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Gap and requirements analysis for IDMP compatible application forms

D3.1: Gap and requirements analysis document

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Deliverable abstract

This document is the summary of the outcome of deliverable “3.1: Gap and requirements analysis for providing the IDMP compliant application dataset”. This deliverable was created within task “*3.1 Perform a GAP-Analysis between the current application datasets and supporting tools and the IDMP standards*”.

In this task, the WP members evaluated the gaps between the AS-IS “PDF based legacy application forms” and the TO-BE “IDMP compatible web forms”. The outcome considered multiple perspectives:

- Data structure
- User Interface
- Data content
- Data authoring process
- Functional and non-functional requirements

A detailed requirements documentation can be found in the AGES confluence wiki.

This deliverable is the input for the following software engineering process, which will deliver the technical implementation in an agile development methodology.

Keywords: AGES, ISO IDMP, SPOR, REFACTORING, WEBFORM, eAF, PDF

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Deliverable review

	Internal reviewer: UNICOM WP3 partners			External reviewer: EMA		
	Answer	Comments	Type*	Answer	Comments	Type*
Is the deliverable in accordance with						
the Description of Action?	☒ Yes ☐ No		☐ M ☐ m ☐ a	☒ Yes ☐ No		☐ M ☐ m ☐ a
the international State of the Art?	☒ Yes ☐ No		☐ M ☐ m ☐ a	☒ Yes ☐ No		☐ M ☐ m ☐ a
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structured, logical and easy to understand?	☒ Yes ☐ No		☐ M ☐ m ☐ a	☒ Yes ☐ No		☐ M ☐ m ☐ a
suitable to meet its intended scope?	☒ Yes ☐ No		☐ M ☐ m ☐ a	☒ Yes ☐ No		☐ M ☐ m ☐ a
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* Type of comments: M = Major comment; m = minor comment; a = advice

List of abbreviations

Abbreviation	Complete form
ADO	Azure DevOps
AGES	Austrian Agency for Food and Health Safety
API	Application Programming Interface
CDM, LDM, PDM	Conceptional, Logical, Physcial Datamodel
CMDx	Coordination Group for Mutual Recognition and Decentralised Procedures (human or vet)
DADI	Digital Application Dataset Integration
DCP	Decentralised Procedure
DES	Data Exchange Standard (eAF PDF)
DoA	Description of the Action
eAF	Electronic Application Form
EC	European Commission
eCTD	Electronic Common Technical Document
ePI	Electronic Product Information
EMA	European Medicines Agency
EMRN	European Medicines Regulatory Network
FHIR	Fast Healthcare Interoperability Resources
IDMP	ISO Standard for the “Identification of Medicinal Products” (also ISO IDMP)
IRIS	A secure online platform for handling product-related scientific and regulatory procedures with EMA
EU IG	EMA EU Implementation Guide
ISO	International Organization for Standardization
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MEA	AGES Medicines & Medical Devices business segment (German: Medizinmarktaufsicht)
MG	Management Group (eAF-MG)
MP	Medicinal Product
MRP	Mutual Recognition Procedure

NCA	National Competent Authority
NtA	The EC group “Notice to applicants”
OMS	Organisation Management Services
PDF	Portable Document Format (mostly known from Adobe)
PHAROS	Pharmaceutical Organisation System at AGES
PM	Project Manager
PMS	Product Management Services
POC	Proof of Concept
RMS	Reference Member State
RMS	Referentials Management Services
SMPC	Summary of Product Characteristics
SMS	Substance Management Services
SPOR	EMA service delivering quality data management services for substances, products, organisations and referentials (SPOR) to power EU regulatory activities.
UX	User Experience (Optimising the user Interface, system interaction and general journey)
vNeeS	veterinary Non eCTD elektronic Submission
WP	Work package
XEVMPD	Extended EudraVigilance Medicinal Product Dictionary
XML	Extensible Markup Language

1 Executive summary

Applying for authorisations for medicinal products and managing their life cycles is a regulated process supported by electronic application forms and supporting electronic tools. At the moment neither the structure of application forms nor the PDF based tools for initial authorisations, variations and renewals are supporting IDMP standards. Thus, it is not possible to automate and feed regulatory processes with IDMP compatible data and easily re-use the data in EU-wide eHealth services. The change to move to online IDMP compatible forms was triggered by the regulatory network. This initiative is now also supported by the EU commission via the Horizon 2020 programme.

