Medicinal Product Data Standardisation – Prerequisite for Efficient Data Exchange Between Stakeholders and Impact on the (Inter)National Health Systems

Medicinal Product Data Standardisation in the Agency for Medicinal Products and Medical Devices (HALMED)

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Abstract - The authors describe challenges and learnings in the process of refactoring internal system for tracking the records of marketing authorization procedures and medicinal product database in the Agency for Medicinal Products and Medical Devices (HALMED) in order to comply with ISO IDMP (International Organization for Standardization, Identification of Medicinal Products) standards. HALMED's plans include the medicinal products data model reconstruction, user interface adaptation, changes on the synchronization processes and establishing connection with SPOR (Substances, Products, Organisation and Referentials) data management services. In a response to the introduction of the ISO IDMP set of standards, the EMA (European Medicines Agency) initiated the SPOR data management service project, with the objective to provide the framework for standardization and structured data in medicinal products description.

Keywords – health informatics; ISO IDMP; SPOR; Substances Management Services; Products Management Services; Organisations Management Services; Referentials Management Services; UNICOM; EMA.

I. Introduction

Medicinal products identification is a global challenge: healthcare stakeholders at each medicinal product life-cycle stage are capturing in their information systems different sets of data, using different codebooks, different languages, and even different abbreviations to describe medicinal products. Simple example might be pharmaceutical form described as "Film-coated tablet" that can be presented as "Coated tablet," "Tablet," or even "Tabl." or "Tbl.". The same product might be available in different countries with different dosage strengths and package sizes, under different brand names. Even the same name might identify different products [1]. Suppose a patient has to take a drug prescribed by a doctor in his/her home country while visiting another county, where drug with the same brand name is not available. The question is whether the adequate replacement drug could be dispensed. Re-identification of medicinal products might be challenging due to insufficient data on the prescription or to unreadable data due to the language barrier or just different terminology and types of data used to describe medicinal products. When an inappropriate drug replacement is dispensed, patient's safety might be jeopardized and the worst possible outcome might be adverse drug reactions [2].

Covid-19 pandemic has shown the importance of introducing "univocal global identification (named Pharmaceutical Product IDentifier or PhPID) as foreseen in the ISO/CEN suite of IDMP standards. The requirement is supported for all medicinal products by the FDA (U.S. Food and Drug Administration) and by EMA, and facilitated by the EU Innovation Project UNICOM" [3].

EC Regulation (EU) 520/2012 (articles 25 & 26) [4] is addressing the above-described challenges by requiring national competent authorities in EU and Marketing Authorization Holders (MAHs) to apply the ISO IDMP standards for identification of medicinal products.

ISO IDMP standards were introduced with the goal to have a standardized set of drug information across the world, across regulatory and medicinal communities, with the aim to fulfil a need in much wider health care areas. The standards were developed by the International Organization for Standardization (ISO) in cooperation with the International Council for the Harmonization of Technical Requirements for Pharmaceutical Products for Human (ICH), Health level Seven (HL7) and many other international stakeholders and experts [5][6]. ISO IDMP consists of five *Health Informatics – Identification of Medicinal Products* standards that were initially published in 2012 [7][8][9][10]:

- ISO 11615 — Data elements and structures for the unique identification and exchange of regulated medicinal product information;
- ISO 11616 — Data elements and structures for the unique identification and exchange of regulated pharmaceutical product information;
- ISO 11238 — Data elements and structures for the unique identification and exchange of regulated information on substances;
- ISO 11239 — Data elements and structures for the unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation, routes of administration and packaging;
- ISO 11240 — Data elements and structures for the unique identification and exchange of units of measurement.

Besides preparing an EU IDMP Implementation guide [13], EMA has established the SPOR data management services (**S**ubstances, **P**roducts, **O**rganisation and **R**eferentials) [11][12]. These management services should ensure that all EU stakeholders are using the same value sets for substances, organisations and referential data (*dose forms, units of measurement, units of presentation, routes of administration)* [14].

Although EMA provided an EU Implementation guide [15], complying with the EC Regulation (EU) 520/2012 (articles 25 & 26) requires the national agencies to design a strategic plan for data management. Such a plan requires significant resources in terms of time, subject matter experts and financial resources. [16] Besides performing a detailed analysis of internal business processes and the assessment of data required by other healthcare stakeholders in order to get the required set of medicinal product data, other important tasks need to be fulfilled: the current data model used in medicinal product database should be evaluated, user interface reconstruction should be considered and data must be corrected, standardized and mapped or replaced with the terms and codes of the SPOR value sets.

In this article we describe the approach and experience of the HALMED in refactoring its information system in order to comply with ISO IDMP standards. We believe it will be instrumental to support other agencies planning their road to ISO IDMP compliance and will also contribute to solve the global challenge of medicinal products identification.

In Section II, we describe the background and challenges related to deficiencies in data model of IT system for marketing authorisation processes and medicinal product database in HALMED. In Section III, we describe the initial step of our project of standardization of medicinal product data in HALMED (defining master data set for medicinal product identification). In Sections IV and V we focus on the analysis of the results and on the plan for the refactoring of the current IT system. Next planned steps and preliminary conclusion are provided in Sections VI and VII.

II. BACKGROUND AND CHALLENGES

HALMED is the Croatian national competent authority that provides regulatory services pertaining to medicinal products, medical devices, homeopathic medicinal products and certain aspects of veterinary medicinal products in accordance with the legislation of the Republic of Croatia.

