclusivity of the orphan medicinal product can be found in the individual product entry at the EC Register of medicinal product accessible via this link.

1.13.4. Medicinal product category – Indication on the type of medicinal product should be included to indicate on whether the medicinal product is biological, vaccine, ATMP, chemical or other product types based on the nature of active substance or combination of substances. The applicable value(s) shall be selected from the term ID as listed in the applicable Referentials Management Service (RMS) list.

1.18.1.1. Identifier value – The ID assigned to the document once it is uploaded to the PMS system, which refers to the medicinal product, shall be specified. This identifier is specific to this version of the document. This unique identifier may be used elsewhere to identify this version of the document. Refer to Annex 9.1.1 of SPOR API technical specifications v2 Not applicable in the case of Nationally Authorised Products during Step 1 of implementation of the TOM, unless the medicinal product data is chosen to be submitted via API.

1.18.1.2. Identifier system – The source system relevant to the attached documentation can be specified. The term "Product Management Service" shall be provided as a term ID from the Source of Information RMS list.

1.18.3. (Attached Document) Type – The value indicating the type of document shall be specified as a term ID. The applicable value shall be selected from the term ID as listed in the applicable Referentials Management Service (RMS) list. In case where the approved SmPC does not state an authorisation number, a date of authorisation/renewal or the MAH, a copy of the document granting or renewing marketing authorisation (i.e., Letter of authorisation) should also be provided as an additional attachment. This list is to be updated with additional required values.

1.18.6. URL value (New) – The URL of the document as identifiable in the Document API of PMS.

1.18.7. (Attached document) Status (New) – This field is mandatory in the FHIR specification. The value 'current' shall be used always.

1.19.1. Product cross-reference type – If applicable, the type of medicinal product that is referenced shall be specified as a term ID. The applicable value shall be selected from the term ID as listed in the Referentials Management Service (RMS) list. This list is to be updated with additional required values.

1.19.2. Product Cross-Reference resource identifier – The PMS ID of the medicinal product that is referenced shall be provided. This applies to products under specific legal basis (e.g., Generic, Hybrid, Biosimilar). Any reference in the resource identifier cross-reference section shall not be a nullified version of the medicinal product. This section is mandatory in case that product reference type is selected.

3.10.5.2. Regulatory application type – The type of regulatory application shall be described using a term ID. The applicable value shall be selected from the term ID as listed in the applicable Referentials Management Service (RMS) list. In case of grouping of variations, the application submission type with the highest ranking of variation shall be selected. This value is an attribute within the Regulatory application procedure Identifier/Number.

4.3. Intended effect – The intended effect (i.e., the part of the indication that describes the result/type of outcome intended for the target condition), aim or strategy to be achieved by the indication as reflected in Section 4.1 Therapeutic Indications of the corresponding SmPC or other regulatory document shall be specified using an RMS term ID. The applicable value shall be selected from the term ID as listed in the applicable Referentials Management Service (RMS) list. Note: Special attention should be given to situations where a drug is indicated also for treatment and not only for prevention. If a medicinal product is also authorised for the treatment of a disease, then the respective disease should also be coded.

4.4.1. Quantity operator – The applicable value corresponding to the quantity operator shall be specified as term ID. The applicable value shall be selected from the term ID as listed in the applicable Referentials Management Service (RMS) list.

4.6.1. Country – The country code of the country where the product is marketed/not marketed should be specified as a term ID. The value(s) shall be selected from the term ID as listed in the applicable Referentials

Management Service (RMS) list. In the case of CAPs, all individual countries of the EU where the product is marketed/not marketed should be selected.

4.6.2. Marketing Status – The status of the marketing of the medicinal product may be specified as a term ID. The value(s) shall be selected from the term ID as listed in the Referentials Management Service (RMS) list.

4.6.7.1. Reason –The information related to the reason of any action taken on the unavailability of the authorised medicinal product on the market of the given European Union (EU) member state shall be specified to prevent the risk of supply shortage. Information shall be provided in cases when the authorised medicinal product is temporarily unavailable (i.e., temporary cessation) or withdrawal of the product from the market (i.e., non marketed).

