TALLINN UNIVERSITY OF TECHNOLOGY
School of Information Technologies

Triin Hirvlaan 212021YVEM

Implementing ISO IDMP in Europe: practical usage of ISO IDMP guideline and FHIR resources for medicinal products

Master's thesis

Supervisors: Kerli Linna MSc
Rutt Lindström MA

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TALLINNA TEHNIKAÜLIKOOL
Infotehnoloogia teaduskond

Triin Hirvlaan 212021YVEM

ISO IDMP kasutuselevõtt Euroopas: ISO IDMP juhendi rakendamine ja FHIR ressursid ravimite jaoks.

Magistritöö

Juhendaja: Kerli Linna MSc
Rutt Lindström MA

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Author’s declaration of originality

I hereby certify that I am the sole author of this thesis. All the used materials, references to the literature and the work of others have been referred to. This thesis has not been presented for examination anywhere else.

Author: Triin Hirvlaan

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Abstract

Background: Interoperability in general is the ability of different information technology systems to securely communicate and exchange data. Interoperability is crucial in healthcare and there are different standards to ensure interoperability, for example HL7 FHIR and ISO IDMP. ISO IDMP is a global standard for uniquely identifying medicinal products and it applies to the whole course of the medicinal product life cycle. HL7 International has created a special set of FHIR resources called Medication Definition module resources for ISO IDMP compatible data exchange. However, implementation of standards can have challenges. Implementing ISO IDMP in regulatory domain creates additional challenges in using the same data in the clinical domain. **Aim:** Firstly, to create Estonian medicinal products data in ISO IDMP format using HL7 FHIR Medication Definition module resources. Secondly, to map Medication Definition module resources to Medication resource in order to analyse how data from Medication Definition module's resources could be used in Medication resource. **Methods**: Descriptive and explorative case study was conducted. Document analysis was used to give a context of the case. **Results:** 38 examples of Estonian medicinal products in ISO IDMP format data in FHIR Medication Definition module resources were created. The examples were used to map FHIR Medication Definition module resources to FHIR Medication resource. Results point out the challenges in creating medicinal product data in FHIR Medication Definition module resources depends on the characteristics of the medicinal product. IDMP-compatible Medication Definition module resources are highly granular and in order to avoid ambiguity, additional rules are needed how to use this data in FHIR clinical resources. **Conclusions**: When creating ISO IDMP format medicinal product data and in mapping FHIR Medication Definition module resources with Medication resource there are still challenges, and interoperability between different systems and countries is put at risk.

This thesis is written in English and is 67 pages long, including 6 chapters, 17 figures and 3 tables.

Annotatsioon

ISO IDMP kasutuselevõtt Euroopas: ISO IDMP juhendi rakendamine ja FHIR ressursid ravimite jaoks.

Taust: Koostalitlusvõime tähendab turvalist andmevahetust erinevate infosüsteemide vahel. Koostalitlusvõimel on tervishoius oluline roll ja koostalitlusvõime tagamiseks on erinevad standardid, näiteks HL7 FHIR ja ISO IDMP. Samas võib standardite kasutuselevõtmine kujuneda keerukaks ülesandeks. Näiteks ISO IDMP andmemudeli kasutuselevõtt ravimiametites võib tekitada lisakeerukust ravimite andmete kasutamisel retseptidel ja muudes kliinilistes andmetes, sest puuduvad selged transformeerimisreeglid. **Töö eesmärk**: Esmalt luua ISO IDMP formaadis Eesti ravimite andmed, kasutades HL7 FHIR Medication Definition mooduli ressursse. Seejärel kaardistada, kuidas samasid andmeid kasutada HL7 FHIR Medication ressursis, mis on mõeldud ravimite kirjeldamiseks kliinilises kontekstis. **Meetod**: Kirjeldav ja uuriv juhtumianalüüs, mille tausta avamiseks kasutati dokumentide analüüsi. **Tulemused**: Valmis 38 ISO IDMP formaadis Eesti ravimite näidisandmestikku FHIR Medication Definition mooduli ressurssidena. Loodud näiteid võrreldi FHIR Medication ressursi andmestikuga. Tulemused näitavad, et peamiseks probleemiks andmete transformeerimisel on FHIR Medication Definition mooduli suurem granulaarsus ja keerulisem andmemudeli ülesehitus võrreldes Medication ressursiga. See võib põhjustada arusaamatusi ja mitmeti mõistetavust, mis tekitab vajaduse selgemate reeglite järele, kuidas seda andmestikku kasutada FHIR kliinilistes ressursides. **Järeldused**: ISO IDMP formaadis ravimite andmete loomisel ja FHIR Medication Definition mooduli ressurssidena loodud andmete üleviimisel FHIR Medicationi ressurssi, on endiselt probleeme ning erinevate süsteemide ja riikide koostalitlusvõime on seetõttu ohus.

Lõputöö on kirjutatud inglise keeles ning sisaldab teksti 67 leheküljel, 6 peatükki, 17 joonist, 3 tabelit.

List of abbreviations and terms

API	Application Programming Interface
EESAM	Estonian State Agency of Medicines
EHDS	European Health Data Space
EHR	Electronic Medical Record
EIF	European Interoperability Framework
EMA	European Medicines Agency
EU	European Union
FHIR	Fast Healthcare Interoperability Resources
HL 7	Health Level Seven
HTTP	Hypertext Transfer Protocol
HTTPS	Hypertext Transfer Protocol Secure
IDMP	Identification of Medicinal Products
IG	Implementation Guide
ISO	International Organization of Standardization
JSON	JavaScript Object Notation
MPID	Medicinal Product Identifier
NCA	national competent authorities
OMS	Organisation Management Service
PCID	Packaged Medicinal Product Identifier
PhPID	Pharmaceutical product Identifier
PMS	Product Management Service
REST	Representational State Transfer
RMS	Referentials Management Service

SMS	Substance Management Service
SPOR	Substances, products, organisations and referentials
WHO	World Health Organization

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1 Introduction

According to the World Health Organization (WHO) pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine related problem [1]. In the European Union (EU) pharmacovigilance is connected to the legal framework: Directive 2001/83/EC [2], Regulation (EC) No 76/2004 and Commission Implementing Regulation (EU) No 520/2012 [3]. These documents determine principles, responsibilities, procedures and standards for pharmaceutical companies and medicines regulatory agencies [4]. The overall goal is the safety of medicinal products.

There are numerous ways to ensure safety, but one is that the collecting and exchanging of data has the same fundamental requirements and standards, that includes that all medicinal product data is structured in a coherent way and are machine readable to establish interoperability between systems and countries [5]. This is also important in cross-border health care in particular electronic prescriptions [6].

Implementation of ISO (International Organization of Standardization) IDMP (Identification of Medicinal Products) standards is for creating a unified information space in the field of medicinal product circulation, that means for regulatory purposes, for example marketing authorisations, but also for clinical purposes [7]. According to Commission Implementing Regulation (EU) No 520/2012 it is mandatory for Member States, marketing authorisation holders and European Agency of Medicines Agency (EMA) to use ISO IDMP in EU countries [3] [8]. EU funded project UNICOM focuses on implementation of ISO IDMP and by doing so the aim is patient safety [9].

ISO IDMP is a conceptual model which is not tied to any specific implementation technology. Health Level Seven (HL7) International has created a special set of FHIR (Fast Healthcare Interoperability Resources) resources called Medication Definition module resources for ISO IDMP compatible data exchange using HL7 FHIR as the standard for information exchange [10]. FHIR has also Medication's module resources

that are in clinical domain and are used in ordering, dispensing, administration of medicinal products and medication use, also for drug information [11].

In order to use medicinal product data that is in FHIR Medication Definition module resources for clinical purposes like ordering or dispensing medicinal products, it is necessary to also use Medication resource that is in FHIR clinical domain. At the moment there is a separation between FHIR resources used for medicinal products for regulatory purposes -Medication Definition module resources- and FHIR resources that are used to describe medicinal products for clinical use - Medication resource. The problem is acknowledged by the UNICOM a but studies have not been conducted to emphasise that problem [12]. There are presentations to illustrate the problem in general, but actual medicinal product data have not been used in making examples of ISO IDMP compatible data in FHIR resources [13].

Within the UNICOM project the Estonian State Agency of Medicines (EESAM) is using the ISO IDMP data model in their internal information system called SamTrack II but Register of Medicinal Products is still working on the old information system called SamTrack [14]. And it is not clear yet how to use ISO IDMP data in EESAM new services that are related to the whole lifecycle of medicinal products including clinical use cases.

Problem statement: Implementing ISO IDMP format for medicinal products has challenges regarding supporting medicinal data flow and interoperability between regulatory module and clinical module [12] as there is no existing specification how to use HL7 FHIR Medication Definition module resources with Medication resource.

Aim:

- Create Estonian medicinal products data in ISO IDMP format in HL7 FHIR Medication Definition module resources.
- Map Medication Definition module resources to Medication resource.

Research questions:

1. What are the challenges when creating ISO IDMP compatible Estonian medicinal product data in FHIR Medication Definition module resources?
2. How data from the Medication Definition module resources can be used in Medication resource?

2 Background

In this section an overview of relevant areas of interoperability, standards and implementation of ISO IDMO is given. First chapter will introduce the concept of interoperability the second chapter is dedicated to HL7 FHIR standard. Then the different stakeholders of implementing ISO IDMP are introduced.

2.1 Interoperability of healthcare systems

According to “HIMSS Dictionary of Health Information Technology Terms, Acronyms, and Organizations” interoperability is the ability of different information systems, devices or applications to connect, in a coordinated manner, within and across organizational boundaries to access, exchange and cooperatively use data among stakeholders, with the goal of optimizing the health of the individuals and populations [15]. Interoperability is crucial in healthcare and to achieve compliance within systems across organizations and countries different stakeholders have to collaborate [16].

Interoperability between healthcare systems, devices and applications improves patient care. When data is accurate and shared efficiently then there are fewer medical errors and time and resources to collect data will decrease and overall healthcare costs may be reduced [17]. There are different levels of interoperability [18].

Technical interoperability establishes elementary data exchange abilities or physical connections from one system to another, for example digital networks and communication protocols. In addition, semantic and syntactic interoperability is necessary to improve data processing and extracting [5] .

Syntactic interoperability means standardisation of the communication between systems, for example the systems have to support specific structured data formats like XML and JSON. The structured health data exchange is endorsed by international standards development organizations like HL7 International [5].

Semantic interoperability defines what kind of ontologies, nomenclatures and terminologies are being used so data is defined by common metadata and data elements, datasets, terminology standards and information models [19]. Semantic interoperability ensures that data is understood and recognized exactly the same no matter when, where and by whom the data is used [16].

Organizational interoperability is connected to governance and legislative decisions and is moving towards shared management of cross-border and global healthcare. In general, organizational interoperability is related to how different stakeholders match their business processes and prospects to achieve accepted and mutually beneficial goals [20].

The European Union has introduced several frameworks, regulations and directives that are connected to interoperability standards. For example, European Commission Implementing Regulation (EU) No 520/2012 sets out rules for use of terminology, formats and standards that is associated with exchange and communication of pharmacovigilance and medicinal product information and data [3]. The European Commission has adopted the European Interoperability Framework (EIF) as part of Communication (COM (2017) 134**)** that provides recommendations on how to implement digital public services. The framework presents a shared understanding of what interoperability is and 12 principles how interoperability can be achieved. EIF has also a conceptual model that is meant for planning, developing and maintaining integrated public services [21]. The European Commission is also supporting rules, standards and governance framework towards regulation to set up European Health Data Space (EHDS). The goal of EHDS is to improve access to health data, support personalized healthcare, prevent and manage diseases. EHDS emphasises on developing technical standards and interoperability [22].

When exchanging health data internationally the challenges that are related to interoperability are significant. When exchanging data about medicinal products between countries similar issues appear and interoperability in technical, syntactic, semantic and organizational levels is required [18]. There are different standards used in healthcare. HL7 FHIR as standard is increasingly being used for exchange of health information [23].

2.2 Fast Healthcare Interoperability Resources (FHIR)

HL7 International has created different standards for exchange, management and integration of healthcare information for clinical and administrative purposes, for example HL7 V2, HL7 CDA and HL7 FHIR [18]. Fast Healthcare Interoperability Resources (FHIR) is a HL7 newest standard for exchanging health information. FHIR is helping to achieve syntactic and semantic interoperability of clinical data [24]. Compared with previous HL7 standards that are document-based, FHIR has modular health data entities [25]. To exchange and access data FHIR uses REST in its application programming interface (API) [18] [26].

The atomic entities of FHIR are resources that enable the exchange of content. FHIR resources have modular data components or elements that have defined structure and hierarchy. Each resource comprises simple properties, complex properties and references to other resources. FHIR resources are categorized as Foundation, Base, Clinical, Financial and Specialized [18]. Currently there are 159 resources, for example medication, patient, diagnostic report, procedure, observation etc. This is one of the reasons why FHIR can be used for transferring wide range of data that is connected to healthcare [15]. The list of resources is increasing in time as novel use cases are added [18]. Additional information about FHIR medication related resources is in chapter 3.2 Data specification.

All resources have XML, JSON and RDF representations of data that implementers can use to make their own completed resource with needed data [25]. There is also a possibility to combine different resources into a bundle for exchanging data [18].