In 2010, HALMED started to build its own IT system to support marketing authorization processes and its medicinal products database, called NRL (abbreviation for Nacionalni Registar Lijekova, i.e., National Medicinal Products Registry). It was decided that the medicinal products database should be based on the data model described in RDM 3.0 model (Reference Data Model published by EMA), that was confirmed as good practice at that time. As the original RDM data model has a lower sophistication level then the ISO IDMP data model, medicinal products are not described with the level of granularity expected for data exchange in the future EU medicinal products database. For instance, the current data are insufficient for cross-border e-prescription exchange. Currently the medicinal product

packaging is described with just a couple of descriptive text fields, and not with the structured data described in ISO 11615 standard [17], on the base of which the EU Implementation guide [18] has been prepared.

Consequences: data exchange with other healthcare stakeholders in the country or abroad is either not possible or very limited or needs to be performed manually. Even internal processes that rely on medicinal products data are missing essential information. For example, data that describe medicinal product packaging is essential for the process of calculating maximal wholesale price based on the comparable medicinal products' prices from reference countries. Each medicinal product packaging from a reference country could be considered the same as domestic packaging if it has the same active substance, the same strength, the same pharmaceutical dose form [33][34], and the same pack size as the domestic packaging. From the listed attributes, the biggest challenge is to compare the packages themselves, especially while in the medicinal products database (that is used for list of domestic products) in internal system called NRL-PKL-PhV (PKL stands for Provjera Kakvoće Lijekova, i.e., Medicinal Products Quality Control and PhV stands for Pharmacovigilance), packages are described with just two descriptive text fields. There is no data describing the container, its volume and whether the vial is for single or multiple use. Standardized description of units of presentation is missing, as is the quantity of pharmaceutical product in the container, the number of containers in package, etc., etc.

A. Description of the IT system at HALMED for core business processes and medicinal product database

NRL system has been developed as a Web-based application that consists of a database, a Web interface, and Web services for integration with other internal IT systems. Although HALMED's IT systems have been developed and upgraded in phases over the years, they are all interconnected with the services for data exchange and automation of process tasks, so that users are enabled to carry out all steps required for a business process via only one application – their core business process application. All process documents are stored on DAIS (Digitalni Arhivski Informatički Sustav, i.e., Digital Archival Information System) [36][37], HALMED's Enterprise Content Management System built on IBM FileNet, and accessed directly from NRL. HALMED used to receive marketing authorisation applications documentation in paper form and those documents were then digitized, enriched with metadata, stored on DAIS and made accessible directly through the NRL application. Through Web services, the system is also connected with the other HALMED's systems such as the filing system (Centrix), Archival Management System (Pismohrana) and invoicing system, so users can complete all their tasks within one interface.

Over the years, the NRL system, built to support medicinal products marketing authorization processes, has grown and even became integrated with two other internal systems that rely on the same medicinal products data into one system called NRL-PKL-PhV.

That system supports core business processes:

- Case tracking for marketing authorization procedures (tracking of all procedural phases, tracking of deadlines and tasks completed by assessors, supporting the Committee for Medicinal Products processes, business reporting).
- Pharmacovigilance tasks (Risk Minimization Measures (RMM) and Referral procedures).
- Inspectorate activities related to planning and executing medicinal products sampling, quality control of medicinal products (Human and Veterinary) in the Official Medicines Control Laboratory (OMCL) (filing incoming samples, sample analysis and analysis task assignment, reagent management and management of standards, reporting of results and filing outgoing documents) [19].

NRL-PKL-PhV system (as shown in Figure 1) consists of three applications that share the same user interface, database, document store on DAIS, administration tools, and codebooks (referential lists). The latter are daily synchronized with SPOR RMS (Referentials Management Services) [20][21] by using the Application Programming Interface (API) lists and EUTCT (European Union Telematics Controlled Terms) substance list.
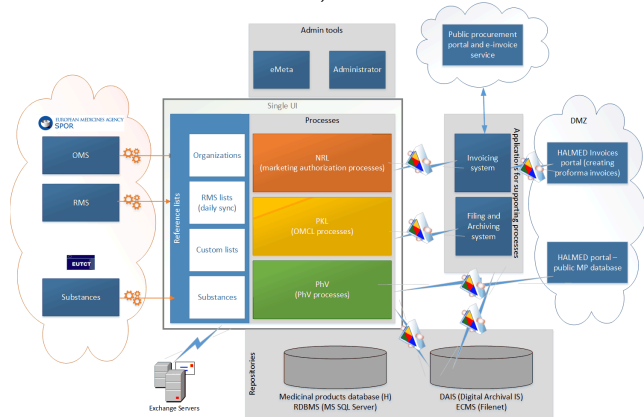

Figure 1. NRL-PKL-PhV system

In order to be able to capture all necessary data describing medicinal products, HALMED had to decide on the best pathway to ensure full compliance with ISO IDMP standards: either by building a new system up from the scratch or either by refactoring the old NRL system. HALMED considered on one hand that medicinal product data stored in NRL-PKL-PhV were not yet exchanged with other national-wide eHealth systems and on the other hand that a number of very complex processes were already supported by the system developed over the years. HALMED decided thus to opt for a refactoring of the NRL-PKL-PhV system, resulting in the reconstruction of the data model, the adaptation of the user interface, and the modification of the synchronisation processes.

With the decision to undertake a NRL-PKL-PhV system refactoring, new questions arose about the complexity and the quality of the data used up to then.

III. ANALYSIS OF THE MASTER DATA SET AND RECONSTRUCTION OF THE DATA MODEL

In order to better understand the business needs, all the processes that rely on the medicinal product data were thoroughly analysed. Besides the NRL-PKL-PhV system, that is supporting above mentioned processes, the following additional processes utilize medicinal products data:

- Calculating the maximal wholesale price of medicinal products,
- Granting authorizations for parallel imports of medicinal products,
- Giving approval for entry and importation of medicinal products and for emergency entry and importation of medicinal products.