It is an objective of UNICOM WP3 to provide basic work to overcome this current situation by developing IDMP compatible online tools, which are able to provide IDMP compatible application datasets. The roll-out of the new tools will be organised by the European Regulatory Medicines Network (EMRN) and is not in-scope of the UNICOM project.

In mobilising activity, the project team assessed the optimal approach to delivering the solution, and ensuring that the solution architecture and technology choices provide a future proof solution. This included discussions with EMA information technology representatives to confirm alignment with the EMA technology strategy in order to enable EMA to provide the long-term support arrangement, hosting and maintenance and continued enhancement of the IDMP compatible application forms in a stable network environment.

The Agency recommended to utilise the platform “Power Apps” which is already in use at the EMA for other types of applications (e.g. for orphan drugs) in the IRIS system. The platform also provides a re-usable integration with SPOR services and EMA’s user management. To evaluate the viability of “Power Apps” as a development platform, a proof of concept (POC) was undertaken by EMA in July which showed first promising results.

After the agreement of the UNICOM partners to follow EMAs recommendation to use “PowerApps”, EMA takes over the responsibility of developing the technical implementation of the application forms as part of the DADI project.

IDMP standards describe the underlying concepts and semantics, while FHIR is the necessary implementation to exchange IDMP compatible data. The FHIR implementation was also chosen by EMA as a foundation technology to establish data interoperability. For these reasons this document considers IDMP, as well as FHIR topics.

This document is the summary of the outcome of deliverable “3.1: Gap and requirements analysis for providing the IDMP compliant application dataset”. This deliverable was created within task “3.1 Perform a GAP-Analysis between the current application datasets and supporting tools and the IDMP standards”. In this task, the WP members evaluated the gaps between the AS-IS “PDF based legacy application forms” and the TO-BE “IDMP compatible Online Tools providing a PDF representation and FHIR message data export”. The outcome of WP3’s work is the basis for the technical implementation in an agile software delivery methodology.

The authors followed the approach to group the analysed gaps into five topics:

Chapter “User experience”

The current application forms are derived from a “paper world”, which was transformed into PDF based forms. There are some improvements being made in the latest versions of the variation form on dynamic data entry, which will be further enhanced. The new web based and IDMP/FHIR structured tool for entering application data will therefore be a significant next transformation. This chapter describes the change of the user experience.

Chapter “Content of application forms”

This chapter describes gaps related with the data content of application forms. Although the content of the application form will remain mostly the same, there are some structural changes necessary to comply with the IDMP model. These changes encompass mostly in the context of “product name”,

"package" and "composition". Structural and content amendments will also be necessary to include "indication" data.

Beside visible changes, the technical data backbone needs to be refactored to follow IDMP/FHIR. The current Data Exchange Standard (DES) will be superseded by FHIR[3] resource definitions.

Chapter "Data authoring Process"

In this chapter the differences in authoring data will be summarised. Current application forms are based on PDF technology. The new forms will be made available as an online toolset based on a new technology. This triggers a process change including stepping away from offline PDF forms towards an integrated online application form environment.

In addition, the SPOR Product management system will be used to feed existing product master data into variation forms. Utilising product master data will simplify the process for applicants and reduce administrative burden because available data doesn't need to be entered again. In a stepwise approach free text fields will be converted into structured data fields (within the UNICOM scope and post UNICOM).

Maintenance and further development

Maintaining the current PDF based application forms and keeping track with legal and business requirements was a challenge in the last years, as a vast community is using them. A maintenance team (eAF MG) is responsible to manage change requests. As the PDF technology doesn't fulfil user requirements anymore and EMA needs to decommission the existing Adobe Infrastructure the new tools will be developed in a new technical framework provided by EMA. This chapter describes this transformation.

Requirements Analysis

This chapter describes the first approach to the requirements analysis process for the new web application forms. It also describes how the intermediate requirement results are transferred to the EMA in the context of the new development approach as part of the joint project "DADI". In essence the new requirement analysis procedures from EMA follow the proposed methodology Microsoft 365.