FHIR can be used for various use cases in healthcare, covering clinical care, administration, human and veterinary medications, clinical trials etc [18]. When FHIR base resources are adjusted or customized to a certain use-case it is called profiling. In general, a profile describes which resource elements are or are not used and whether additional elements are added to the base specification, rules about particular terminologies that are used, rules about API and descriptions of how elements and API features map to particular implementations and requirements [27].

FHIR standard is extensible, providing an opportunity to add new elements to the core specification the new element is called an extension [28] [29]. Any element can have one

or more extension elements on top of base content. Implementers can define and publish their own extensions but it is advised to use existing extensions. It is also possible to register extensions. In FHIR there is 80/20 rule that means FHIR only includes an element if 80% of systems implement it and 20% can be as extensions [30]. However, each implementation choosing to extend the core specification in their own way can reduce data interoperability with other stakeholders [18].

Closely related to profiling are implementation guides (IG) that are a set of guidelines for how FHIR resources should be utilized to address a certain issue, together with supporting and illustrative documentation. IG resource is used to compile each component of an implementation guide into a comprehensible whole and to produce a computer-readable definition of every component [31].

FHIR uses HTTP or HTTPS as the communication protocol and RESTful API. Rather than asking the server to execute some operation, in FHIR it is possible to tell the server what interactions to do or what the content of the record should be. It is possible to filter and retrieve specific data elements when querying FHIR resources [18] [26].

2.3 ISO IDMP standard

In the scope of European Union Commission Implementing Regulation (EU) No 520/2012 under the Articles 25 and 26 European Union member states and marketing authorization holders have to adopt and enforce ISO IDMP standard [32].

ISO IDMP is a global standard for uniquely identifying medicinal products and it applies to the whole course of the medicinal product life cycle. ISO IDMP is focused on data interoperability. It provides a standardized format for representing and sharing medicinal product data across various systems and organizations [33]. The main benefits of ISO IDMP are improving data reliability and integrity, facilitating reuse of data beyond different regulators and procedures, reducing repeated information submission, and rapid medicinal product identification globally [34]. The stakeholders who gain from IDMP are pharmaceutical companies, medicines regulatory agencies, healthcare providers, public health authorities and patients [35].

IDMP also aims to facilitate easy cross-border healthcare, in particular the exchange of electronic prescriptions and the safe dispensing of prescription drugs [36]. The IDMP

affects many acute areas within the pharmaceutical field, from regulatory, development and research to manufacturing, product safety and distribution [37].

ISO IDMP incorporates five data standards that are shown in Table 1 [38].

Table 1. ISO IDMP incorporates five ISO data standards [38]

ISO 11616	Health informatics – Identification of medicinal products – data elements and structures for the unique identification and exchange of regulated pharmaceutical product information.
ISO 11615	Health informatics – Identification of medicinal products – data elements and structures for the unique identification and exchange of regulated medicinal product information.
ISO 11238	Health informatics – Identification of medicinal products – data elements and structures for the unique identification and exchange of regulated information on substances.
ISO 11239	Health informatics – Identification of medicinal products – 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	Identification of medicinal products – data elements and structures for the unique identification and exchange of units of measurement.

These standards together form the core of a system for the globally distinctive identification of medicines that is endorsed by organizations and health authority agencies [32].

2.4 European Medicines Agency and ISO IDMP

In the EU European Medicines Agency (EMA) is foreseeing the implementation of ISO IDMP. There are numerous steps and stages in implementing ISO IDMP standards, it is done through a series of projects called SPOR data management services that consist of Substance Management Services (SMS), Product Management Services (PMS), Organisations Management Services (OMS) and Referentials Management Services (RMS) [39]. The benefits of SPOR services are increased data quality, efficiency because

pharmaceutical companies have to supply regulatory data only once, data integrity and reliability, reducing data silos and improved interoperability between EU systems [40].

In spite of the fact that there is no mapping between SPOR and five ISO IDMP standards the goal for EMA is that SPOR would cover all requirements of IDMP [33]. The SPOR API was built by using HL7 FHIR R3 as an overarching standard [41] but at the moment they are implement FHIR release 5 [42].

EMA has published IDMP Implementation Guide (EMA IG) for requirements in exchange of medicinal product data in EU. The IG is a set of documents [43]. According to EMA IG FHIR is the data standard supporting exchange of information about medicinal products, substances, and related referential data in the European medicines regulatory field but the IG does not include FHIR profiles [41].

2.5 UNICOM

UNICOM is an EU-funded project that concentrates on the use of IDMP standard throughout the medicinal product life-cycle, that means in regulatory and clinical processes, contributing to EU and later to global medicinal product data interoperability. The main goal is facilitating the free flow of semantically coded interoperable medicinal product information and to connect all relevant stakeholders to the implementation IDMP of EU and national SPOR databases, including establishing an EU Substance Reference System (EU-SRS). UNICOM aim is to support pharmacovigilance and cross border digital health services involving medicinal products and safe electronic prescriptions and electronic dispensation of medications. The project started in 2019 and will end 2024 [44]. To achieve their goals UNICOM has several distinct work packages that focus on different areas of project actions. Work package 1 is concentrating on IDMP- related standards and terminologies, work package 4 is focusing on implementing IDMP at national drug agencies. Work package 5 focuses on the implementation of ISO IDMP in the eHealth services, such as electronic prescriptions and electronic dispensation of medications and data exchange at the national and cross-border levels [9].

Before and during current study there was no automated way to get ISO IDMP data about medicinal products from national databases. The data had to be created manually. Also, as national competent authorities (NCA) systems were not adjusted to send FHIR

messages there was a necessity to make first examples. The first three examples were done by UNICOM work package 4. The first examples were based on: HL7 FHIR 4.6 documentation (Medication Definition module), EMA ISO IDMP Implementation Guide 2.1, EMA SPOR RMS, SMS and OMS, LOSEC 20 mg full application FHIR example provided by EMA [45].

UNICOM working groups agreed what kind of data specifically will be used when creating the medicinal product data. Pilot medicinal product list data was composed by the UNICOM project in May 2020. The list consisted of 35 active ingredients or combinations of active ingredients of medicinal products. The criteria for choosing the substances were as follows: the principles of ISO 11238, substances that are frequently used in patient care (for example medicinal products used in treatment of cardiovascular diseases), substances that may be a challenge in describing in ISO IDMP data standard (for example active ingredients that are have a variation of dose forms), substances that have numerous products [46]. After the first three examples it was clear that more examples were needed for several reasons and further mapping on ISO IDMP data with FHIR Resources was necessary because different medicinal products data in FHIR resources could influence the data exchange. Various examples of medicinal products would show the gaps and problems in aligning IDMP format data to FHIR Resources. Also, more examples give a chance to make conclusions about what kind of automation of data can be done [45].

2.6 ISO IDMP in Estonian State Agency of Medicines

In the Estonian Health Information System FHIR will also be implemented [47] that will affect how healthcare related data is going to be collected and created. Estonian State Agency of Medicines (EESAM) is a governmental body under the Ministry of Social Affairs, the main responsibility of EESAM is supervision of medicines for human and veterinary use to protect and promote public and animal health [48]. Within the UNICOM project the Estonian State Agency of Medicines (EESAM) was one of the first who began to use the ISO IDMP data model in their internal information system called SamTrack II. Before EESAM had SamTrack I as a primary source of medication information for health care service providers and for Medicinal Product Registry. At present EESAM has a SamTrack II drug information database based on ISO IDMP standard and is compatible

with EMA SPOR. SamTrack II is used for medicinal product marketing authorisation and licensing, it is also a central database that provides data flow to other IT systems used by national Health Service providers. SamTrack II enables automated information exchange with the services of the European Medicines Agency [49]. EESAM is also participating in UNICOM work package 4. [14]

In Estonia prescription is based on active ingredient of the medicinal product, the prescription is based on attributes and not trade name and there is no code for virtual medicinal product that could be used on a generic electronic prescription [6]. FHIR Medication resource has a principle that a medicinal product has a code in the system and in prescribing the medication this code is always used. So, it is possible to prescribe a prescription that is based on that code. The similar approach is in cross border electronic prescriptions where it is possible to have codes for medicinal products, but they are not the same as in other countries, so one way to solve that problem is to describe the medicinal product by attributes [6].

3 Materials and methods

This chapter of the thesis will give an overview of methods that were used and how the study was conducted. The data specification subchapter will elaborate the FHIR resources that were used in data collection and data analysis and how they are connected to IDMP standard, also how EMA SPOR and EMA IG is used in creating the medicinal product data.

3.1 Study design

Current study is inspired by a pragmatic worldview. This study focuses on actual practical problems and the goal is to find out how to clarify it rather than find the „truth“ [50]. Pragmatism is based on the idea that researchers should use methodological approach that suits best for the particular research problem [51]. As pragmatism prioritizes experimentation and testing of ideas instead of depending on philosophy or theories and ideologies it suits the goal of this study [52].

The study design is qualitative descriptive case study. Case study approach is an accepted research strategy in the field of information systems and researchers have chosen this method [53] [54]. Case study has also been a preferred practice in studies concerning data interoperability in healthcare [55] [56] [57]. Case study approach was selected because the study aims to analyse a particular circumstance connected with one complex case [51]. Current study can also be called exploratory case study analysis that includes thorough exploration of a real-life contemporary case [58]. Implementing ISO IDMP is the case in this study. The goal of this case study is to get broader understanding of the case challenges. Case study approach has been chosen to explore the case in the current situation because the outcomes of it are not yet clear. The research questions are defined that are focused on a selected case. The type of question that is used in this study is „why“ and „how“ this is the reason this study is exploratory [58].

One source of evidence in this study are documents because document analysis is especially suitable for qualitative case studies [59]. The documents have been selected

firstly to give an overview and the context of the case. And secondly documents were used for input for data collection and guideline for creating medicinal product data in FHIR resources. In choosing the documents the author of current study considered a number of factors, they were credibility, authenticity, meaning and representativeness [60]. Documents that were selected are official documents of EMA [43], International Organization of Standardization [61] [62] [63] and UNICOM [64]. A list of documents that were used in this study is in table 2. The documents were chronologically arranged and then analysed using themes to structure them. The documents were read through and the facts about the case were highlighted [59]. The documents were most beneficial in establishing the facts but also used as a guideline to create Estonian medicinal product data.

Table 2. Documents used in analysis

	Document name	Organization	Year
1.	Substances, Products, Organisations, Referentials (SPOR). SPOR API v2 Specification	European Agency of Medicines	2020
2.	Product Management Service (PMS) - Implementation of International Organization for Standardization (ISO) standards for the Identification of Medicinal Products (IDMP) in Europe. Chapter 1: Registration requirements	European Agency of Medicines	2021
3.	Product Management Service (PMS) - Implementation of International Organization for Standardization (ISO) standards for the identification of medicinal products (IDMP) in Europe Chapter 2: Data elements for the electronic submission of information on medicinal products for human use	European Agency of Medicines	2022
4.	Product Management Service (PMS) - Implementation of International Organization for Standardization (ISO) standards	European Agency of Medicines	2022

	for the identification of medicinal products (IDMP) in Europe Chapter 8 – Practical examples		
5.	Products Management Services (PMS) - Implementation of International Organization for Standardization (ISO) standards for the identification of medicinal products (IDMP) in Europe Chapter 7: xEVMPD and SIAMED II to PMS - Migration guide	European Agency of Medicines	2022
6.	Working paper: an analysis of the IDMP medicinal product identification data provided by NCAs (and SPOR) compared to that needed in MPD for clinical care and for secondary uses	UNICOM	2020
7.	WP4 IDMP implementation at National Drug Agencies D4.2: ESTONIA: Progress report on implementation	UNICOM	2022
8.	Working Paper: Implementation Guidance for Identification of Medicinal Products (IDMP) in Medicinal Product Dictionaries	UNICOM	2022
9.	ISO 11239:2012 ISO, Health informatics - Identification of medicinal products - 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 1, 2012.	International Organization for Standardization	2012
10.	ISO 11240:2012 Identification of medicinal products – data elements and structures for the unique identification and exchange of units of measurement.	International Organization for Standardization	2012

11.	ISO, Health informatics - Identification of medicinal products -Data elements and structures for the unique identification and exchange of regulated medicinal product information (ISO 11615:2017), 2017.	International Organization for Standardization	2017
12.	ISO, Health informatics - Identification of medicinal products - Data elements and structures for the Unique Identification and Exchange of regulated Pharmaceutical Product Information (ISO 11616:2017), 2017.	International Organization for Standardization	2017
13.	ISO, Health informatics - Identification of medicinal products - Data elements and structures for the unique identification and exchange of regulated information on substances (ISO 11238:2018), 2018	International Organization for Standardization	2018
14.	ISO 11240: Identification of medicinal products – data elements and structures for the unique identification and exchange of units of measurement.	International Organization for Standardization	2012

Due to the documents that were used in this study and as the author of current study belongs also in UNICOM working package 4, the additional information was also gathered in numerous webinars, interviews with different stakeholders were not carried out.

Secondly data was collected and analysed by creating medicinal product data in ISO IDMP standard format in FHIR resources to identify how data would be used. [58]. Core FHIR resources were used as templates from which a profile was created. This was a manual process that consisted of creating and editing an XML file: adjusting data content, adding bindings creating extensions. ISO IDMP compatible data was used when altering

FHIR Medication Definition module resources to understand how to use IDMP compatible data in describing medicinal products. Pilot medicinal product list data that was composed by the UNICOM project in May 2020 was used in the current study as a source of what kind of medicinal products data is needed for the project. The list consisted of 35 active ingredients or combinations of active ingredients of medicinal products [46].