4.8.6.1. Identifier value – The outer-most packaging carrier identifier (GTIN/NTIN/PPN) should be specified.

4.8.6.2. Identifier system – The source system relevant to the reported identifier can be specified. The applicable term shall be provided as a term ID from the Source of Information RMS list.

4.10.1. Type of medical device used in combination with medicinal product – The type of medical device used in combination with medicinal product shall be specified when using a term ID if applicable. The applicable value shall be selected from the term ID listed in the applicable Referentials Management Service (RMS) list.

4.10.2. Medical device type – The Type of the device or device system of the medicinal product shall be specified when using a term ID if applicable. The applicable value shall be selected from the term ID listed in in the applicable Referentials Management Service (RMS) list.

4.10.5. Medical device quantity – The quantity (number of units) of the device(s) in the medicinal product package, shall be specified as a value and units (as per section 6.5 of the SmPC). If RMS list “Unit of presentation” does not contain the applicable type of device, the term “countable unit(s)” from Unit of Measurement List shall be selected.

4.10.5.1. Quantity operator – The applicable value corresponding to the quantity operator shall be specified as term ID. The applicable value shall be selected from the term ID as listed in the applicable Referentials Management Service (RMS) list.

4.10.6. Medical device description – The high-level description of the applicable medical device shall be reported in this data element. Information comprehensive of the different and single component(s) of the medical device used (i.e., smart tools etc.) shall also be provided, when available. Products authorised through MRP/DCP/NP routes: The medical device description is to be provided in English or in the local language(s) of authorisation, or optionally in all of them. Products authorised through the centralised procedure The medical device description is to be provided in English.

4.10.6.1 Language – The language of the medical device description as specified in previous section shall be specified. The applicable value shall be selected from the term ID as listed in the applicable Referentials Management Service (RMS) list.

4.10.7. Medical device description of intended purpose – The description of the intended purpose of the type of medical device shall be reported in this data element. The description of the intended purpose shall reflect the text as reported in the CE certificate released by the relevant Notified Body. Products authorised through MRP/DCP/NP routes.

4.10.7.1 Language – The medical device description of intended purpose is to be provided in English or in the local language(s) of authorisation, or optionally in all of them. The medical device description of intended purpose is to be provided in English.

4.10.8. Medical device classification – The relevant classification of the type of medical device shall be specified by using a term ID, as applicable. The applicable value(s) shall be selected from the term ID as listed in the applicable Referentials Management Service (RMS) list.

4.10.9. Medical device manufacturer – The reference to the relevant Manufacturer of the medical device shall be selected from the list of manufacturers recorded in section 1.20 Manufacturing business operation.

4.11.2.1. Quantity operator – The applicable value corresponding to the quantity operator shall be specified as term ID. The applicable value shall be selected from the term ID as listed in the applicable Referentials Management Service (RMS) list.

4.11.5.1. Language – The language of the manufactured item description, as approved by the regulatory authority and indicated in the corresponding regulatory document(s) shall be specified as a term ID. The applicable value shall be selected from the term ID as listed in the applicable Referentials Management Service (RMS) list.

4.12.1. Shelf Life Type – The type of the shelf life such as the shelf life applicable to the whole Packaged Medicinal Product itself, or more granular values such as the shelf-life after transformation, shelf life after the initial opening of a bottle or any other scenario covered in the product information, shall be specified as a term ID from the Shelf Life Type List in the Referentials Management Service (RMS) list. This information is to be completed as per section 6.3 – Shelf life of the SmPC and section 2.2.3 of the electronic application form (eAF). This field is repeatable to cover multiple different Shelf-Life conditions.

4.12.2. Shelf Life Time Period and Units – The shelf life time period shall be specified using a (1) numerical value for the period and (2) its unit of time measurement. Multiple shelf life periods may be listed for different types. This information is to be completed as per section 6.3 – Shelf life of the SmPC and section 2.2.3 of the electronic application form (eAF). This field is repeatable to cover multiple different Shelf-Life conditions. This field is an attribute within Shelf Life Type.