[3] See https://build.fhir.org/

2 Content of the deliverable

2.1 Contents of the deliverable

Application forms to apply for an authorisation, variation or renewal of medicinal products are the source of structured medicinal product data in Europe. With the publication of the IDMP standard and its goal to harmonise data structures and align semantics, it makes sense to review the current situation and to utilise new opportunities in order to benefit from IDMP compatible medicinal product data in relevant regulatory or eHealth related processes.

Work package 3 within UNICOM is one of the first initiatives to create an implementation of IDMP utilising the FHIR backbone. FHIR is being used to define the message structure containing the information from the eAF. A web technology stack[4] was chosen to provide the forms to the users.

This deliverable will describe the transformation needs from the legacy PDF based application forms towards IDMP/FHIR compatible web-based forms and data export. It will describe gaps around functionalities, data content and structural representation. This deliverable is the basis for the detailed requirements analysis (use cases and user stories) which are contained in the documentation from WP3. It is also a basis document for the upcoming software development process run by EMA.

2.1.1 Additional information

Further information about the current application forms can be found here:

https://ec.europa.eu/health/documents/eudralex/vol-2_en

http://esubmission.ema.europa.eu/eaf/index.html

2.2 Authorship and responsibilities

This deliverable is created by members of the WP3 team and the work is led by AGES – Austrian Medicines Agency.

[4] The WP3 steering group decided to follow EMA's recommendation to use EMA's technology stack for the technical implementation of the web forms.

3 User experience

This chapter describes the differences between the current forms and the future situation how users will interact with the system as well as the genesis.

The current PDF based application forms for new marketing authorisation, variation and renewal are originally based on paper and later on MS Word templates.

The following overviews explain the genesis and the pros and cons in the context of the user experience of the underlying technologies.

MS Word based forms

Advantages	Disadvantages
• Lots of freedom due to free text fields • Easy to fill in by applicants • MS Word formats widely accepted	• No possibility for applicants to automatically import data into Word files • No possibility for regulators to automatically extract data and import into IT systems • Ambiguity is possible, as information in the same field may vary in semantics for different applications resulting in low quality, high error rates and resubmission • No IT support to ensure the usage of controlled dictionaries

Table 1: MS Word based forms

These Word templates were then transformed into PDF based forms and over the years many extensions, such as comfort features to improve user experience and data quality have been implemented.

PDF based forms

Advantages	Disadvantages

• Mandatory usage of controlled dictionaries
• Selection from catalogues and organisations from RMS/OMS
• Pre-filter for some lists where necessary
• Introducing Automatic duplication of data to be used in different sections of the form
• Validation on required fields and sections
• Comfort features like
  ○ Copy data between similar sections
  ○ Copy entire sections
  ○ Enhanced implementation of business rules for user guidance
	• User needs to enter the same data multiple times in certain sections.
	• Response time when opening the PDF is very slow
	• Some functions like selection of RMS controlled terms are disabled when working offline
	• PDF technology requires security settings to enable web service connections. This increases the complexity for users
	• Further improvements in the user experience is hindered by the PDF technology