38 examples of medicinal products in ISO IDMP format data in FHIR Medication Definition module resources were created by the author of this study in June 2022 to August 2022. Different medicinal products were chosen to see if the data creation in FHIR could be repeated with the same results. The results were validated by UNICOM and the findings have served as an input in UNICOM FHIR IG [65] and some of them are uploaded in the UNICOM server [66]. The example of Estonian medicinal product Agen 10 mg tablets in UNICOM server is in appendix 1.

For each FHIR resource corresponding data from Estonian Register of Medicinal Products and EMA SPOR [67] was used. The data from Estonian Register of Medicinal Products [68] was unstructured and the data had to be mapped to EMA SPOR master data lists and values and then it was used in making Medication Definition module resources.

Thirdly, Estonian medicinal products data in FHIR Medication Definition was used in mapping HL7 FHIR Medication Definition module's resources to the Medication resource and the aim was to understand how Medication Definition module resources data could be transformed to Medication. Mapping was done in Altova XML Spy software where validation with FHIR schemas [69] was possible. The outcomes of different medicinal product data content analysis were used in results.

3.2 Data specification

ISO IDMP is a collection of five standards that provide terms, definitions and framework to describe and identify medicinal products. The key data elements in IDMP data model: medicinal product, pharmaceutical product, manufactured item, packaged medicinal product and substances.

Medicinal Product is any substance or combination of substances that can be administered to patients and is intended to prevent, diagnose or treat the disease or to modify, restore or correct physiological functions. A medicinal product may consist of

one or more manufactured items and one or more pharmaceutical products [61]. For example, medicinal products are powder for solution for infusion and solvent for solution for infusion. Medicinal Product has a unique identifier (MPID) that incorporates a specific pattern: a part of country code, a part of marketing authorisation holder code and a part of the Medicinal Product code [61]

Pharmaceutical Product describes substances, the pharmaceutical form, the route of administration and the strength of a Medicinal Product. Pharmaceutical Product is a medication that is ready to be administered to patients [61]. For example, when powder for solution for infusion is mixed with solvent for solution for infusion then the result is solution for infusion that is ready to be administered to the patient. Pharmaceutical product also has a unique identifier [61].

Manufactured Item is the substance and amount of substances of a product as contained in the packaging of the Medicinal Product. There can be one or more manufactured items in a Medicinal Product. Pharmaceutical product can be equal to the manufactured item. It is possible that two or more manufactured items are combined in a specific way to produce a single pharmaceutical product. If a manufactured item is transformed before being administered to the patient (as the pharmaceutical product) then the two are not equal [61]. Figure 1 illustrates when one Manufactured Item is powder for solution for infusion and the other Manufactured Item is solvent for solution for infusion.

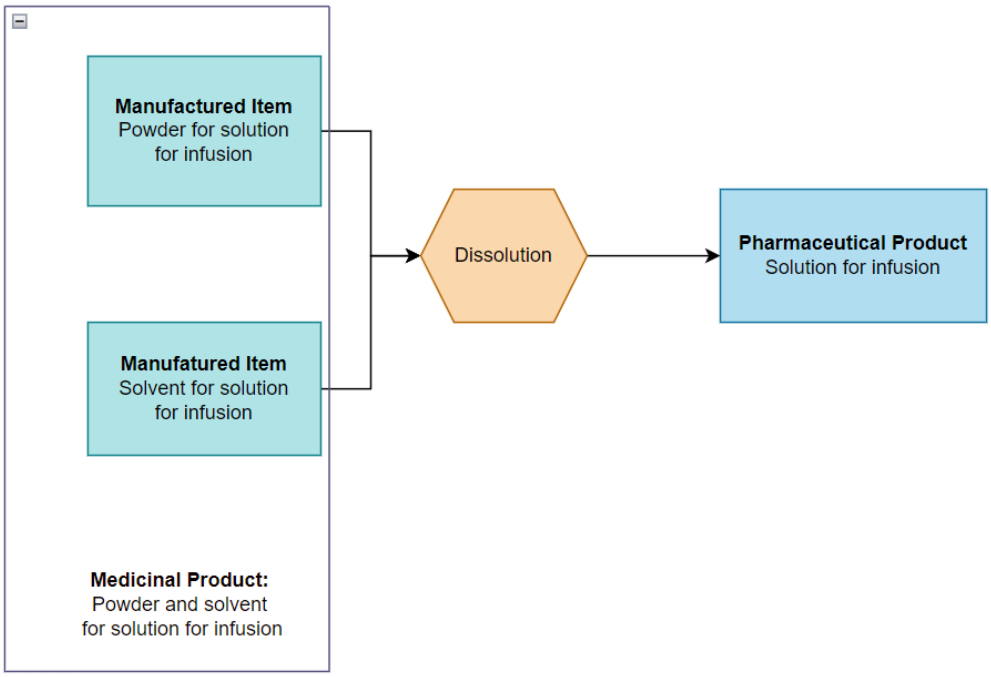

Figure 1. Medicinal Product in relation with Pharmaceutical Product, based on ISO 11239 [70]

Packaged Medicinal Product is a "medicinal product in a container being part of a package, representing the entirety that has been packaged for sale or supply" [63]. A package medicinal product can incorporate a single item or multiple items. These items may be the same kind or different kind [63].

A Packaged Medicinal Product has a unique identifier (PCID) that incorporates a specific pattern: MPID for the Medicinal Product and a part of the package description code, referring to a distinctive identifier for each package [63].

Substance. The ISO IDMP standards accept the representation of the active and inactive ingredients in the medicinal product based on the substance terminology. Ingredients can consist of one or more substances [43]. Substance has determined composition and it can be biological, mineral or chemical origin. A substance may describe an active moiety inside a pharmaceutical product [62]. Figure 2 illustrates the model of data elements in the ISO IDMP model.

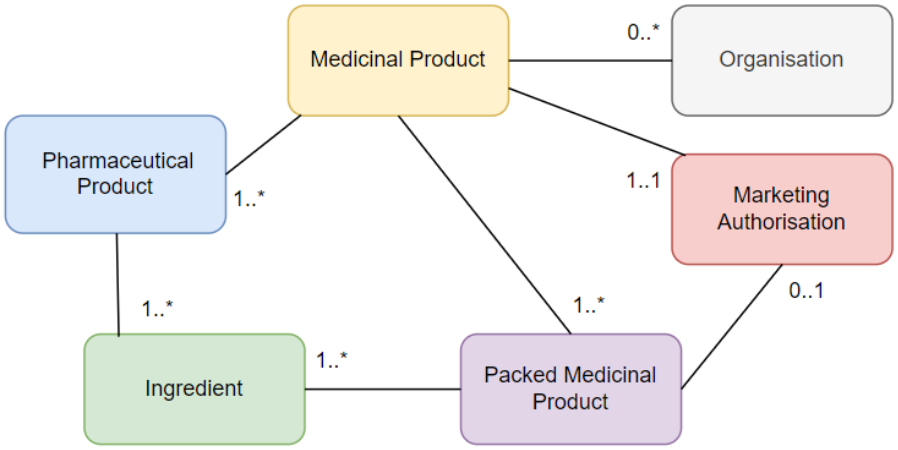

Figure 2. ISO IDMP Medicinal Product overarching model based on ISO 11615 [63].

ISO IDMP data model uses FHIR as a technical standard in particular Medication Definition module resources. Figure 3 illustrates how FHIR Medicinal Definition module resources are connected to each other.

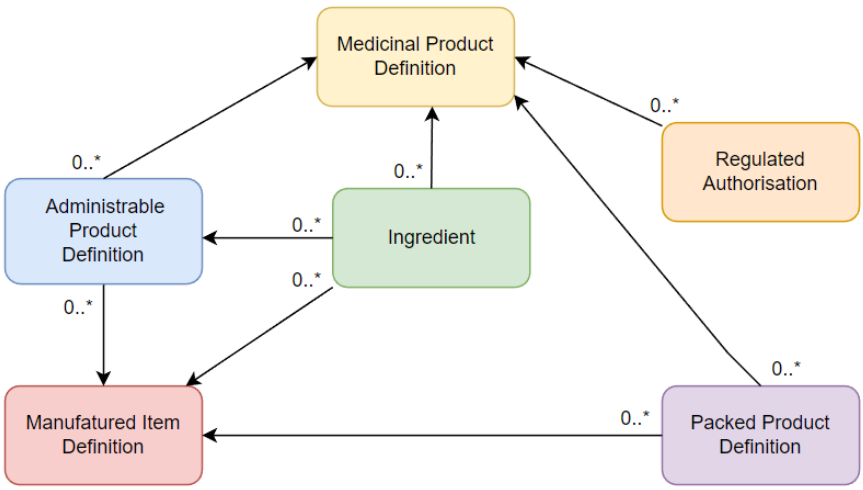

Figure 3. FHIR Medicinal Definition Resources relationship data model based on Medication Definition module resources [71].

ISO IDMP Medicinal Product is compatible with FHIR **MedicinalProductDefinition** resource. MedicinalProductDefinition resource in FHIR is intended to characterize and determine medicinal products and their properties, for regulatory uses and for medicinal product glossaries or dictionaries and is not directly meant to be used for direct patient care or for prescribing a medicine. MedicinalProductDefinition resource demonstrates the product as a whole although some components of the full data model are scattered in other resources of the module. So, the full product data is actually represented by several resources working together [72]. This FHIR resource has more data points than actually needed in ISO IDMP. The whole FHIR MedicinalProductDefinition resource data set is seen in Figure 4.

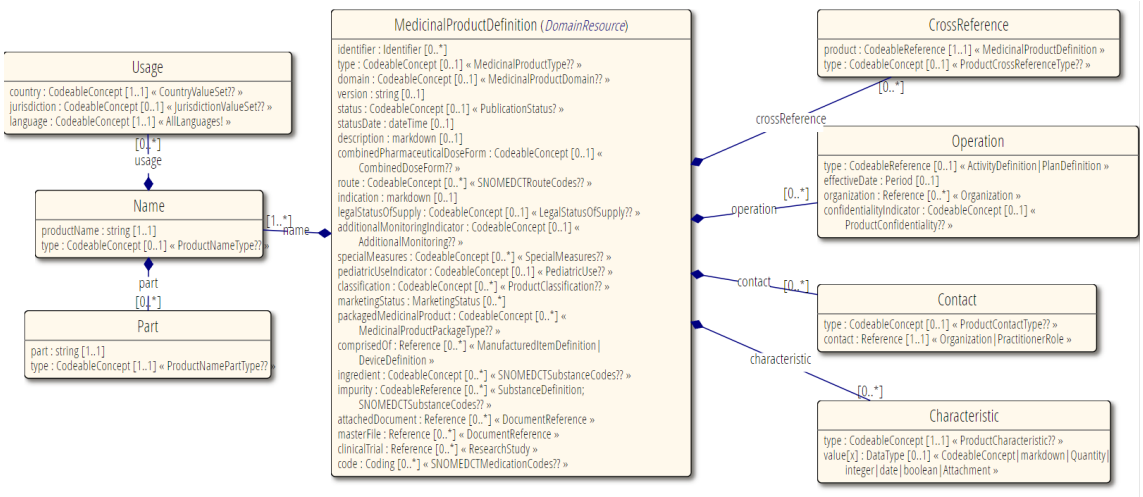

Figure 4. Whole MedicinalProductDefinition resource data set in UML format [72].

IDMP-s Pharmaceutical Product is described in FHIR with an **AdministrableProductDefinition** resource that refers to a medicinal product that is a medicine that is ready to use and in its final form, meant for administering to a patient. Thus, it can be a medicine after merging or blending of multiple components or multiple manufactured items. In some occasions the administrable product does not need any transformation from the manufactured item [73].

In the IDMP data model there is not a separate concept for Manufactured Item, it is part of Medicinal Product and Pharmaceutical Product, but in FHIR it is defined in the **ManufacturedItemDefinition** resource. ManufacturedItemDefinition is for describing a real tangible medication item such as suppositories, a tablet or a capsule. This resource is

not usually applied for prescribing or dispensing a medication but is more applicable for regulatory or manufacturing use cases [74].

FHIR **PackagedProductDefinition** is used to describe IDMP Packed Medicinal Product. PackagedProductDefinition refers to medicinal product related item or items in a package or container. It means the unit that has been produced for supply or sale. Mostly it incorporates packaged medications and devices. This resource describes the entire package of items, and all the inner packaging within and not so much the individual items. In some cases, a medicinal product has multiple available packages in different sizes [75].

IDMP-s substance is described in FHIR **Ingredient** resources. According to the FHIR resource, an ingredient is part of a product, it can be the only substance or combination of substances in a medicinal product. It is a substance with a determined role in the product. It can be an active or inactive substance. The ingredient is described in the context of a specific, it is connected to its role and strength. The same substance with a different strength and different use case, is considered a different Ingredient resource instance [76].

Marketing Authorisation in ISO IDMP corresponds to **RegulatedAuthorization** in FHIR. RegulatedAuthorization is a resource for the authorization of a type of regulated product, therapy, treatment, facility or activity. Regulated products cover human and veterinary medicinal products, devices, nutritional products, software etc. which are dependent on regional or international legislation for their use. The resource is for general authorization and is not related to specific instances of use or single patient. In creating ISO IDMP compatible data this resource was used only for marketing authorisation [77].

In this study FHIR Medication Definition module resources are mapped with Medications module **Medication** resource. Medication resource is mostly used for distinguishing and defining a medication and ingredients that are being used for prescribing, dispensing, and administering a medication as well as explanations about medication use.