The Master data set for medicinal product was defined after a number of workshops with subject matter experts, resulting in a thorough analysis of internal processes that generate or utilize medicinal products data. In addition, requests from external consumers of medicinal products data were analysed.

When defining the master data set, we also analysed the data models described in ISO IDMP standards. First and the most frequently used in our analysis was the ISO 11615:2017 for the unique identification of regulated medicinal product information [17]. When it came to questions on how to describe complex compositions of pharmaceutical products, ISO 11238:2018 [22] was studied for deeper understanding of Substances identification data and ISO 11616:2017 [23] for Pharmaceutical Product information.

During the process of drafting NRL-PKL-PhV system refactoring plan, we obtained very valuable guidance through the EU Implementation Guide v.2.1 [15] where all the medicinal product data that are required by EMA for future PMS (Products Management Services) and medicinal product data exchange are described with full details.

Relying on the results of the analysis of processes utilizing medicinal products data, a detailed assessment of current data model was performed, resulting in a thorough comparison with ISO IDMP standards (especially ISO 11615 for medicinal product [17]) in order to detect the gaps. First findings have shown two important refactoring areas:

- Packaged Medicinal Product: Manufactured Item (and its composition) should be introduced into the data model, as well as Packaging Item (Container) and Device
- Pharmaceutical Product needs some adjustments: mandatory specification of the modifiers for chemical substances; introduction of Specified substance (for proteins and biologicals) and Strength (Reference Strength as Presentation and Concentration strength were already implemented).
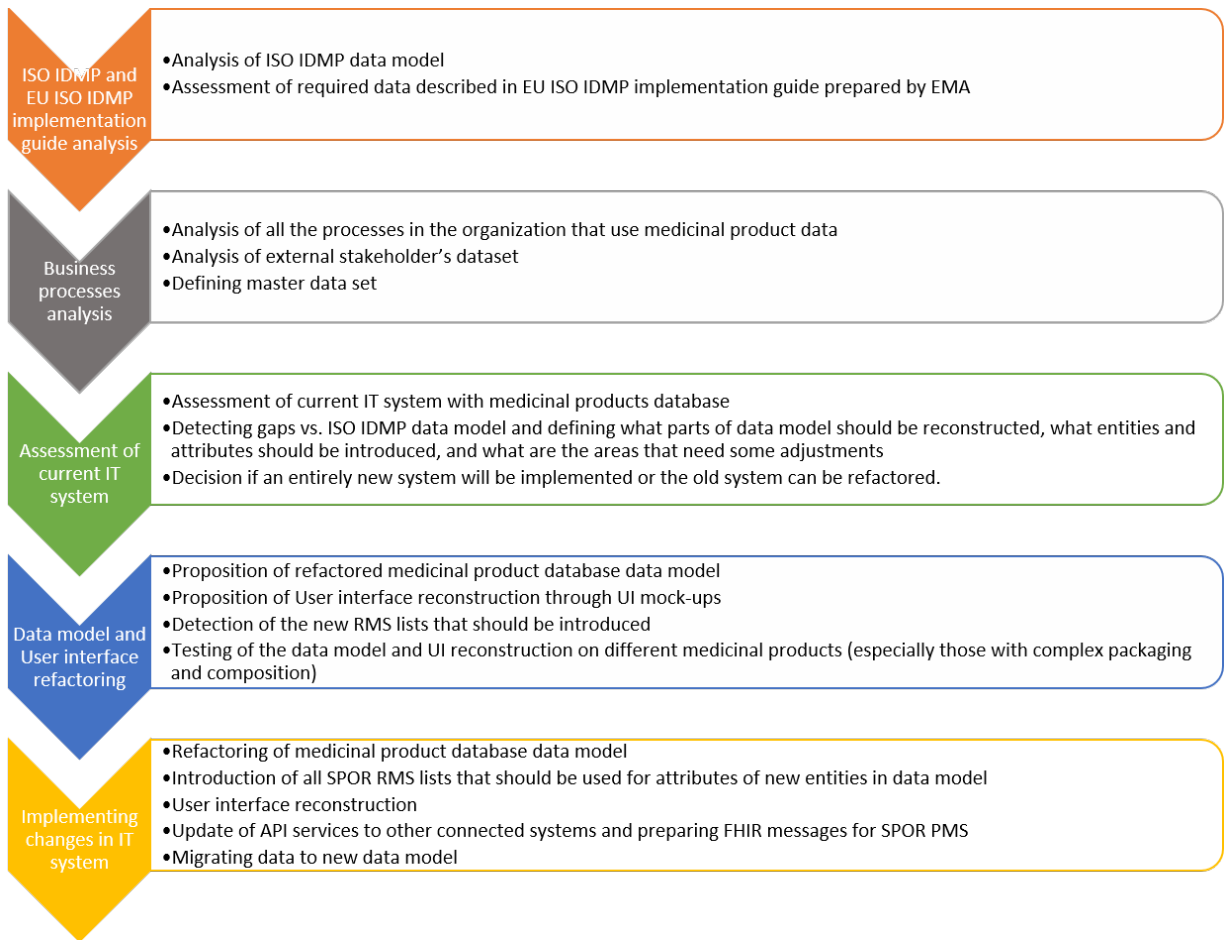
ISO IDMP and EU ISO IDMP implementation guide analysis
- Analysis of ISO IDMP data model
- Assessment of required data described in EU ISO IDMP implementation guide prepared by EMA

Business processes analysis
- Analysis of all the processes in the organization that use medicinal product data
- Analysis of external stakeholder's dataset
- Defining master data set

Assessment of current IT system
- Assessment of current IT system with medicinal products database
- Detecting gaps vs. ISO IDMP data model and defining what parts of data model should be reconstructed, what entities and attributes should be introduced, and what are the areas that need some adjustments
- Decision if an entirely new system will be implemented or the old system can be refactored.