Table 2: PDF based forms

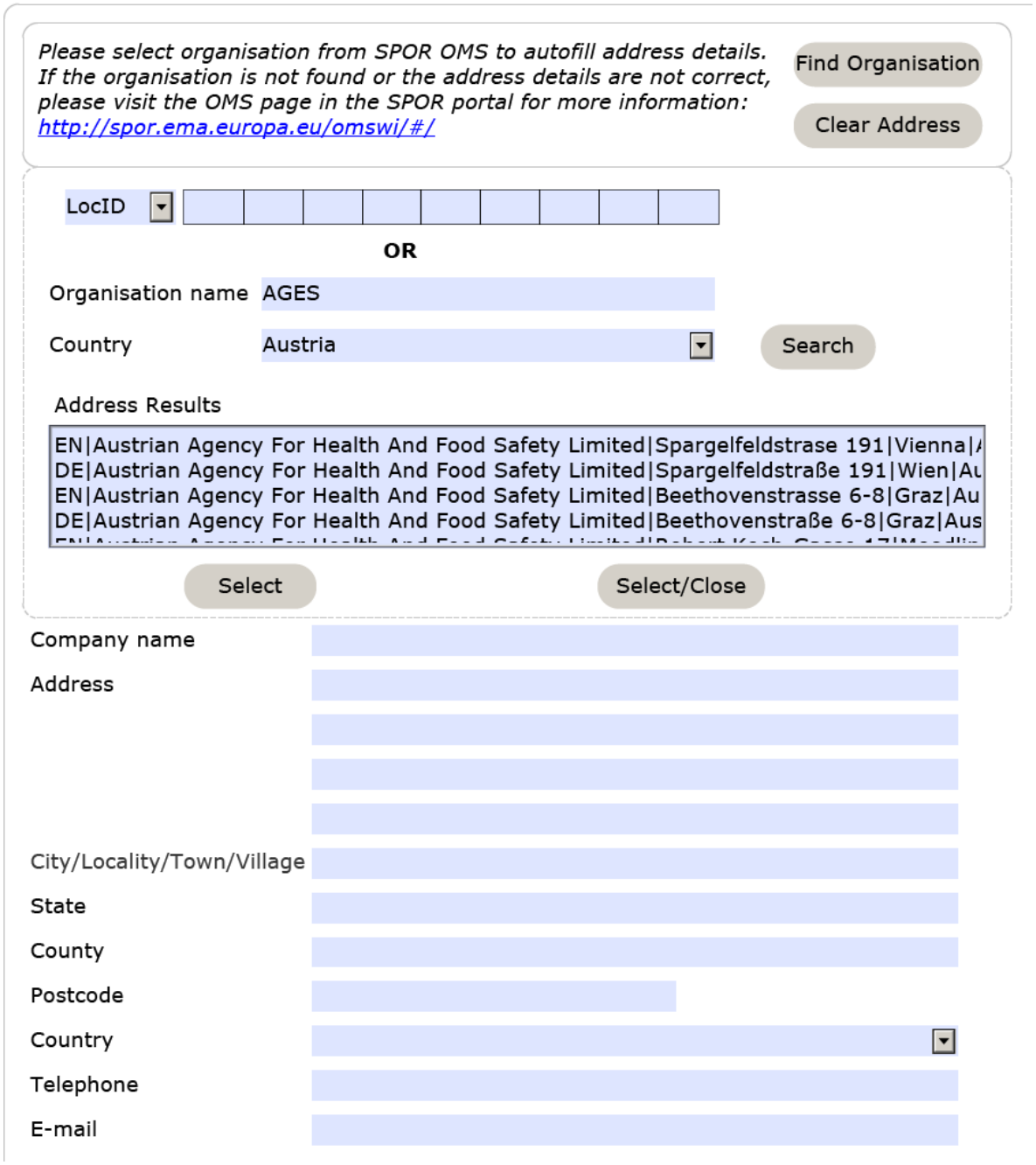

Figure 1: eAF PDF OMS selection

One of the reasons to choose a new technology basis is that some user experience related requirements cannot be fulfilled anymore with the current PDF technology and a new framework had to be chosen to be fit for the future[5].

Based on the recommendation from EMA the platform “Power Apps” will be used to develop the user interface as this technology is also used for other application form at the agency (see Executive summary).

The anticipated state of user experience supported by the new technical possibilities will be as following:

Goals and principles of the anticipated state

• Higher performance due to replacing PDF XFA technologies
• Improved integration of SPOR web services increase UX and performance
• Reuse and import of master data for products available from PMS rather than typing in[6]
• Exclusive use of master data for organisations, referentials and substances by selecting from SPOR to increase data quality
• Easier maintainability due to the use of a maintained standard development system
• Data input is optimised
  ○ User interface control elements are state-of-the-art for online based tools
  ○ Comforts of browser add-ons (fill in helper / suggestions, etc.)
  ○ Further minimising duplication of data entry
  ○ Intermediate input validation rather than all validation at the end of the form
  ○ Better structural overview, logical structuring of data elements on input pages
• Enabling co-authoring by inviting other users
  ○ Organisations can handle their security authorisations online to allow for consultants
• Improving the management of application sets
  ○ Users get an overview of their draft datasets in an online portal

Implications for the anticipated solution
• Online presence is required to fill in data • Users need to get registered with EMA in advance • OMS/RMS/SMS registrations need to happen before the application is drafted. This is the case for all organisations if OMS use shall become mandatory. • Some more advanced user experience features will become available incrementally via follow up production releases according to the agile software methodology • Users need to get trained with new layout and ordering of the data input • The look and feel while entering data is different from the official NtA form. The official representation of data (eAF PDF representation) will be available on demand and used for regulatory activities.