Medicinal product data is using FHIR message format in EMA SPOR data management services. Most data for FHIR resources that follow ISO IDMP standard are collected through EMA SPOR data management services. There are four domains of SPOR master data [67], they are seen in Table 2.

Table 3. EMA SPOR master data

Substance Management Service (SMS)	To identify medicinal product materials and ingredients and for harmonized data and definition [78].
Product Management Service (PMS)	To identify medicinal product regulated information and for harmonized data and definition [67].
Organisation Management Service (OMS)	Has manufacturers, sponsors, marketing authorisation holders and regulatory authorities' data, consisting of organization name and location address [79].
Referentials Management Service (RMS)	Has lists of terms to describe attributes of products, for instance lists of dosage forms, units of measurement and routes of administration. There are 202 lists of value sets in EMA SPOR Referentials Management System [80] [67].

EMA has published an implementation guide „Product Management Service (PMS) - Implementation of International Organization for Standardization (ISO) standards for the identification of medicinal products (IDMP) in Europe for the implementation requirements and submission and exchange of medicinal product data [43]. The implementation guide has nine chapters, five of them have been published and four are not yet available [41] [81] [82] [83] [84]. The scope of IG is to describe the technical details of standards, for example specific fields, their formats and business rules and their use. The IG defines the messages that are used to exchange IDMP information that are derived from FHIR standards. Also, the IG gives instructions on the interpretation of data fields specially for the EU regulatory domain as well as direction on the processes for submitting and updating data. It can be said that EMA IG combines ISO IDMP, SPOR

and FHIR with specific medication data examples, for instance IG Chapter 8 is focusing on practical examples [81]. Figures 5 and 6 illustrate a data model that is described in EMA IG. IG is a pdf format document and does not include FHIR profiles and therefore it is not automatically possible to validate the messages [43].

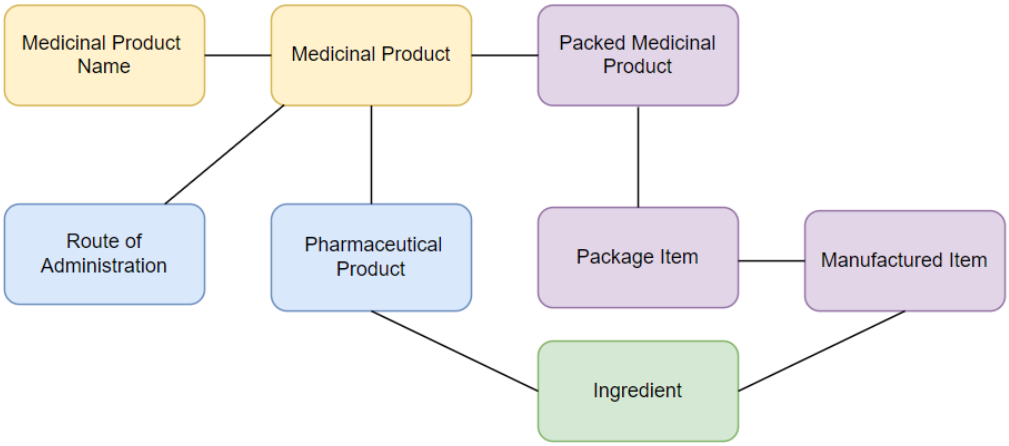

Figure 5. EMA IG data elements relationship model based on EMA IG 1 [81].

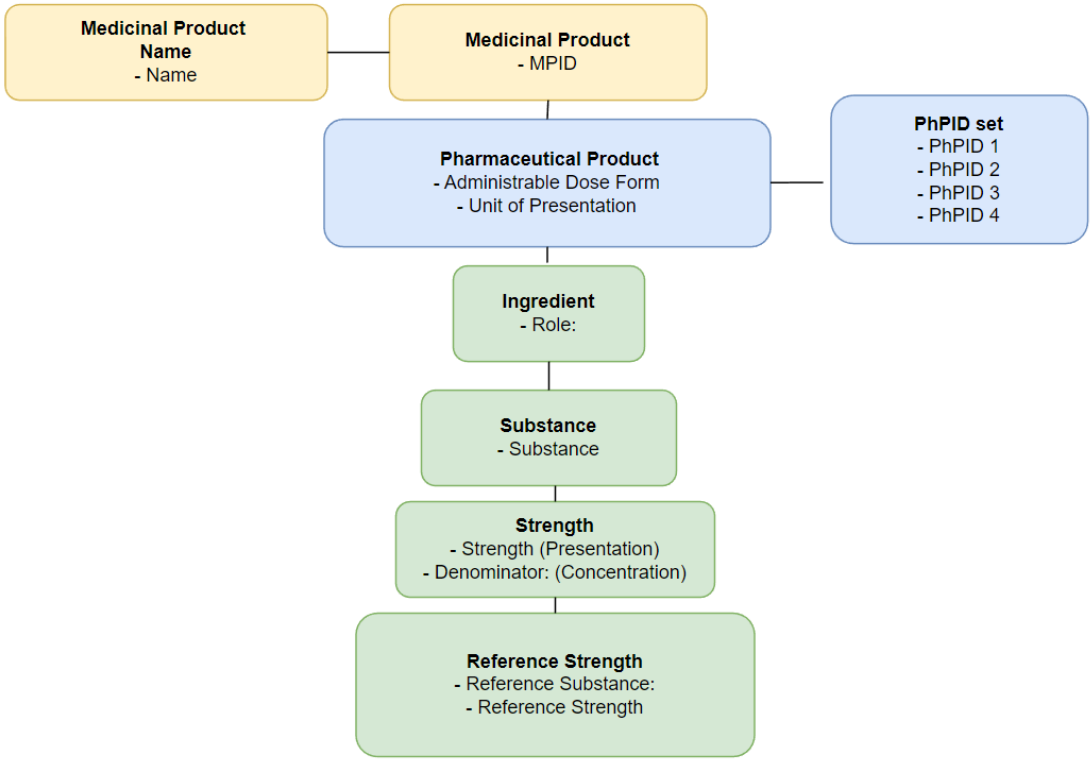

Figure 6. EMA IG data elements relationship model, based on EMA IG 2 [81].

3.3 Data collection

The one source of evidence in this study were documents. The documents were selected to give an overview of the case and were a part of data collection. Documents that were selected were official documents of EMA [43], International Organization of Standardization [61] [62] [63] and UNICOM [64]. The documents were available in the homepages of the organizations. Also, some of the documentation was received from UNICOM work package 4. As the author of this study is also participating in UNICOM work package 4, additional information was also gathered in numerous webinars.

The second part of data collection was creating medicinal product data in FHIR Medication Definition module resources. As the focus of this study was creating the Estonian medicinal product data that was aligned with ISO IDMP standard format, in current study it is also called ISO IDMP compatible data. The data was created using EMA ISO IDMP Implementation Guide 2.1, FHIR R5 core specification (Medication Definition module), Estonian State Agency of Medicines Register of Medicinal Products and EMA SPOR Referentials Management System and the first three examples that were made by UNICOM work package 4. At that time the UNICOM FHIR Implementation Guide was not created yet.

As the main content types for FHIR resources are JSON and XML [18], the author of this study chose XML to create the FHIR examples with Altova XML Spy Software. At first Medication Definition module resources were altered one at a time. But for the purpose of grouping, necessary resources to act as an exchangeable and persistent collection, a bundle of resources was made from every medicinal product data [85]. Six resources from the Medication Definition module were used to make a bundle of resources.

For each FHIR resource corresponding data from Estonian Register of Medicinal Products [68] and EMA SPOR [67] was used. Since the data from Estonian Register of Medicinal Products was unstructured, the data was first mapped to EMA SPOR master data lists and then data was used in modifying Medication Definition module resources. From EMA 202 lists of value sets in EMA SPOR Referentials Management System about 17 lists were used in making the examples. For example, EMA SPOR Referentials Management System legal status of supply is from list 100000072051, classification of

the substance of medicinal product is from list 100000093533 [86]. Some lists that are used in Medication Definition resource are shown in figure 7.

```
<domain>
  <coding>
    <system value="http://spor.ema.europa.eu/v1/lists/100000000004"/>
    <code value="100000000012"/>
    <display value="Human use"/>
  </coding>
</domain>
<status>
  <coding>
    <system value="http://spor.ema.europa.eu/v1/lists/200000005003"/>
    <code value="200000005004"/>
    <display value="Current"/>
  </coding>
</status>
<legalStatusOfSupply>
  <coding>
    <system value="http://spor.ema.europa.eu/v1/lists/100000072051"/>
    <code value="100000072084"/>
    <display value="Medicinal product subject to medical prescription"/>
  </coding>
</legalStatusOfSupply>
<classification>
  <coding>
    <system value="http://spor.ema.europa.eu/v1/lists/100000093533"/>
    <code value="100000095065"/>
    <display value="amlodipine"/>
```

Figure 7. A part of the Medication Definition resource bundle in XML format.

Thirdly, FHIR Medication Definition module resources were mapped to Medication resource. The previously created Estonian medicinal product example data in FHIR Medication Definition module was used in mapping different resources between Medication Definition module resources and Medication resources. In Medication resource the data was also collected from Estonian Register of Medicinal Products [68] and EMA SPOR [67]. Altova XML Spy Software was used to generate XML-s.

3.4 Data analysis

Data analysis was done mainly as content analysis [59] when collecting the documents, creating Estonian medicinal product data in FHIR Medication Definition module resources and when mapping FHIR Medication Definition module resources with Medication resource. But also, comparative analysis was used when comparing the different data of medicinal products and in mapping FHIR Medication Definition module resources with Medication resource.

The documents that were chosen were chronologically arranged and analysed using themes to structure them. The documents were read through and the facts about the case were highlighted [59]. The documents were most beneficial in establishing the facts but also used as a guideline to create Estonian medicinal product data.

38 examples of Estonian medicinal products data in FHIR Medication Definition module resources were analysed. Altova XML Spy Software was used in analysing the data. As FHIR specification provides schemas for all the resource and datatype content models it describes [69] the bundles made in the current study were validated using corresponding FHIR schemas. The Estonian medicinal product data was compared with EMA ISO IDMP Implementation Guide practical examples [81].

In the current study first medicinal products with one active substance were chosen, also medicinal products with tablets as a pharmaceutical dose form were the first as in general medicinal products that have tablets as a pharmaceutical dose form only have one manufactured item and there is no transformation in administrable product. To get different examples of medicinal product data in FHIR resources the aim was to use medicinal products with different dose forms and with multiple active substances or with medicinal products that had multiple pharmaceutical products in one package. The list of Estonian medicinal product that were used in the current study are in appendix 2. The Estonian medicinal products data was compared to find the similarities and differences when making the examples in Medication Definition module resources.

Data was also analysed while mapping FHIR Medication Definition module resources to Medication resource. Fist medicinal products data with tablets as a pharmaceutical dose form were used after that medicinal product with several active ingredients and multiple manufactured items were selected to find out how mapping of data would differ. Mapping was done in Altova XML Spy software where validation with FHIR schemas [69] was possible. The outcomes of different medicinal product data analysis were used in results.

4 Results

This chapter provides an overview of the study results. It is divided into three subchapters First the results of document analysis are briefly referred to as the main method of current study was not document analysis, but documents were used to establish the facts but also used as a guideline to create Estonian medicinal product data. The two last subchapters are divided according to the research questions. Secondly, the results of creating Estonian medicinal product data in FHIR Medication Definition module resources are brought out and examples are given. The subchapter is split up according to results. The third subchapter provides outcomes of how data from Medication Definition module resources can be used in Medication resource. This subchapter is divided into six subchapters as six FHIR Medication Definition module resources were mapped to Medication resource. The figures illustrate the mapping of different resources. The continuous line means that mapping between data elements is straightforward but dashed line indicates that the data elements are not unambiguously transferable.

4.1 Document analysis results

The chronologically arranged documents were analysed using themes to structure them. The documents were read through and the facts about the case were highlighted [59]. From the content analysis it can be said that the documents were genuine, valuable and had both unique and repetitive information in them, also the documents were reliable [60]. Overall, it can be said that the documents were relevant to this case study, covered the topic from different angles and completed each other, still there was some repetition of information.

4.2 Creating medicinal product data in FHIR

One of the aims of the thesis was to create Estonian medicinal products data in ISO IDMP format in HL7 FHIR Medication Definition module resources. By creating Estonian medicinal products data in ISO IDMP format in HL7 FHIR Medication Definition module it would be possible to point out the challenges of implementing ISO IDMP. Although the data was based on Estonian medicinal products from these examples also other countries could benefit from.

4.2.1 Creating medicinal product data with different pharmaceutical dose forms

When a medicinal product has a pharmaceutical dose form, for example a suppository, a tablet or a capsule where the medicinal product does not transform before administration, it is fairly straightforward to create medication product data in FHIR Medication definition module. For example, Agen 10 mg tablets [87], where the manufactured dose form is a tablet and administrable dose form is also a tablet, so the same dose form could be used in describing medicinal product.

In case of combined pharmaceutical dose form when there is a need to merge two or more manufactured dose forms into a single pharmaceutical product for administration to the patient, the creating of medicinal product data is more challenging. When a medicinal product transforms, there is a difference between describing the medicinal product that is administered from the medicinal product that is manufactured. That means in case a medicinal product has one manufactured dose form, for example powder, but in order to be administrable to the patient, needs to be fused with a solution, then after the medicinal product has been mixed with the solution, it has a different dose form, solution for injection. To illustrate the example a medicinal product Kadcyla 100 mg [88], where the manufactured dose form is powder for concentrate for solution for infusion, but after the transformation the administrable dose form is solution for infusion (Figure 8).