Data model and User interface refactoring
- Proposition of refactored medicinal product database data model
- Proposition of User interface reconstruction through UI mock-ups
- Detection of the new RMS lists that should be introduced
- Testing of the data model and UI reconstruction on different medicinal products (especially those with complex packaging and composition)

Implementing changes in IT system
- Refactoring of medicinal product database data model
- Introduction of all SPOR RMS lists that should be used for attributes of new entities in data model
- User interface reconstruction
- Update of API services to other connected systems and preparing FHIR messages for SPOR PMS
- Migrating data to new data model

Figure 2. The methodology of refactoring internal IT system and medicinal product database in order to comply with ISO IDMP standards

After thorough analysis of the current data model, ER (Entity Relationship) diagrams and restructured data models were prepared for Packaged Medicinal Product and for Pharmaceutical Product. In the next section the reconstruction plan for Packaged Medicinal Product is described in more details.

Analysis has shown that the data set defined in the EU Implementation Guide [15] was sufficient with the exception of some additions like Specified Substances and some physical characteristics of containers and devices.

The whole process and methodology of refactoring internal system with medicinal product database, in order to comply with ISO IDMP standards, is shown on Figure 2.

A. Reconstruction of data model related to Packaged Medicinal Product

On Packaged Medicinal Product ER diagram (Figure 3) we colour-coded the entities:
- Red rectangles are those entities that should be introduced in currently implemented data model (Device, Packaging item (container) and Manufactured Item)

- Yellow rectangles would need some adjustments (Packaged Medicinal Product, Pharmaceutical Product, Ingredient),
- Green rectangles are already compliant with ISO standards (Medicinal Product and Substance):
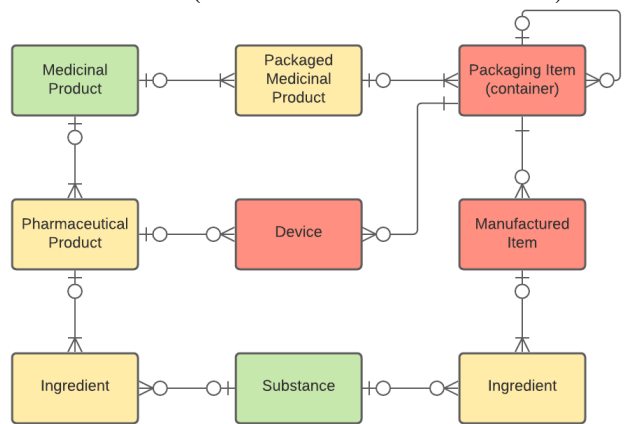

Figure 3. Entity Relationship Diagram: Packaged Medicinal Product

As for the user interface (UI) reconstruction, on tab "Packaging" (both in the module where medicinal product

data can be reviewed and in module for case management) changes should be made that enable:

- Input of more Packaged Medicinal Products (i.e., outer packages)
- Input of more Package Items (Containers) with the possibility of copying data from existing Package Items
- Input of Devices with possibility of copying data from existing Devices
- Input of Manufactured Items with possibility of copying data from existing Manufactured Items
- Input of Ingredients for Manufactured Items: Substance and Specified Substance, with the Strengths and Reference Strengths (concentration and presentation)
- Copying/relating Ingredients for Manufactured Items and Ingredients for Pharmaceutical Products.

In Sections III.A.1) - III.A.3) the introduction of new entities is described in more details.

1) Introduction of a new entity in the data model: Container

When introducing Container as new entity in the data model, the following aspects need to be considered (Figure 4):

- Container can have zero or more Containers that are referencing it as parent.
- Container can be referenced by different Devices or Manufactured items.
- Attributes that are describing Container: Container Type, Material and Quantity should be added to the data model.
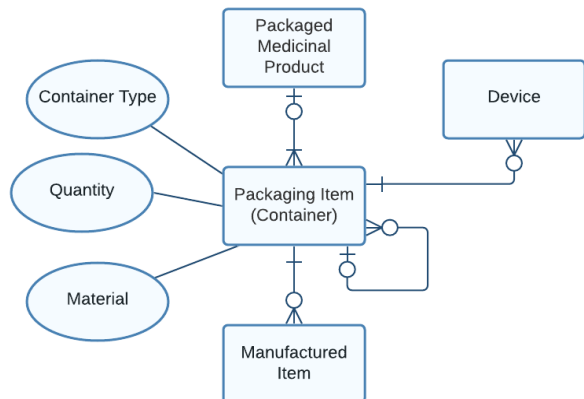
Figure 4. Entity Relationship Diagram: Packaging Item (Container)

2) Introduction of a new entity in the data model: Device

There are two possible relationships between Device and Package Item (Figure 5):

- The medical device is integrated and contains the medicinal product for administration (e.g., pre-filled syringes, pre-filled pen). In this case Device is also the primary packaging/package item container for the medicinal product.
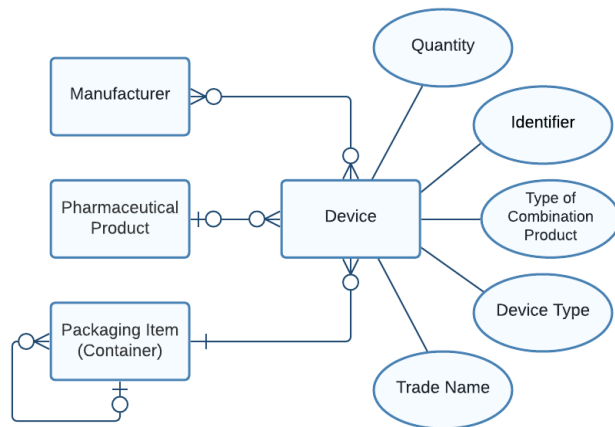- Device as independent element contained within secondary packaging (for example in outer box).