Table 3: Web form as data entry

[5] The other main driver is data integration;

[6] Supporting updates from PMS during the authoring of the dataset from either the authorised product or a running variation is an option and potential solutions will be discussed during implementation

4 Content of application forms

The content of application forms is defined by legal and regulatory needs. The EC group “Notice to applicants” (NtA) is responsible for the content definition of the application forms (see https://ec.europa.eu/health/documents/eudralex/vol-2_en). Changes triggered by NtA or by regulatory needs are organised in the eAF Maintenance Group (eAF MG)[7] at EMA.

The IDMP standard together with the FHIR model will have an indirect impact on the content of the eAFs. The scope of the content will not be changed but the standards will have a major impact on the data representation and details in the future. There will be a significant change how the information is structured. This will require some logical additions to existing content. Such modification will enable, among other things, linking of the composition to a specific product contained within an initial marketing authorisation application for centrally authorised products.

These changes will also introduce further improvements for e.g. “Name”, “Substance”, “Strength” content elements. These elements currently have to be entered in multiple sections of the the PDF (e.g. in the declarations), causing potential discrepancies and inefficacy. As IDMP approaches data grouping as an “entity relation model data” this content will be linked rather than duplicated.

The goal of the new implementation is to keep it as close as possible to the NtA defined content scope, without sacrificing usability. This is due to the endeavour to make the transitions for users easier and avoid long NtA change processes. Therefore, even though the input of data might be structured differently, at the end of the process a PDF representation can be exported that will look the same as the PDF forms today.

4.1 Transformation of content

Although the goal is to transform as little content as possible, amendments are necessary to become compatible with IDMP and FHIR and some changes in synergy with the general change process as they make sense in conjunction.

This chapter provides an overview of currently identified main impacts on the eAF content. For a better illustration, examples are included.

4.1.1 Package

Although the information about packages is the same, the new forms will ensure a more structured data content which provides additional flexibility without the need to enter data in free text. The order of container and package elements have changed and the package can now be entered in a recursive way – to say an (inner) package can be part of an (outer) package, that is part of a (primary) package, and so on. This has to be supported by the user interface and the FHIR resource structuring.

The illustration below displays the current structure of packages in an eAF where the package describes the container involved and the different pack sizes available.