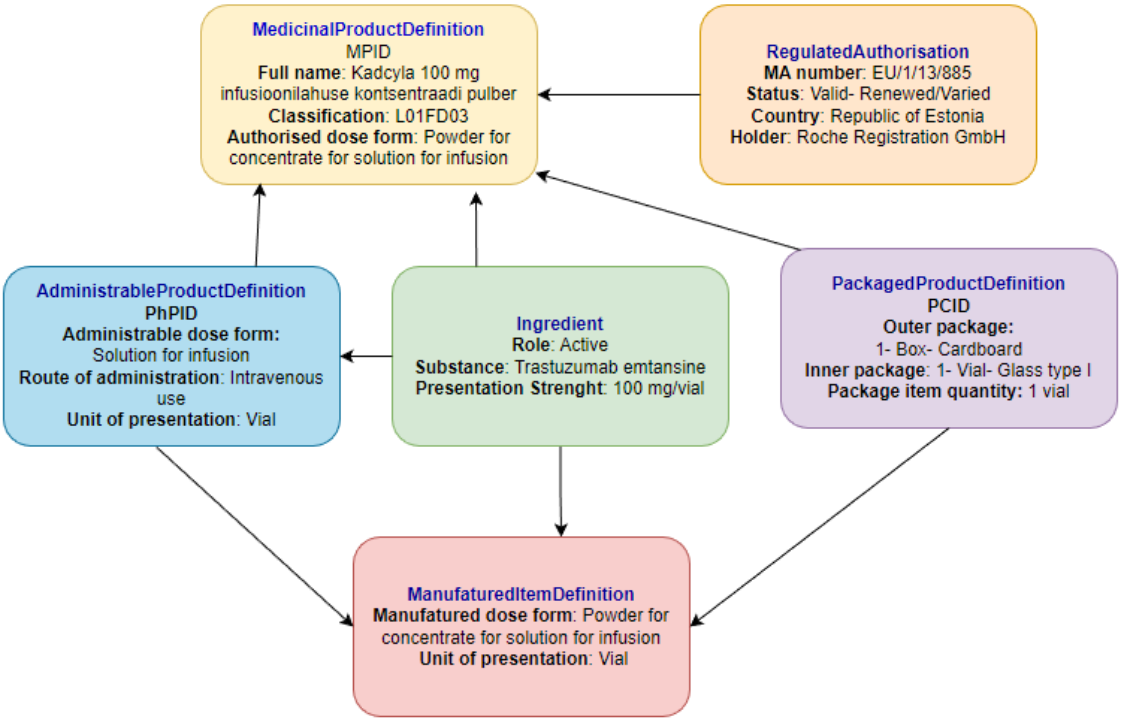

Figure 8. FHIR Medicinal Definition Resources relationship data with Kadcyla 100 mg.

4.2.2 Creating medicinal product data with different strength

One of the most prominent issues concerns granularity of data when describing the active substances and the strength of medicinal product. Whether the active ingredient substance and reference substance should be described with as much granularity as possible is a problem that emerged in almost every Estonian medicinal product example. Particularly dominant was the question where to get the needed information if it is not in the medicinal product information leaflet. The precise active ingredient substance can be the same as the reference substance or in some cases it is different. To create medicinal product data is fairly simple when there is sufficient information about the medicinal product. For example, Diclofenac Mylan 180 mg medicated plaster [89]. The active substance is diclofenac epolamine and each medicated plaster contains a total of 180 mg of diclofenac epolamine, corresponding to 140 mg diclofenac sodium, then it is possible to describe the substance and reference substances and their strength.

The other example to illustrate the issue is in the case of two medicinal products, Agen 10 mg [87] and Hipres 10 mg [90]. These medicinal products have different active substances but the same reference substance. The reference substance is amlodipine and

the reference strength is 10 mg in both of the medicinal products. The difference is in active substances, in case of Agen 10 mg, the precise active substance is amlodipine besylate and the precise quantity is indicated in the information leaflet. In case of Hipres 10 mg, the precise active substance is amlodipine maleate, but the precise quantity of amlodipine maleate is not indicated in the information leaflet. The examples are illustrated in figure 9 and figure 10.

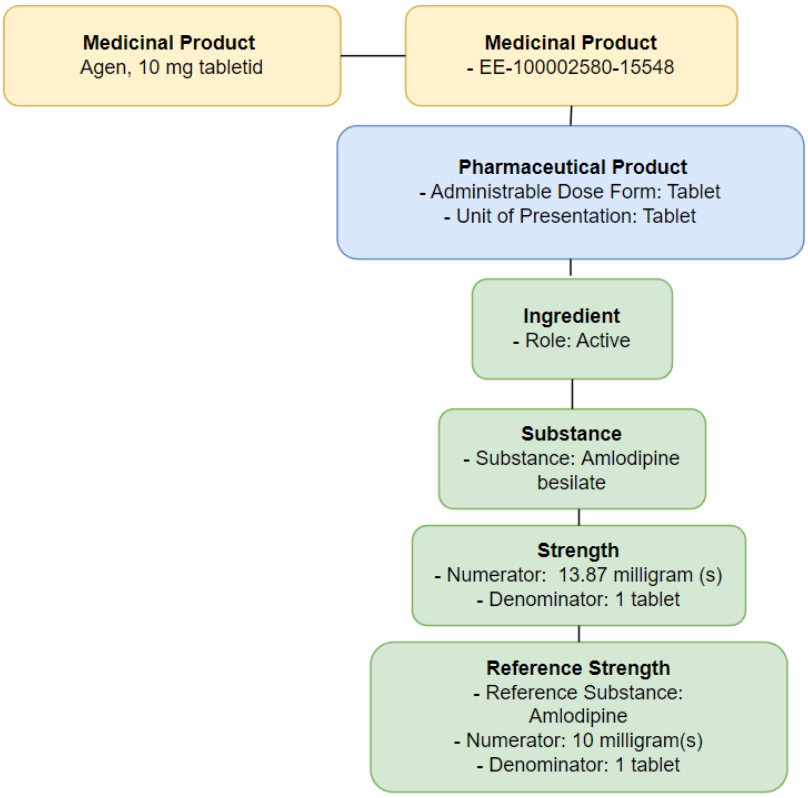

Figure 9. Agen 10 mg substance strength and reference strength [81].

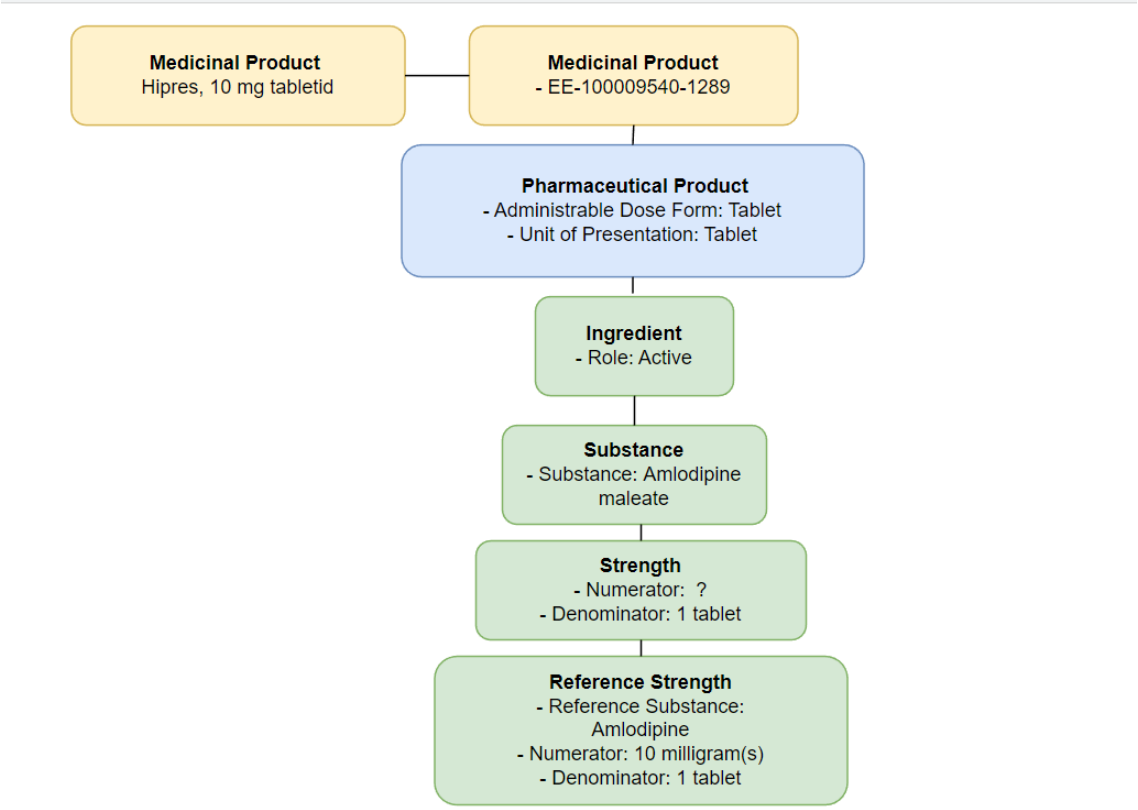

Figure 10. Hipres 10 mg reference strength but no substance strength [81].

Another question arises when a medicinal product has two or more active ingredients like Calcigran Forte 500 mg/400 IU chewable tablets [91], that has calcium and cholecalciferol as active ingredients, it is a challenge to describe substance strength since it is not clearly pointed out in the database or information leaflet. One of the active ingredients, cholecalciferol, was in the medicinal product made from concentrate then there is a possibility to describe substance strength as "more than" 10 mg. But does it follow the suggestion to describe the medicinal product as granular as possible.

In case of combined pharmaceutical dose form the strength can be the most problematic to describe. And in case of various concentrations of medication after the transformation in different patient groups the strength would vary also. It can be inferred that there is a difference in terms of the dose form and also of the strength. For example, Paracetamol Kabi 10 mg/ml, solution for infusion [92]. The manufactured item dose form is solution for infusion but after mixing it with solution the administrable dose form is solution for solution for infusion. Before the transformation 1 millilitre of solution for infusion contains 10 milligrams of paracetamol, but after it has been mixed with solution it can contain different amounts of paracetamol depending on how much medicinal product

(paracetamol) and solution has been used. Similar example is the medicinal product Kadcyla 100 mg powder for concentrate for solution for infusion [88]. One vial of powder for concentrate for solution for infusion contains 100 mg of trastuzumab emtansine but after reconstitution one vial of 5 ml solution contains 20 mg/ml of trastuzumab emtansine.

4.2.3 Creating medicinal product data with different units

There can be complications with alternative ways of describing units of active substances. For example, when a medicinal product has active ingredient quantity both in milligrams and in international units. To illustrate the issue, the medicinal product Toujeo 300 units/ml DoubleStar [93], solution for injection in a pre-filled pen has alternative units. Each millilitre contains 300 units of insulin glargine that is equivalent to 10.91 milligrams, or 3 ml of solution is equivalent to 900 units. Another example that can be challenging is when a medicinal product is described millilitres and drops at the same time. For example, Valocordin Diazepam 10 mg/ml [94], one millilitre of solution is 28 drops containing 10 mg of diazepam. Similar occurrence is with Taflotan, 15 micrograms/ml eye drops [95], solution, 1 ml of solution contains 15 micrograms of tafluprost and one drop contains about 0,45 micrograms of tafluprost. In all of these examples the question of which unit to use to be correct and to preserve interoperability.

4.2.4 Creating medicinal product data with different medicinal product combination packs

The most challenging is creating medicinal products data that is composed of two pharmaceutical products that have two different administrable dose forms and manufactured dose forms. As a result, a medicinal product can have two different dose forms for the pharmaceutical product and manufactured item. And these pharmaceutical products can have the same or different routes of administration. For example, Canifug Cremolum, 10 mg/g +100 mg, cream + pessary [96]. The complexity of Canifug Cremolum, 10 mg/g +100 mg, cream + pessary is illustrated in figure 11.