Figure 5. Entity Relationship Diagram: Device

3) Introduction of a new entity in the data model: Manufactured Item

Manufactured Item is the product as it is authorised and before transformation into the administrable pharmaceutical form [18].
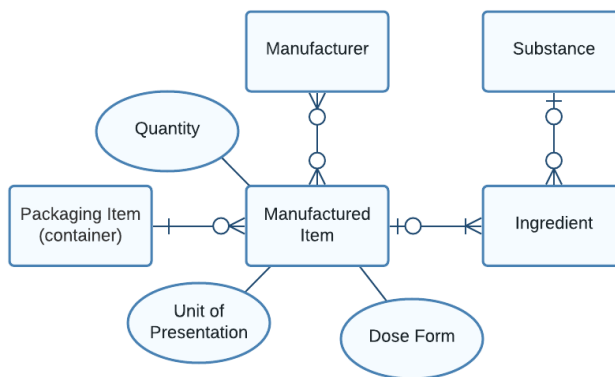

Figure 6. Entity Relationship Diagram: Manufactured item

When introducing Manufactured Item as new entity in the data model (Figure 6), following attributes that are describing Manufactured Item should be introduced: Dose Form, Unit of presentation, Quantity.

B. Reconstruction of the data model related to Pharmaceutical Product

In the Pharmaceutical Product entity relationship diagram (Figure 7), red rectangles are those entities that need to be introduced in the currently implemented data model (Manufactured Item, Device, Strength (Presentation, Concentration)); yellow ones are those that need some transformation (Pharmaceutical Product, Ingredient, Reference Strength (Presentation, Concentration)) and green ones are those that don't need any changes (Medicinal Product, Substance and Administrable Dose form).
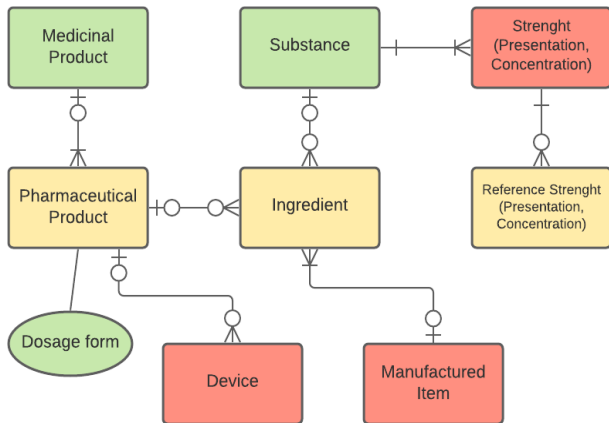
Figure 7. Entity Relationship Diagram: Pharmaceutical Product

Reconstruction activities related to Pharmaceutical Product should include the introduction of new entities in the data model: Specified Substance; Strength (presentation) and Strength (concentration); also, the user interface needed reconstruction so that Strength (presentation) and Strength (concentration) could be recorded, as well as the Specified Substances. Reference strength (presentation) and Reference strength (concentration) needed to be migrated to new database tables.

The structure of related tables currently enables data entry for the majority of entities, but does not (fully) comply with ISO IDMP data model. The Ingredients table should be thoroughly analysed and, based on findings, new table structure and relations should be defined, as well as data migration.

Pharmaceutical Product name/description is necessary when medicinal product has more than one Pharmaceutical Product and currently, in many cases, this is not recorded in the correct form (physical characteristics plus units of presentation).

In the next section of this paper, the transition to SPOR RMS referential lists for internal codebooks is described.

IV. INTRODUCTION OF RMS REFERENTIAL LISTS

In order to ensure data consistency in describing medicinal products, common referential lists (codebooks) should be used. Fortunately, HALMED has been using EUTCT lists [24] for internal codebooks from the early stages of NRL system development and those codebooks were synchronized on a daily basis. Table 1 shows the EUTCT lists that were used in marketing authorisation processes and related NRL lists.

Until recently, it was allowed to add user-defined terms in NRL-PKL-PhV codebooks. Planning for transition to RMS lists requires assessment of different scenarios:

- Codebooks with EUTCT terms and no custom-added terms
- Codebooks based on EUTCT lists and with user added terms
- Custom codebooks in NRL-PKL-PhV system
- Introduction of new RMS codebooks to NRL-PKL-PhV system (no codebooks were used)

TABLE 1 EUTCT LISTS THAT WERE USED IN MARKETING AUTHORISATION PROCESSES

EUTCT list	NRL codebook
Substance (still in usage)	Tvari
Country	Države
Dosage Form Category	Grupe farmaceutskih oblika
Dosage Form	Farmaceutski Oblici
Units of Measurement	Jedinice mjere
Route of Administration	Put primjene
Authorisation Status	Registracijski status lijeka
Marketing Status	Status lijeka na tržištu
Ingredient Role	Vrste sastojaka
Container	Vrste pakiranja
Supply	Mjesto izdavanja
Legal Status for the Supply	Način propisivanja
Special Precaution for Storage	Uvjeti čuvanja
Quantity Operator	Operatori količine

Different scenarios related to the usage of the codebooks and the associated implementation steps are described in Sections IV.A - IV.D. In all the described scenarios, we consider an automatic daily synchronisation with the Referentials Management Services via the Application Programming Interface (API).