[7] http://esubmission.ema.europa.eu/eaf/

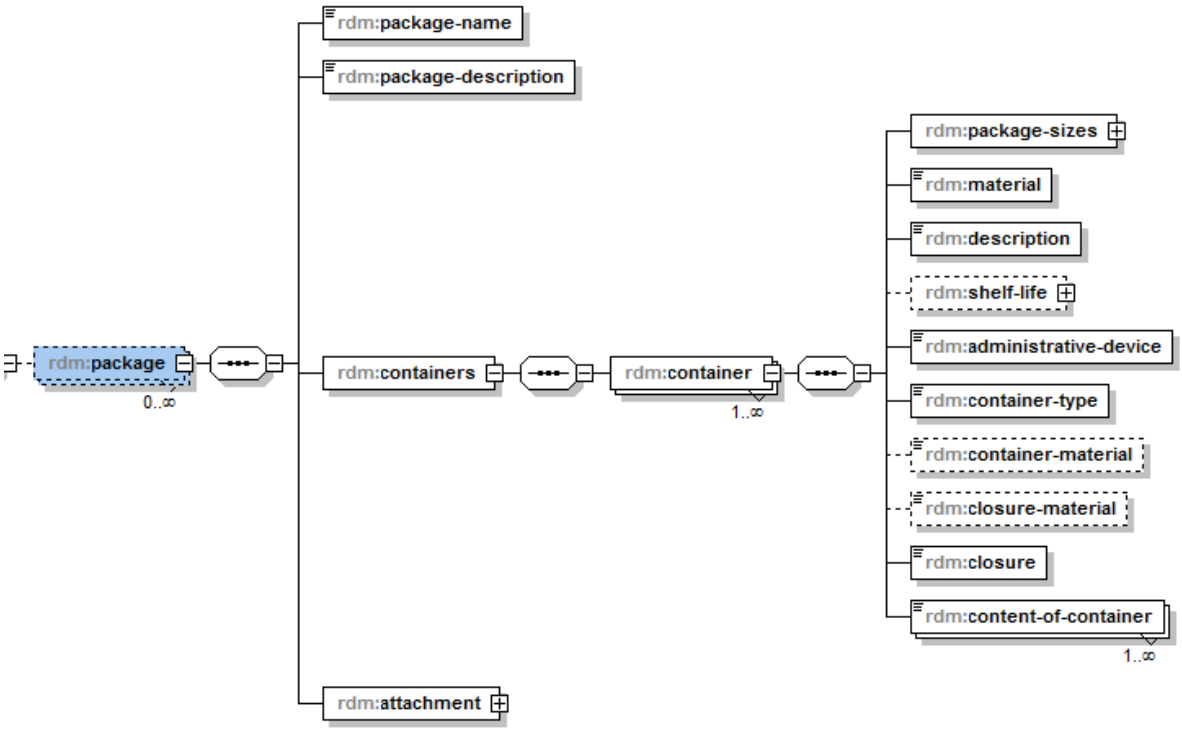

Figure 2: eAF AS-IS structure of a package

In contrast, the TO-BE structure in FHIR depicts a scenario where a “packaged product” contains a packaged item that has a type of package and a self-reference to allow for containers in container. In addition, the packaged item contains a reference to a number of manufactured items. This allows for needed hierarchies and linkage of manufactured items and packaged products.

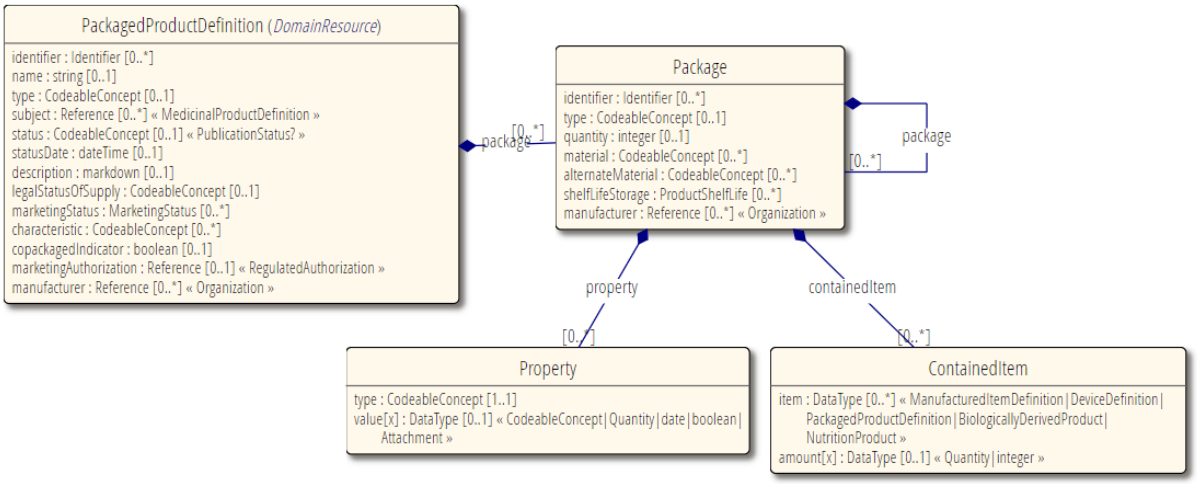

Figure 3: TO-BE FHIR structure of a package

Furthermore, the IDMP standards clearly define the semantics on how to describe a package data in a more defined way than the current eAF, e.g. rather than text

1. the package size is clearly defined as a number,
2. material is a choice of controlled terms from RMS
3. the manufacturer is linked by a reference identification
4. characteristics/properties have separate fields and don’t need to be all within “description”

4.1.2 Organisation and Contacts

Organisations and contacts in the current eAF are used in several sections e.g. to include a person for a manufacturer, MAH, responsible persons for various obligations. The new tool will introduce improvements.

The detailed representation of an “Organisation” and its locations” will be described only once preferably based on mandatory selection from OMS. This will avoid administrative effort when entering data.

Contact persons will be mainly structured in a “Contact lists and attributed with their role rather than scattered throughout different sections of the form. To enable a list of different types of contacts RMS has created a contact type list and FHIR a section for medicinal product contacts.