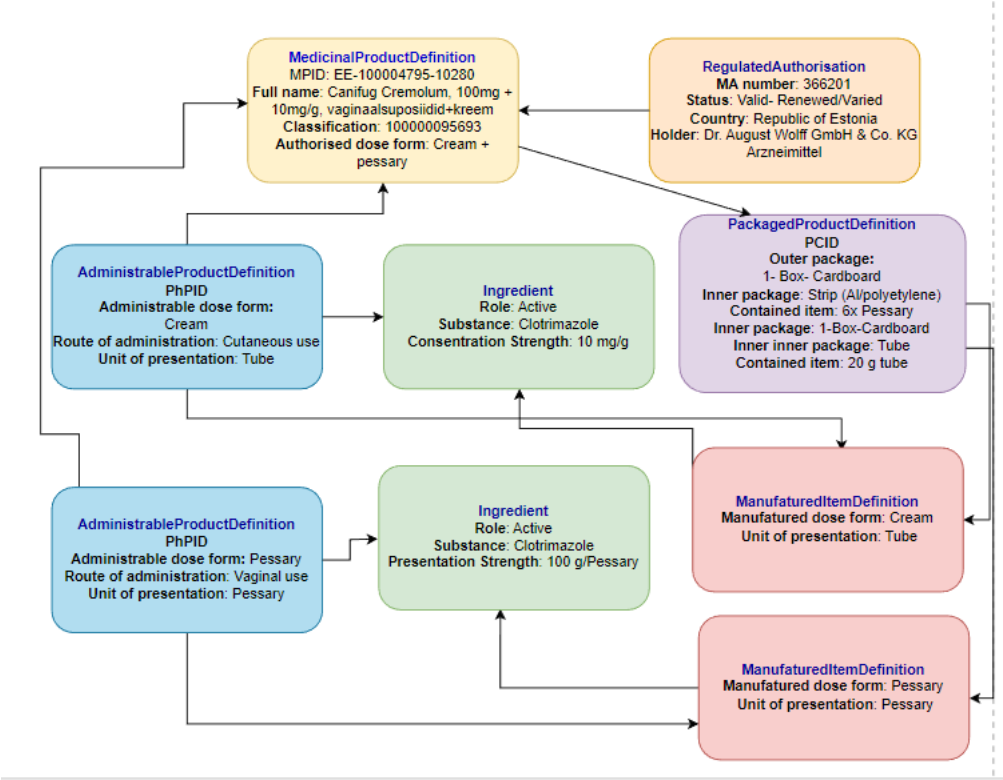

Figure 11. FHIR Medicinal Definition Resources relationship data with Cremolum, 10 mg/g +100 mg, cream + pessary

4.2.5 Active substances order

When creating the data about medicinal products that had one or more active substances the question in what order to describe the active substances. For example, Betaklav 875 mg/125 mg film coated tablets [97] that has two active ingredients amoxicillin and clavulanic acid and what is the "right" order or which of the two to describe first.

4.2.6 Medicinal product packaging

There are some uncertainties that concern pack size and packaging of medicinal products. The medicinal product that has one marketing authorization number can have different pack sizes in one country. When creating medicinal product data is it necessary to add all of the pack sizes available in a particular country. For example, Paracetamol Kabi 10 mg/ml, solution for infusion [92] has 13 different pack sizes and to describe all of them means to repeat the similar data in PackagedProductDefinition resource 13 times.

In some cases, medicinal products that have one marketing authorization licence differ only by package material, for example Agen 10 mg [87] where the blister for the same

medicinal product has two different materials, and in that case the both materials have to be described separately.

When describing the outer package of medicinal products there can be several layers and materials, and in most of the examples the outermost package information is not available. For example, the medicinal products where cardboard box or a film is around cardboard boxes or blisters. To illustrate the example, Qlaira film coated tablets [98] have cardboard boxes around the medicinal product and the outermost package is film.

4.3 Mapping Medication Definition module resources with Medication resource

When mapping resources from the Medication Definition module with Medication resource, it becomes apparent which data from the former is applicable to the latter. This correlation helps to understand if the Medication resource could be sufficient in identifying and defining medicinal product data for safe prescribing, dispensing, administering, including in the context of cross-border healthcare. Although the comparison was made from the point of view of the data of Estonian medical products, the same task is the same for all countries that will implement ISO IDMP, and Estonian examples and challenges can also be useful for them.

4.3.1 Mapping MedicinalProductDefinition resource data to Medication resource

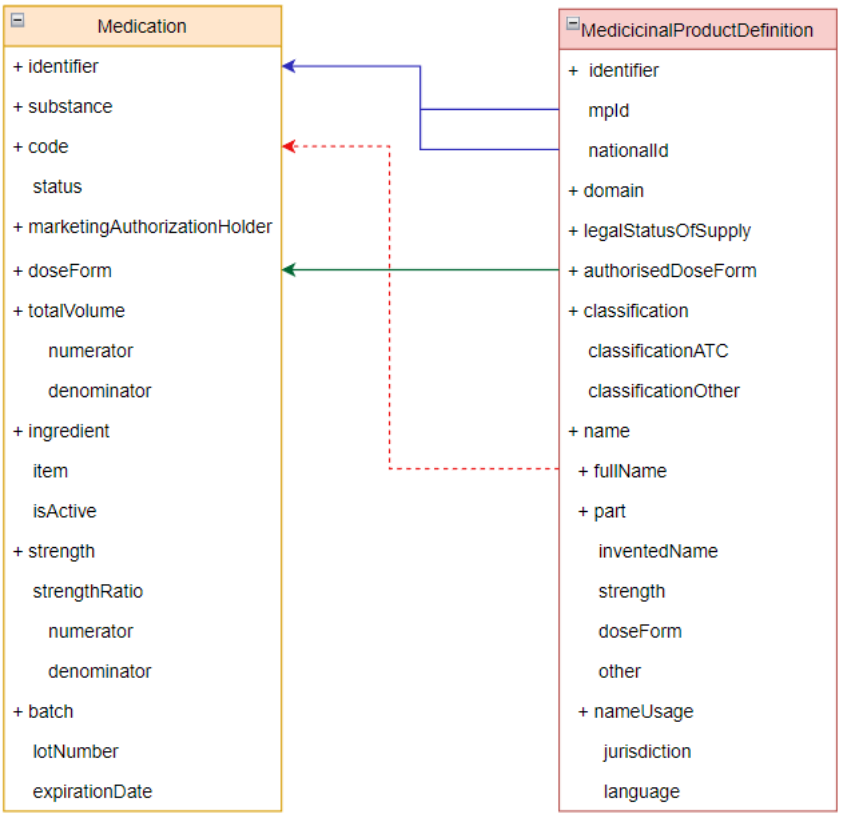

Figure 12. Mapping MedicinalProductDefinition resource to Medication Definition resource.

Comparing MedicinalProductDefinition resource and Medication resource it is possible to map identifiers that can be MPID in both resources. Authorised dose form can be mapped with dose form. Full name in MedicinalProductDefinition resource is a string with the medicinal product name but in the Medication resource it is a codable concept, so it is not unambiguously transferable. The strength in MedicinalProductDefinition is part of an invented name and is not transferable to the Medication resource (Figure 12). At first medicinal product with tablets as a pharmaceutical dose form was used in this study when comparing FHIR MedicinalProductDefinition resource with Medication resource. In case of medicinal product with tablet as a pharmaceutical dose form, like Agen 10 mg tablets [87] the mapping of previously brought out data is straightforward, but in case of combined pharmaceutical dose form, like Kadcyla 100 mg powder for concentrate for solution for infusion [88], there is a question whether to use the manufactured dose form or administrable dose form. And in case of combination pack medicinal products, like Canifug Cremolum, 10 mg/g +100 mg, cream + pessary [96], the medicinal product has two different dose forms for different manufactured items.

4.3.2 Mapping PackagedProductDefinition resource data to Medication resource

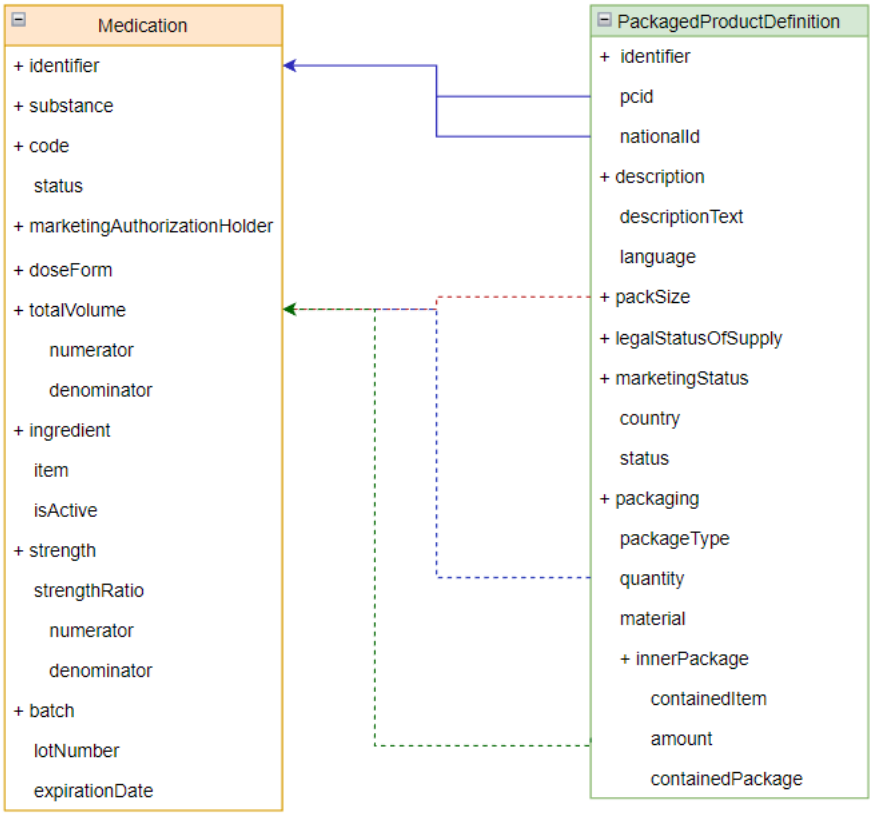

Figure 13. Mapping PackagedProductDefinition resource to Medication resource.

Comparing PackagedProductDefinition resource to Medication resource it can be said that it is possible to map identifiers that can be PCID in both resources. Pack size, quantity and amount can be mapped with total volume in some cases but they are not unambiguously transferable (Figure 13). In the case of a medicinal products with tablets as a pharmaceutical dose form, like Agen 10 mg tablets [87], the mapping of amount and pack size data from PackedProductDefinition with Medication resource total volume is possible. But in case of Toujeo 300 units/ml DoubleStar [93] solution for injection in a pre-filled pen, the pack size from PackedProductDefinition is not unambiguously transferable to amount data in Medication resource, because pack size in current medicinal product refers to a number of pre-filled pens in the package. And in case of combination pack medicinal products, like Canifug Cremolum, 10 mg/g +100 mg, cream + pessary [96], the medicinal product has two different pack sizes and amount data.

4.3.3 Mapping AdministrableProductDefinition resource data to Medication resource

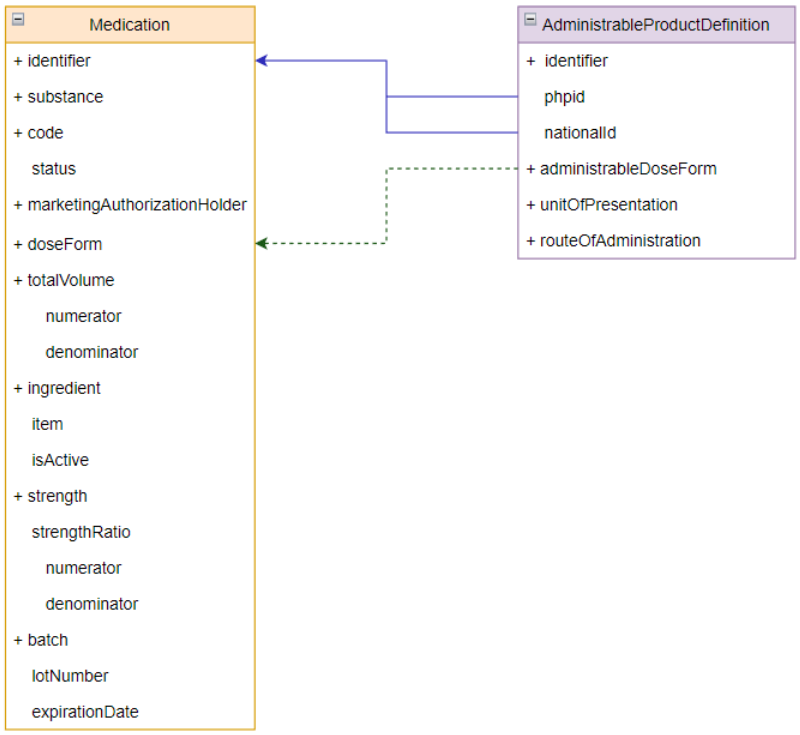

Figure 14. Mapping AdministrableProductDefinition resource to Medication resource.

When comparing the AdministrableProductDefinition resource with Medication resource it can be said that it is possible to map identifiers that can be PhPID or national ID in both resources. Administrable dose form can be mapped with dose form in case of some medicinal products but they are not unambiguously transferable (Figure 14). In the case of medicinal products with tablets as a pharmaceutical dose form, like Agen 10 mg tablets [87] the mapping of administrable dose form data is the same as manufactured dose form and could be mapped to Medication resource dose form. In the case of combined pharmaceutical dose form, like Kadcyla 100 mg powder for concentrate for solution for infusion [88], there is then only possible to use administrable dose form. And in case of combination pack medicinal products, like Canifug Cremolum, 10 mg/g +100 mg, cream + pessary [96], the medicinal product has two different dose forms for different manufactured items.