A. Codebooks with EUTCT terms and no custom-added terms

In the case of internal codebooks that were synchronized with EUTCT lists (no longer allowing custom-added additional terms), transition to RMS lists started with the detection of corresponding items in the RMS SPOR list. In the NRL-PKL-PhV system, changes to the database (adding new fields for RMS list) and user interface were made. In order to keep the record of the change of localized terms, term versioning was introduced, and likewise for the three other scenarios, as described in Section IV.E.

B. Codebooks based on EUTCT lists and with user-added terms

For user-added terms, we performed a data cleansing, deactivating user-added terms and disabling the possibility of adding new custom terms in the codebook. After detecting the corresponding RMS list, all necessary changes were made in database and user interface. For data cleansing and for mapping old terms to RMS terms, a custom-made administration tool was used.

C. Custom codebooks

Before connecting to corresponding RMS list, data quality analysis and data cleansing were performed; all the changes in database structure and user interface were also completed so that the new RMS list could be imported and custom (old) terms mapped with RMS terms and redundant terms could be deactivated.

D. Introduction of new RMS codebooks to NRL-PKL-PhV system

Business experts with the IT team are continuously assessing the RMS referential lists and are prioritizing their adoption in NRL-PKL-PhV system. Reconstruction of the database and changes in system functionalities were only introduced once a full agreement had been reached on the final RMS list.

During the data model reconstruction, introduction of new RMS lists should be planned, based on the entity's attributes.

E. Term versioning in internal codebooks

With the introduction of RMS lists, SPOR and NRL term versions are stored separately in internal codebook. That intermediary step is needed as the old terms cannot be changed before the product information documents are officially changed. This requires a new submission by the Marketing Authorisation Holder. Until then, old terms remain intact and NRL users are being informed about the term change via an e-mail notification (Figure 8). Moreover, users are also notified in the user interface: on the status bar of the opened case and/or medicinal product (Figure 9) and on the list of terms in the field where it appears (Figure 10). Besides, in the search engine both old and new term versions are detectable.

Figure 8. Localized term versioning – e-mail notifications
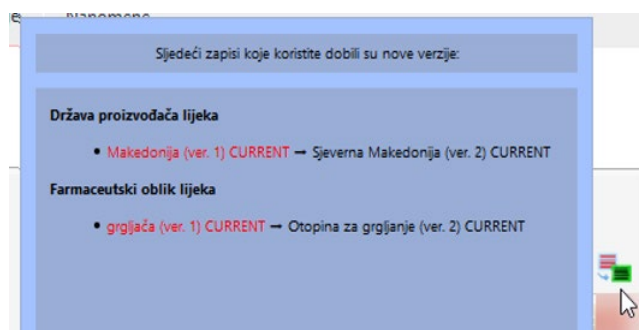

Figure 9. New term indicated on status bar

Old terms are displayed in red letters when they appear in the user interface and in drop down lists. In marketing authorization application for a new medicinal product, only new terms will be shown on all lists (Figure 10).
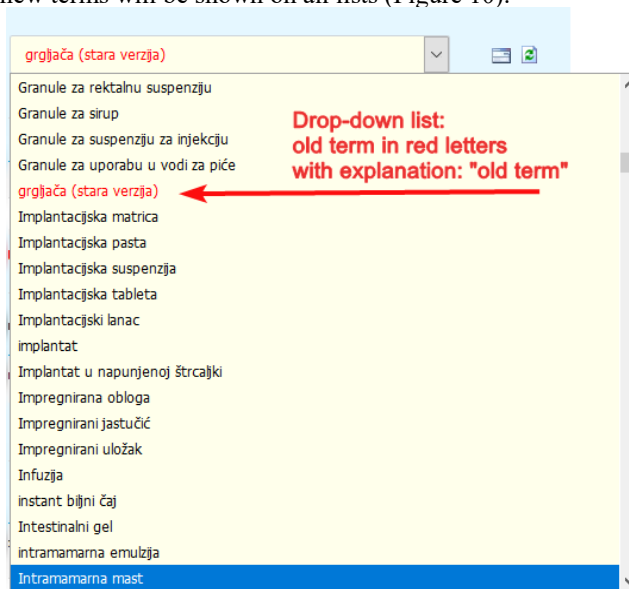

Figure 10. Indication of old term version in use

V. USER INTERFACE RECONSTRUCTION

In following paragraphs, proposed changes in user interface are described.

A. Packaged Medicinal Product

During the marketing authorisation procedure HALMED is allocating a unique Marketing Authorisation Number to a Medicinal Product and that number will not change during the whole Medicinal Product life-cycle, regardless of changes on the product name, marketing authorisation holder or any other data. Furthermore, all packaging's of the same medicinal product are designated with a packaging digit code (from 01 to 99) and with the Marketing Authorisation Number of the Medicinal Product, followed by the packaging digit code. These elements together are forming the Marketing Authorisation Number for Packaging. In the NRL-PKL-PhV system, all packaging of the same medicinal product are listed in one tab in the module *Medicinal product list (Središnji podaci o lijekovima)* and in the module *Processing applications (Obrada predmeta)*. Currently in the "Packaging" only a few descriptive text fields are available so this tab should be reconstructed in order to enable entering all data for Packaged Medicinal product.