4.12.3. Special Precautions for Storage – Special precautions for storage of the relevant Package Item Container of the packaged medicinal product should be specified using the appropriate value(s). The controlled term and the controlled term identifier shall be specified. The term “This medicinal product does

not require any special storage condition" shall be selected if no special precautions for storage apply to the packaged medicinal product. This information is to be completed as per section 6.4 – Special precautions for storage of the SmPC and section 2.2.3 of the electronic application form (eAF). This field is repeatable to cover different Storage Conditions per Shelf life.

5.5.4.1. File type – The applicable type of master file should be specified. The applicable value shall be selected from the term ID as listed in the applicable Referentials Management Service (RMS) list.

5.5.4.2. File code – The file code shall always refer to the current version to the last submitted version. The File code sub-class and its attributes are mandatory and not repeatable.

5.5.4.2.1. File identifier type – The applicable certificate provided by the relevant Competent Authority following successful submission shall be specified in PMS. The file code shall always refer to the current version to the last submitted version.

6.5.4.2.2. File Identifier – The applicable identifier as assigned by the relevant Competent Authority following successful submission shall be specified in PMS.

6.5.4.3. Submission date – The date when the certificate was submitted to the relevant Competent Authority shall be specified.

Transition to PMS: latest recommendations

In January 2024, EMA published the Chapter 9 of the PMS guide defining process for submitting existing data to PMS on medicinal products authorised for human use. The guide outlines the set of rules for transition from SIAMED or XEVMPD to the PMS system. They are summarized below.

SIAMED to PMS

SIAMED is an internal EMA database that contains centrally authorised products. It is maintained by EMA and once the regulatory procedures (variations, transfers of marketing authorisation holder, line extensions, etc.) are approved, the relevant data is updated or included as new. This database plays a critical role in maintaining accurate product information, with updates reflecting regulatory procedures such as variations, transfers of marketing authorization holders, and line extensions.

The set of rules driving the SIAMED to PMS:

- Updates in SIAMED II adhere to specific mapping rules and cover additions like new presentations and changes in manufacturers.
- These updates are swiftly propagated to PMS, ensuring synchronization between the two systems.
- Applicants can rectify inaccuracies via system Service Now, ensuring seamless correction processes.
- SIAMED II is a primary data source, complemented by rules governing data from other sources like XEVMPD, for comprehensive product information management.

XEVMPD to PMS

The set of business rules driving the XEVMPD to PMS:

- XEVPRMs with positive 2nd acknowledgments are processed; negative acknowledgments are not sent to PMS.
- EMA data stewards oversee XEVMPD data validation and may standardize data, with resulting changes submitted to PMS.
- Deltas from XEVMPD to PMS are intended to be processed almost in real-time, but delays may occur due to queue processing. If changes take longer than a day to reflect in PMS, users should raise a ticket in Service Now.
- PMS data for a medicinal product with multiple packaged products is overwritten by each EV code from XEVMPD.
- If a term in XEVMPD isn't mapped to a SPOR term, its value in PMS remains 0 until mapping is established.
- Currently, updates to PMS data are only possible through SIAMED and XEVMPD submissions; EMA aims to transition away from XEVMPD submissions once direct PMS updates are enabled.

Match and merge for CAP products

For successful transition from XEVMPD and SIAMED to PMS, the data needs to be matched and merged from both sources. It is important to note that two medicinal products will only be matched when all presentations in XEVMPD match the presentations from SIAMED II. Also, The MAH (LOC ID) in SIAMED II and XEVMPS must be the same.

What to prepare for in nearest future?