4.3.4 Mapping RegulatedAuthorization resource data to Medication resource

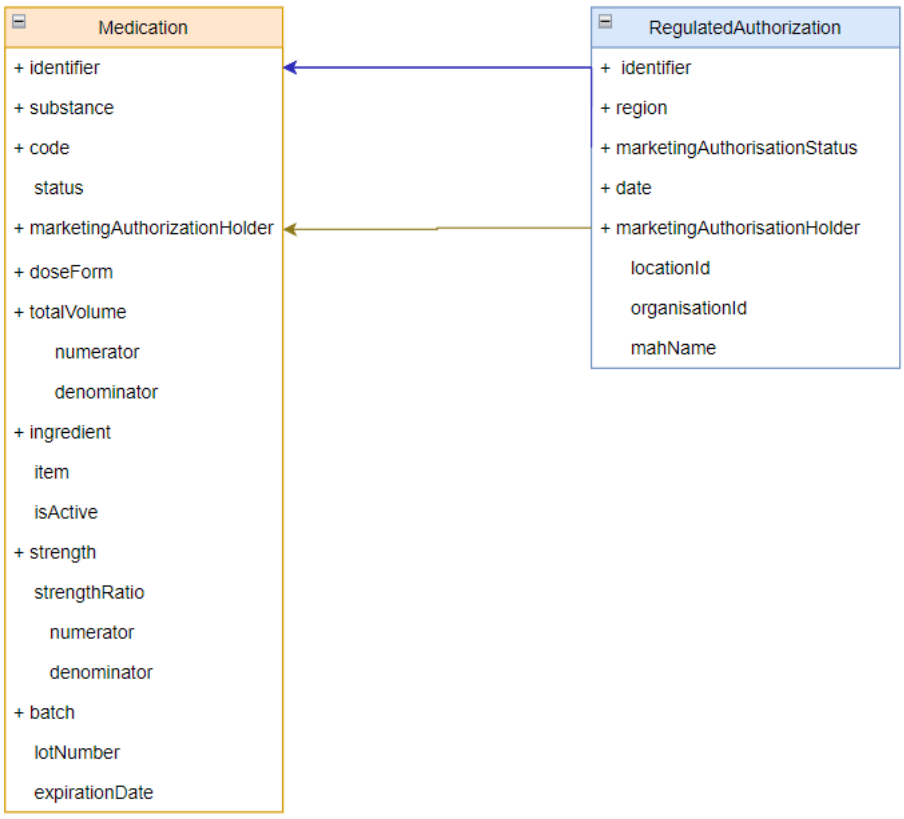

Figure 15. Mapping Regulated Authorization resource to Medication resource.

Comparing RegulatedAuthorization resource to Medication resource it can be said that it is possible to map identifiers, marketing Authorization number can be one identifier. Marketing authorisation holder can be mapped with marketing authorization holder (Figure 15). This mapping can be done with all different kinds of medicinal products.

4.3.5 Mapping ManufacturedItemDefinition resource data to Medication resource

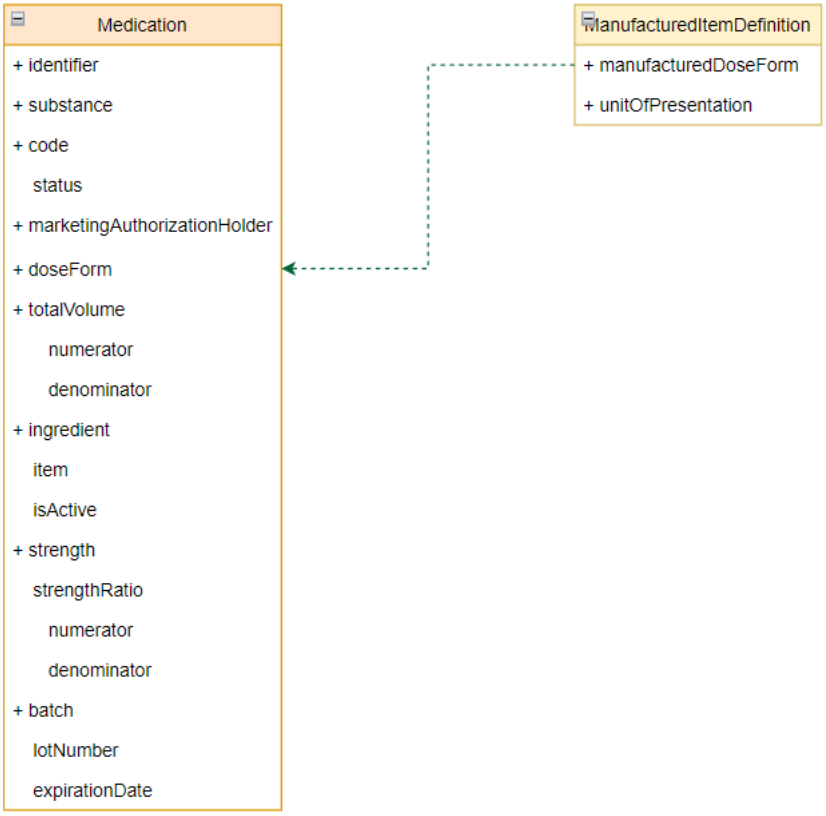

Figure 16. Mapping ManufacturedItemDefinition resource to Medication resource.

Comparing ManufacturedItemDefinition resource to Medication resource it can be said that manufactured dose form can be mapped with dose form in some cases but they are not unambiguously transferable (Figure 16). In the case of medicinal products with tablets as a pharmaceutical dose form, like Agen 10 mg tablets [87] the mapping of manufactured item dose form data is the same as administrable dose form and could be mapped to Medication resource dose form. In the case of combined pharmaceutical dose form, like Kadcyla 100 mg powder for concentrate for solution for infusion [88], there is then only possible to use manufactured dose form, because administrable dose form is different. And in case of combination pack medicinal products, like Canifug Cremolum, 10 mg/g +100 mg, cream + pessary [96], the medicinal product has two different dose forms for different manufactured items.

4.3.6 Mapping Ingredient resource data to Medication resource

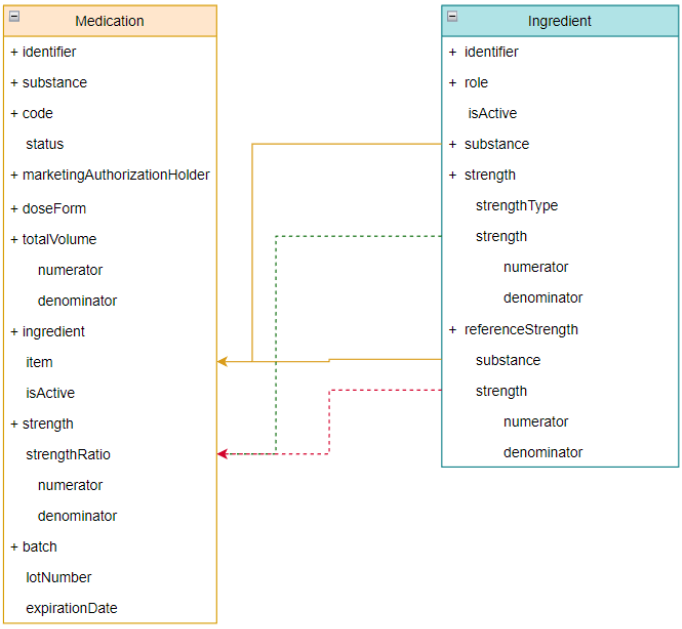

Figure 17. Mapping Ingredient resource to Medication resource.

Comparing Ingredient resource to Medication resource it can be said that substance can be mapped with ingredient item and strength and reference strength can be mapped with strength ratio but they are not unambiguously transferable (Figure 17). It is possible to describe a tablet with multiple active ingredients with both of the resources. But there is a question about the granularity in describing the strength of active ingredients. In Ingredient resource it is possible to describe precise active ingredient or reference substance but in Medication resource it is possible to describe strength in only one way whether it is strength or reference strength. For example, in Ingredient resource Diclofenac Mylan 180 mg medicated plaster [89] can be described by the active substance diclofenac epolamine and each medicated plaster contains a total of 180 mg of diclofenac epolamine, corresponding to 140 mg diclofenac sodium, then it is possible to describe the substance and reference substances and their strength. In the Medication resource it is not possible to describe the medicinal product in this level of granularity.

5 Discussion

This chapter of the thesis discusses the results combining them with document analysis that was done to give an overview and the context of the case. The author of the current study answers the research questions, also study limitations and future work will be brought out at the end of the chapter.

5.1 Analysis of results

The main aim of the thesis was to create Estonian medicinal products data in ISO IDMP format in HL7 FHIR Medication Definition module resources and then to map Medication Definition module resources to Medication resource. This aim was fulfilled in the current thesis. By creating Estonian medicinal products data in ISO IDMP format in HL7 FHIR Medication Definition module it was possible to point out the challenges of implementing ISO IDMP. The mapping of Medication Definition module resources to Medication resource to explore how data from Medication Definition module's resources could be used in Medication resource.

To achieve the aim of the current thesis case study method was chosen. According to Yin case study is suitable for thorough exploration of real-life contemporary and complex case and when the outcomes of the case are not clear yet. The type of question that is used in this study is „why" and „how" this is the reason this study can be also called exploratory case study [58].

Implementing ISO IDMP has become an important issue for EMA, EESAM and other NCA-s is due to Commission Implementing Regulation (EU) No 520/2012 that is mandatory for EU Member States, marketing authorisation holders and European Agency of Medicines Agency (EMA) to use ISO IDMP in EU countries [3] [8]. Currently there is limited data available about how other countries in the EU have created medicinal product data in FHIR Medication Definition module resources that is compatible with ISO IDMP and what have been the results when doing so. Also, it is not yet decided how the ISO IDMP compatible data would be used in the whole lifecycle of a medicinal product.

One source of data were documents in the current study. The documents were selected to give an overview and the context of the case. Also, documents were used as a guideline in creating Estonian medicinal product data in FHIR resources, especially EMA IG [43]. The chronologically arranged documents were analysed using themes to structure them. The documents were read through and the facts about the case were highlighted [59]. Content analysis was done and it is that the documents were genuine, valuable and had both unique and repetitive information in it, also the documents were reliable [60].

From the documents mostly EMA ISO IDMP IG that is a set of documents was used, because it consisted of requirements for exchanging medicinal product data in EU [43]. The IG is quite comprehensive and points out the conditional and mandatory attributes [81]. Regrettably the IG does not include FHIR profiles [41] and in making the Estonian medicinal products examples in Medication Definition module resources was an experimentational and to meet the mandatory attributes also extensions had to be used. UNICOM has published several analyses to help implement ISO IDMP and to address some of the obstacles [45] [12] [49].

Both EMA and UNICOM documents that are about implementing ISO IDMP share the common goal of pharmacovigilance and safety of medicinal products. One way to achieve pharmacovigilance and safety of medicinal products is if the data about medicinal products is created and collected using common standards. ISO IDMP as conceptual standard and FHIR as a standard to exchange healthcare related data are suitable to provide syntactic [5] and semantic [19] interoperability. The EU healthcare data related regulations [3], directives [2] and interoperability frameworks [21] are to improve organizational interoperability [20]. Achieving interoperability in digital health is essential to avoid data silos and fragmentation of care and to improve patient care and safety. Although even if all the different layers of interoperability are seemingly achieved there can still appear challenges. And this was one of the reasons why the current study chose to look into implementing ISO IDMP. And as within the UNICOM project the EESAM was one of the first who began to use the ISO IDMP data model in regulatory purposes in their internal information system but it is not clear yet how to use ISO IDMP data in EESAM new services that are related to the whole lifecycle of medicinal products including clinical use cases [49]. This is one on the reasons why the findings of the current study will be of interest to those who are implementing ISO IDMP and for the UNICOM project. This study can provide knowledge or base for Estonian medicinal product related

digitisation projects, such as FHIR-compatible services for Register of Medicinal Products, hospital medication digitalisation or current medications' list on health care professional's desktop.

The first research question of this thesis was about the challenges when creating ISO IDMP compatible Estonian medicinal product data in FHIR Medication Definition module resources. To identify these problems 38 examples of Estonian medicinal products data was made by the author of this study that followed ISO IDMP standard.

One of the main results that emerged from the analysis is that challenges in creating medicinal product data in FHIR Medication Definition module resources depends on the characteristics of the medicinal product. If medicinal product has one pharmaceutical dose forms such as a tablet or a capsule and it does not transform before administration of the medicinal product then the generating of medication data in FHIR Medication definition module is more straightforward. However, if the medicinal product has two or more active ingredients, then describing the medicinal product has several nuances. For example, EMA IG does not have clear guidelines which ingredient data comes first [43]. Although this may not interfere with interoperability it can still influence how data is displayed in different systems user interfaces.

Generating the data that is ISO IDMP compliant is more strenuous in case of combined pharmaceutical dose form. When combining two or more manufactured dose forms into a single administrable product, the medicinal product will transform and medicinal product that is administered to patient is different from the medicinal product that is manufactured. That means that manufactured item has one dose form and administrable product has another dose form is another. According to EMA IG both of the dose forms have to be pointed out comprehensibly [43].

Another aspect to point out is whether the medicinal product is at all times described as granular as recommended. From the results it can be said that this is the problem in case of active substances strength and reference strength. According to EMA IG [43] the active ingredient substance and reference substance strength should be described with as much granularity as possible and when possible. Unfortunately, there can be inconsistencies due to the limited data in case of some medicinal products. This problem refers that it is important to have rules in place when the medicinal product data is collected and created

for the first time, so there is clear understanding what data is needed. In case of medicinal product that has combined pharmaceutical dose form the strength is the most problematic. When medicinal product that is not yet transformed has one strength and after transformation has another strength then according to EMA IG medicinal product strength before transformation should be described but the strength after transformation is not indicated anywhere. For the safety and clinical use cases it would be important to have the information about the medicinal product strength after transformation.

One of the results indicate that there are issues when there are alternative ways of describing units of active substances. Especially when one medicinal product has active ingredient quantity in different units. EMA IG has different examples of medicinal products [81], but the IG does not give clear instructions which unit to prefer and if there is a difference in units in different systems there is a risk of losing interoperability.