The proposed solution is to introduce a hierarchical tree-list grid (Figure 11) for the presentation of all the levels of Medicinal Product Package data:

- from outer package
- containers inside outer package,
- containers inside containers,
- devices that might be included in outer package or in container,
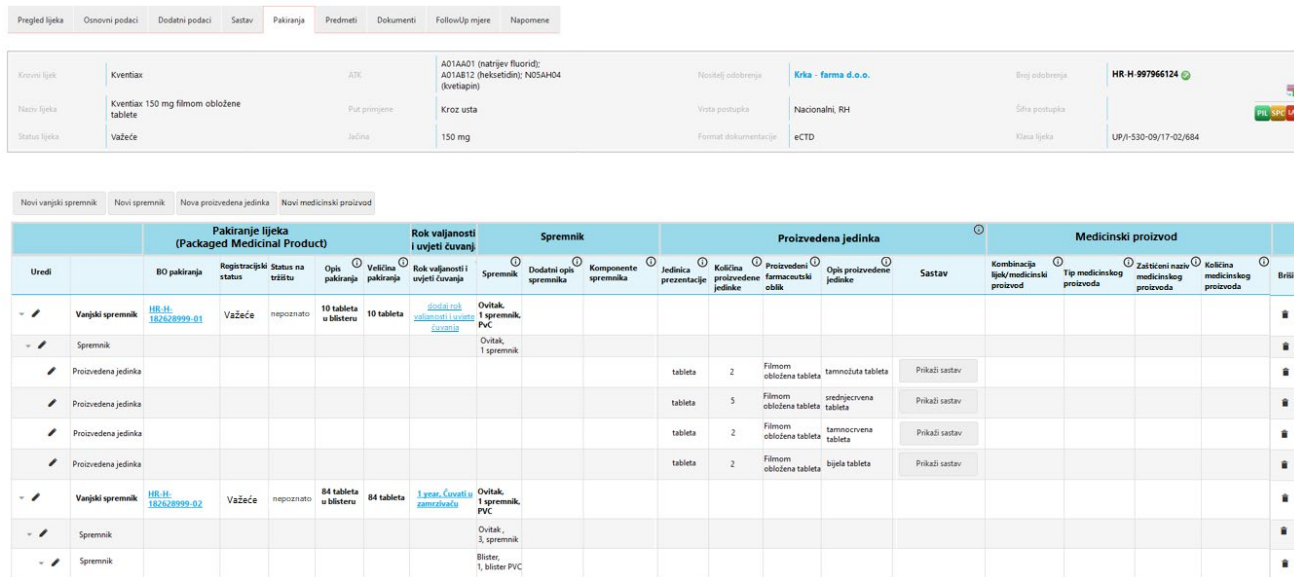- integral or co-packed device.

Figure 11. Packaged Medicinal Product – proposed UI (user interface) mock-up

The tree-list ends on the level of immediate container with details about the manufactured item and its composition. Furthermore, all additional attributes like shelf life and special precautions for storage will be visible in the grid, often with concatenated values from more fields that were used to describe the entity. For example, for the presentation strength, all data entered in separate fields (fields: Quantity operator, Strength (Presentation single value or low limit) - numerator and denominator, Strength (Presentation high limit) - numerator and denominator) in the pop-up will be presented in one field on grid Manufactured Item composition Strength (Presentation) as shown on Figure 12.

Adding data for new outer packages, containers, devices and manufactured items will be enabled with new buttons positioned above the grid. For editing, the pen symbol on the left edge of the grid opens the same pop-ups. Each pop-up consists of text fields, such as fields for the description of outer packages or manufactured items. In addition, there are fields with controlled number values and fields controlled by drop down lists where only the attributes from RMS reference lists would be available for selection.

While the Medicinal Product could have more packaging's that might be similar in their components, the user will be able to copy data from one outer packaging / container / device / manufactured item to the other in order to save time for entering all the required details.

Composition of Pharmaceutical Product is currently presented via the tab "Ingredients," where Substances and Reference Strengths (concentration and presentation) are recorded. In the reconstructed user interface, adding and editing Specified Substances and Strengths (concentration and presentation) are enabled and a very similar solution will be implemented for capturing Manufactured Item composition.

Dialog boxes for adding and editing information about the Manufactured item and Pharmaceutical product composition facilitate the definition of the Ingredient role (for e.g., substance (or ingredient) with the role of precise active substance, excipient…), adding Substance and/or Specified Substance and describing their Strength (Presentation and Concentration) and Reference Strength (Presentation and Concentration) (Figure 13).
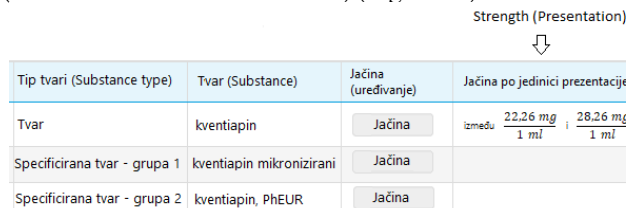

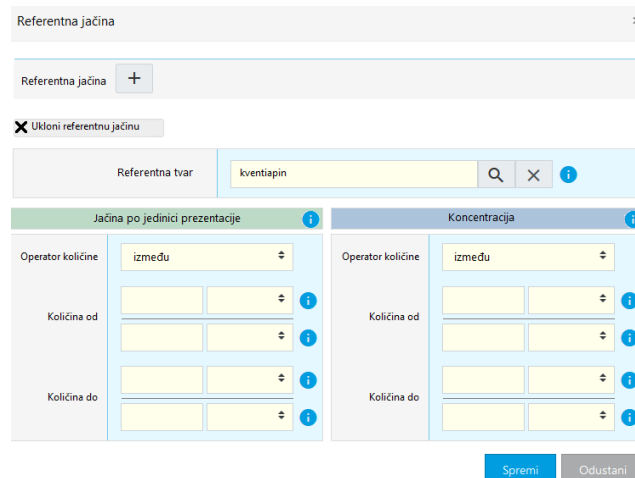Figure 12. UI mock-up: Manufactured item composition

Figure 13. UI mock-up for Manufactured item composition editing pop-ups (adding reference substance and strength)

For a significant number of medicinal products, the Pharmaceutical Product composition and the Manufactured item composition would be the same and the plan is to enable copying composition data for some or all substances and strengths from one to another.