In February 2024, EMA shared guidance outlining the expectations for MAHs in the near future. One significant aspect of this guidance is the anticipation that PMS will incorporate both CAP and non-CAP product data by the Q2 of 2024. To ensure the efficient functioning of this process, several essential processes are currently under development:

1. **SIAMED II data mapping and initial data migration:** Integration of SIAMED data mappings with other SPOR (Substance, Product, Organization, and Referential) services such as SMS (Substance Management Service), OMS (Organisation Management Service), and RMS (Referential Management Service), along with the initial migration of data. This process is performed by EMA.
2. **XEVMPD data mappings and initial data migration of CAPs and non CAPs.** Similar to the SIAMED II process, this involves mapping XEVMPD data with other SPOR services and conducting the initial migration of CAPs and non-CAPs. Specific business rules govern this migration process, including considerations such as authorization status and required fields within the records. Some business rules provided by EMA:
    a. Only latest version of non-nullified records is migrated to PMS.

b. Authorization status should not be "Not Valid – Superseded by Marketing Authorization Transfer" or "Not Valid – Superseded by Marketing Authorization Renewal/Variation" for successful migration.
c. Records must include certain mandatory fields like Authorised Pharmaceutical Form, Legal Basis, and Medicinal Product Type to be migrated successfully.

3. **Match and merge of CAP products across SIAMED II and XEVMPD** – To ensure the smooth operation of this process, typos, legacy terms and splittable terms should be taken into consideration when checking data in XEVMPD, by selecting correct term or updating XEVMPD to use approved standard term. EMA highlights the importance of splittable terms – they must be corrected in XEVMPD to refer to more than one term. It is also critically important to ensure that MAH (LOC ID) in SIAMED II and XEVMPD are the same. Notably, only EU records from XEVMPD will be considered for matching.

To avoid incorrect data migration which could result in delays of eAF application submission and impact CAP procedures such as parallel distribution, inspections, etc., EMA recommends the following steps that should be followed before the Q2 of 2024:

1. **Familiarize with the EU IDMP Implementation Guides.**
2. **Check the XEVMPD data to avoid Data Quality issues:**
    a. Authorisation Status – check it not only for valid but also for withdrawn records. Transferred records shall have the status "non valid – superseded by MA transfer"
    b. Legal basis – cannot be null/empty
    c. Product full name – check that product full name is consistent (no spaces, typos etc.) across similar/grouped EV codes;
    d. Authorisation number – for CP ensure it aligns with Annex A.
    e. EU number – for CAPs should be the same as the Authorisation number.
    f. MRP/CP number – for CP ensure it aligns with Annex A and for BE products is consistent across frouped EV codes.
    g. Authorised Dose Form – check mapping across EV and RMS.
    h. Administrable Dose Form – refers to the dose form administered to the patient (might not be the same as the authorised dose form).
    i. Active substance – check mapping to SMS, If SVG flag = 0 select another substance for the product.
    j. Strength – shall be consistent among EV codes to be grouped.
    k. MAH – check mapping to OMS (LOC ID). If missing/wrong, open a request in Service Now to correct the mappings.
    l. Packages – ensure all packages for CAPs are entered separately (one EV code per package), even if they were withdrawn or surrendered.
    m. Grouping – for records grouped by name, check that EV codes belonging to the same medicinal product have the same name, active substance and strength. For records grouped by MA number, check that EV codes belonging to the same medicinal product have the same MA number, same active substance and strength.

n. It is advised to use XEVMPD or the export tool to extract full list of EV codes in Excel or CSV to see full information.

3. **Ensure any Data Quality findings are permanently solved.**
   a. EMA will contact QPPVs requesting the update of XEVMPD to solve data quality issues. MAHs must ensure that QPPV/company email is monitored and that data is corrected in XEVMPD system. It must be ensured that emails from Art57-QC@ema.europa.eu are not sent to spam folder.
   b. MAHs shall review the 3rd Ack after EMA performs validations and if needed, update their systems. If they don't agree with the change, a ticked should be raised to system Service Now.
   c. For records where "Product vailidity" is "Not Assessed", the reason should be reviewed why it was not assessed. It might be a duplicate of another record or there is missing information/documentation.
4. **Support web-based eAF**
   a. XEVMPD can also have products not in scope of Art. 57 such as herbal or homeopathic products. If needed in a variation form, MAHs can submit these products to XEVMPD following instructions in chapter **3.II** in XEVMPD.
   b. If needed, pack sizes for medicinal products where the MA number is assigned at medicinal product level can be suubmitted as well. Package description in XEVMPD should be populated correctly.
   c. Pending MRPs and DCPs will be submitted to XEVMPD when eAF allows NAPs variations.