Results show that the level of granularity and accuracy is especially needed when medicinal product is composed of two pharmaceutical products. Because then medicinal product has different administrable dose forms and manufactured dose forms and every medicinal product may have two different dose forms for the pharmaceutical product and manufactured item also these pharmaceutical products can have the same or different routes of administration. Unfortunately, in EMA IG [81] did not include practical examples that would illustrate the complexity of creating this kind of medicinal product data.

It is also relevant to point out that almost in every medicinal product example there was question about different pack sizes of medicinal products that have one marketing authorization in one country. Sometimes the medicinal product that has one marketing authorization product has different inner package materials. According to EMA IG [43] it is necessary to add all of the pack sizes available in particular country. Also, if the inner package material is different in different pack sizes, then it should be also described as a separate part of the resource. When describing the outer package of medicinal products there can also be several layers and materials. According to EMA IG [43] the outermost package has to be always “box” even if in the reality it is not.

In following the EMA IG results suggest that IDMP data is very fragmented and that could cause ambiguity and contradictions. Improving data quality is a challenge even

when there is thorough implementation guide written. For effective and granular data, it would be still vital to have clearer agreements how to use extensions in FHIR when creating the data, because implementing ISO IDMP is for global benefit, there should be interoperability between countries not just organizations. Therefore, common rules for data conversion and resource extensions are needed re-use of profiles remains challenging [30].

Second research question of this study was related with mapping FHIR Medication Definition module resources to Medication resource. In order to use medicinal product data that is in FHIR regulatory domain that is Medication Definition module resources for clinical purposes like ordering or dispensing medicinal products it is necessary to also use Medication resource that is in FHIR clinical domain. At the moment there is a separation between these FHIR resources [12]. Although there have been presentations to illustrate the issue, the mapping of Medication Definition module resources to Medication resource have not been done with real medicinal product data [13]. Therefore, it can be said there are challenges regarding supporting medicinal data flow and interoperability between regulatory module and clinical module in FHIR as there is no existing specification how to use HL7 FHIR Medication Definition module resources with Medication resource.

In the current study when mapping Medication Definition module resources with Medication resource the same Estonian medicinal product data that was created before was used. Due to the fact that in mapping Medication Definition module resources to Medication resource was done using the same Estonian medicinal product data that was used in the first phase of this study the results are also dependent on what kind of medicinal product data was used.

From the results it can be said that the data that could be mapped straightforward from Medication Definition module resources to Medication resource are the identifiers and data about marketing authorization holders. In case of all other attributes that are in Medication resource mapping differed depending on medicinal products characteristics.

If the medicinal product is tangible medication item such as suppositories, a tablet or a capsule the mapping was possible between some attributes, for example dose form and amount of medicine.

In case of medicinal products with combined pharmaceutical dose form or medicinal products that have combination pack the data that was not unequivocally transferable.

One of the most interesting result comes from mapping the name of medicinal product. In Medication resource name is a codable concept in MedicinalProductDefinition resource full name is a string with medicinal product name, so it is not unambiguously transferable. This is also where the biggest difference can be pointed out because Medication resource has a principle that a medicinal product has a code in the system and in prescribing the medication this code is always used [6]. But in MedicinalProductDefinition name is not connected to this one code, but there are other attributes in addition.

ISO IDMP format data in Medication Definition module resources is very granular and this is the reason why considerable amount of data from Medication Definition is not straightforwardly mappable or is not at all mappable to Medication resource, for example rout of administration, unit of presentation and data about jurisdiction and country and language that is connected to the medicinal product. Medication resource does not have to fit all of the data from Medication Definition module resources but if it is agreed on what data from Medication Definition resource could be used then the data attributes should comply.

It is possible to use extensions to alter Medication resource, but the use of extensions should be also agreed especially when talking about global standard of identification and describing of medicinal products. It is theoretically possible with FHIR different resources to make a bundle of resources that have Medication resource, ManufaturedItemDefinition resource and AdministrableProductDefinition resource to use these resources in regulatory but also in clinical use cases. But thinking about interoperability between different stakeholders it is not justified and can it be said then that data is compatible to ISO IDMP standard.

Although FHIR resources are modular, flexible and easy to use there can still be the question of interoperability between systems and especially countries.

in data interoperability between different countries that contribute low quality of cross-border healthcare provision

5.2 Limitations

Implementing ISO IDMP in the scope of UNICOM project is not yet finished. This case study does not compare implementing ISO IDMP with other projects that aim to implement global standards. Also, the current study did not compare Estonian medicine data creation with other countries examples. There are numerous stakeholders who are involved in implementing ISO IDMP and the comparative analysis of how different organizations are contributing would give a large picture to this case study.

5.3 Future research

Further research is necessary to address the problems in data interoperability between different countries. In the future mapping between Medication Definition module resources to other Medications module resources would be useful to see how data can be used between these resources. Also, it would be useful to give remedies how to address or solve the separation between FHIR resources used for medicinal products for regulatory purposes and FHIR resources that are used to describe medicinal products for clinical use. It would be beneficial to analyse how EESAM will be using ISO IDMP compatible data in their different applications not only in regulatory, but also clinical field.

5.4 Conclusion

Based on the results from documents, Estonian medicinal products data in ISO IDMP format in HL7 FHIR Medication Definition module and mapping Medication Definition module resources to Medication resource several aspects of creating and exchanging medicinal product data came to light.

The concept of using medicinal product data in a coherent way throughout the medicinal product lifecycle and in different use cases, whether it is connected to regulatory or clinical domain, is still a problem to acknowledge.

One of the main results that emerged from the analysis is that challenges depend on the characteristics of the medicinal product. Both the creation of Estonian medicinal product data in ISO IDMP format in Medication Definition module resources and mapping this data to Medication resource proved that.

Medication resource data is not as granular as Medication Definition module resources and considerable amount of data from Medication Definition module resources is not straightforwardly mappable or is not mappable at all to Medication resource.

6 Summary

The aim of this study was to create Estonian medicinal products data in ISO IDMP format in HL7 FHIR Medication Definition module resources and to map Medication Definition module resources to Medication resource in order to analyse how data from Medication Definition module's resources could be used in Medication resource. The author of this study conducted a descriptive case study analysis to identify the challenges in implementing ISO IDMP and using ISO IDMP format data not only in FHIR Medication Definition resources but also in Medication resource.

Firstly, challenges in creating medicinal product data in FHIR Medication Definition module resources depends on the characteristics of the medicinal product.

Secondly, IDMP compatible Medication Definition module resources are very granular and this is the reason why considerable amount of data from Medication Definition module resources is not straightforwardly mappable to Medication resource.

Finally, improving data quality is a challenge even when there is thorough implementation guide written. For effective and granular data, it is still vital to have clear rules and agreements how to use ISO IDMP.

To conclude the thesis, it can be said that if ISO IDMP format data is used in all of the medicinal product lifecycle there is a need to use different FHIR resources, not only from regulatory domain but also from clinical domain and there should be specification how to use HL7 FHIR Medication Definition module resources with Medication resource.

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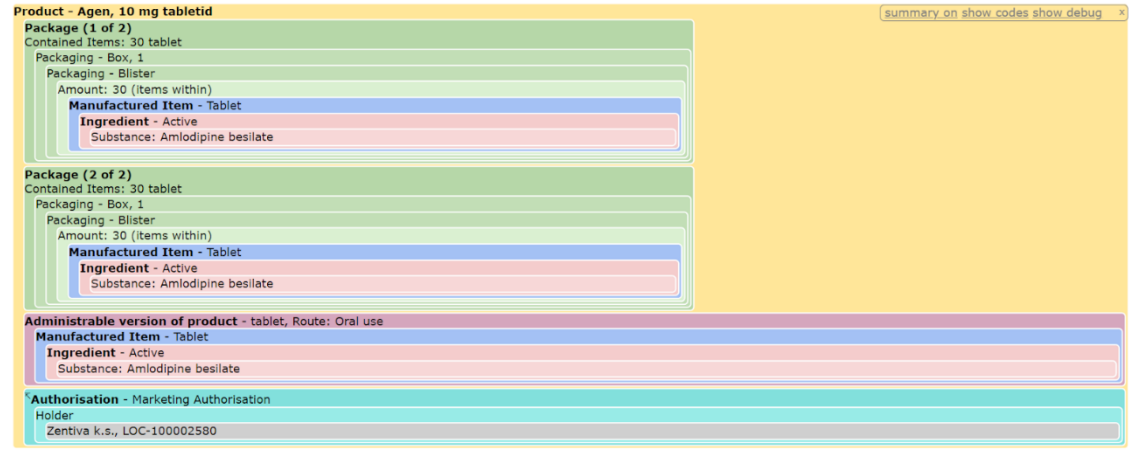
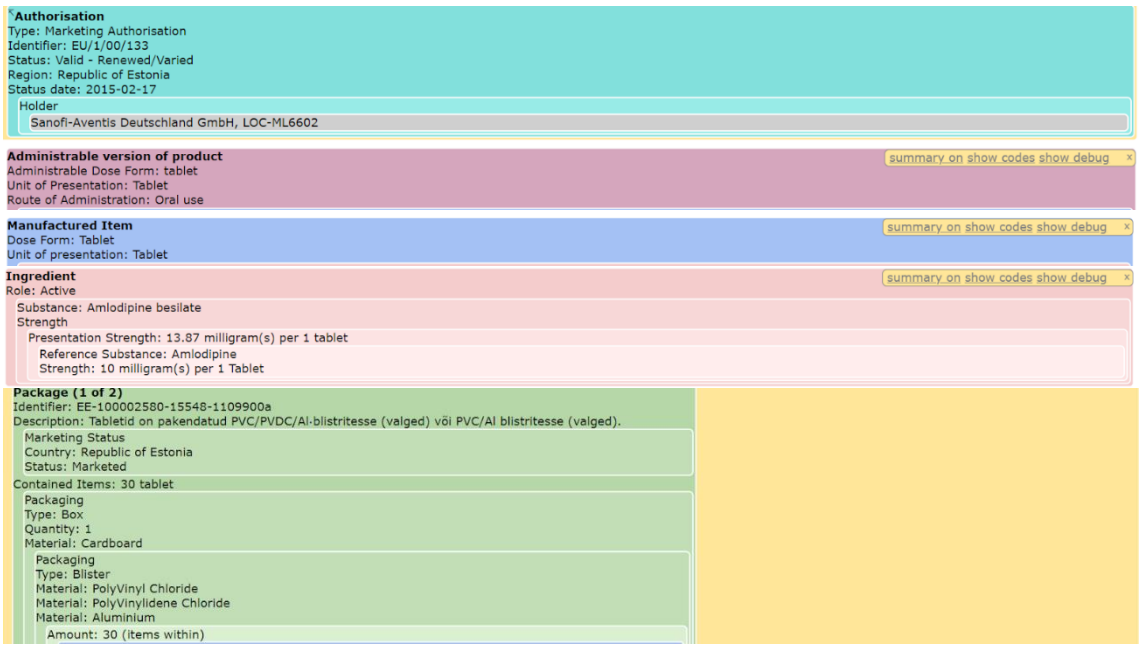
Appendix 1 – Agen 10 mg in UNICOM server [66]

Product
Name: Agen, 10 mg tabletid
Invented Name Part name part: Agen
Strength name part: 10 mg
Pharmaceutical dose form name part: tabletid
Country: Republic of Estonia
Language: Estonian
Identifier: EE-100002580-15548
Domain: Human use
Status: Current
Authorised Dose Form: Tablet
Legal Status of Supply: Medicinal product subject to medical prescription
Classification: amlodipine, amlodipine





Appendix 2 – Estonian medicinal product used in the current study

Agen 5 mg tablets
Agen 10 mg tablet
Amoksiklav, 1000 mg/200 mg powder for solution for injection/infusion
Amoxicillin-ratiopharm 750 mg film coated tablet
Anafranil 25mg coated tablet
Betaklav 875mg/125mg film coated tablet
Calcigran Forte 500mg/400IU chewable tablet
Canesten 500mg vaginal soft capsule
Canifug Cremolum 100mg 10mg/1g Cream+Pessary
Canifug Vaginal Creme 2g/100g vaginal cream
Carbalex 200mg tablet
Cefuroxime MIP 1500mg powder for solution for injection/infusion
Clexane 60mg 0.6ml solution for injection
Diclac 10mg/1g gel
Diclofenac Mylan 180mg medicated-plaster
Enalapril Vitabalans 5mg tablet
Gasec Gastrocaps 40mg hard capsules
Hipres 5mg tablet

Hipres 10mg tablet
Hydrocortisone DAK 10mg 1g ointment
Jangee 0.03mg/3mg film coated tablet
Jangee0.02mg/3mg film coated tablet
Kadcyla 100mg powder for concentrate for solution for infusion
Lidocaine Grindeks 100mg/1ml solution for injection
Metfogamma850 850mg film coated tablet
MXL 30mg prolonged release hard capsule
Paracetamol Kabi 10mg/1ml solution for infusion
Prokanazol 100mg hard capsule
Qlaira film coated tablet
Sandimmun Neoral 25mg soft capsule
Simvacor 10mg film coated tablet
Zoladex 3.6mg implant
Taflotan 0.015mg 1ml eye drops solution
Toujeo 300 units/ml solution for injection
Tramadol KRKA 100mg Prolonged release tablet
Valocordin Diazepam 10mg 1ml oral drops solution
Vendal retard 60mg prolonged release tablet
Ventolin 100mcg pressurized inhalation suspension