VI.   FURTHER WORK

The work presented in this document is just the beginning of the refactoring of the current system, step one on the Figure 14. This refactoring is relying heavily on the assessment of internal business processes which are generating or utilizing medicinal product data and on the thorough analysis of the gaps in the data model of the current system, in comparison with the data model provided by the ISO IDMP standards. Besides data model reconstruction and user interface adaptation, connection to the new RMS referential lists that are used to describe medicinal product packages should be established; and this is also needed for SMS (Substances Management Services) and future PMS (Products Management Services). In order to make this effective, applications that will send and receive data from future PMS and which receive substance data from SMS, will be programmed using FHIR (Fast Healthcare Interoperability Resources). [25][26][27][28] Moreover, web services will be built to send data from the HALMED database to the national medicinal product dictionary database that is part of the EU funded project eLijekovi [32].
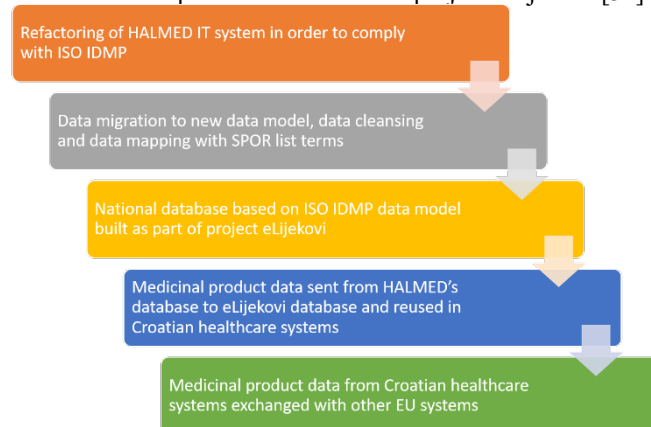

Figure 14. The process and the impact of HALMED IT system refactoring on national and EU wide healthcare systems

VII.   CONCLUSION

The complexity of the processes related to the marketing authorisation of medicinal products and to the production of reliable medicinal product data is immense. It implies taking into account different healthcare stakeholders and their activities and processes that are utilizing data in different medicinal product life-cycle stages. The more obvious ones are prescribing, capturing patients' medical records and dispensing but there are many others. It also implies dispensing the products that are prescribed in another country where the same product is registered with different brand name, or the same brand name is used for a completely different medicinal product.

The possibility of uniquely identifying medicinal products globally [29] is becoming top priority, as was demonstrated by the need of tracking the global use of COVID-19 vaccines during the pandemic [3]. The cross-border mobility scenarios where e-prescriptions and patient summaries would be easily exchanged between countries offer a unique opportunity of getting closer to this ultimate goal, with direct positive impact on patients' safety[3][30].

With the introduction of the ISO IDMP set of standards, EMA initiated the SPOR project to define four domains of master data in regulatory processes: Substance, Products, Organisations and Referentials [9]. RMS lists and OMS (Organisations Management Services) organisations registry are ready to use while SMS and PMS are expected to become available soon for substance and medicinal products data exchange. The UNICOM project (funded by the European Union's Horizon 2020 research and innovation program under grant agreement No 875299) is an essential accelerator of the ISO IDMP standards implementation. Its ambition is to improve patient safety by ensuring that "any medicine and what it contains can be accurately identified anywhere in the world." The project gathers 40 partners representing all the actors of the value chain. 11 participating National Medicines Authorities are concretely experimenting ISO IDMP implementation; together they build a common understanding of what needs to be done towards successfully implementing IDMP, and how to learn from each other and share best practices.   [30].

Nevertheless, the implementation process is very demanding for the industry, the healthcare organisations or the regulators. It requires a deep assessment of all internal business processes that rely on medicinal product data and an analysis of external stakeholder's dataset needs so that a master data set can be defined; Organisations need to become acquainted with the ISO IDMP data models and the EU IDMP Implementation guide [13][31]. One of the first decisions to be made is whether an entirely new system (off-the-shelf or custom made) needs to be implemented or whether the old system can be refactored. HALMED opted for the refactoring of the existing system NRL-PKL-PhV. It consists of three distinct applications that are sharing the same medicinal products database, same document repository, referential lists, administration tools and integration services to other HALMED's information systems. Significant adaptations of the user interface are also needed in order to enable entering and reviewing medicinal product data related to Packaging, Manufactured item and its composition and the Pharmaceutical Product composition. Once the old data model and the user interface reconstruction will be fully completed and the new RMS referential lists introduced, HALMED will then be able to exchange all data required by the EU IDMP Implementation guide with the Product Management Services. Moreover, as part of the EU funded project eLijekovi, the future national medicinal product database (that will be foundation for all the future eHealth services consuming medicinal products) will be built in accordance with the ISO IDMP set of standards. By complying with ISO IDMP standards, the national medicinal product database will significantly impact the Croatian

eHealth system in general. It will provide an essential contribution to data interoperability throughout the Croatian healthcare systems and therefore enable a meaningful and quality data exchange between all stakeholders.

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