4.1.3 Manufacturers

The list of fields used to describe a manufacturer will be standardised, so that all types of manufacturers have a similar level of information.

The only difference will be that some have a link to another resource in addition e.g.:

- substances – substance manufacturer
- package – package manufacturer
- device –device manufacturer

There will no longer be a different section for each manufacturer, but one consolidated section containing all manufacturer described by their details and manufacturing activities (or “Operation” as it is named in FHIR).

4.1.4 Ingredient

The concept of “ingredients” is defined by the IDMP standards. The list of ingredients can be compared to “qualitative and quantitative composition” in the current eAF.

IDMP standards enable a more specific description of the eAF content:

- A more specific strength definition for each ingredient, whereas the current eAF has limitations.
- It allows both a “low” and a “high value” to be specified, upper and lower range, as well as a comparator for each value, whereas in the eAF the comparator is used to depict only one of these options.
- Enables to specify a reference strength and an active moiety, whereas the eAF allows for either a base strength or an active moiety.
- There will now always be a presentation strength and in addition, a concentration strength can be specified as well

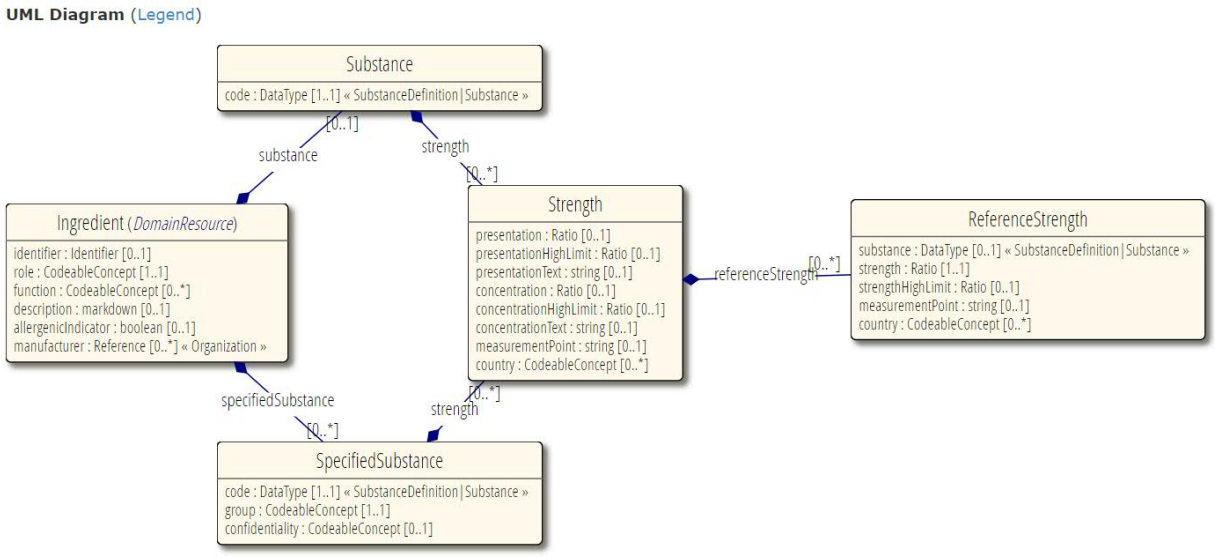

Figure 4 IDMP Ingredient represented in FHIR #R5

4.1.5 Manufactured item and Pharmaceutical product

Pharmaceutical products are administered to the patient in contrast to the manufactured item, which is the way it is produced and contained in a package.

The current application forms are not able to distinguish these two elements (manufactured item and pharmaceutical product) and usually only describe the manufactured item, although the header is called “pharmaceutical product” (see eAF MAA section 2.6).

ISO IDMP standards introduce a more detailed concept to distinguish between the “pharmaceutical product” and “manufactured items”. This required split could be considered as additional information in relation to the current NtA form, or as another way of representing current information.

In case the product is administered as it is manufactured, the ingredients (see chapter 4.1.1) will be linked and reused and the content is the same as for the manufactured item.

In other cases there will be individual compositions defined.

What is missing in IDMP standards and the EU IG is a more refined grouping of ingredients into logical parts to depict e.g. capsule core, capsule shell, printing ink as a composition group, as it is used in the eAF today.

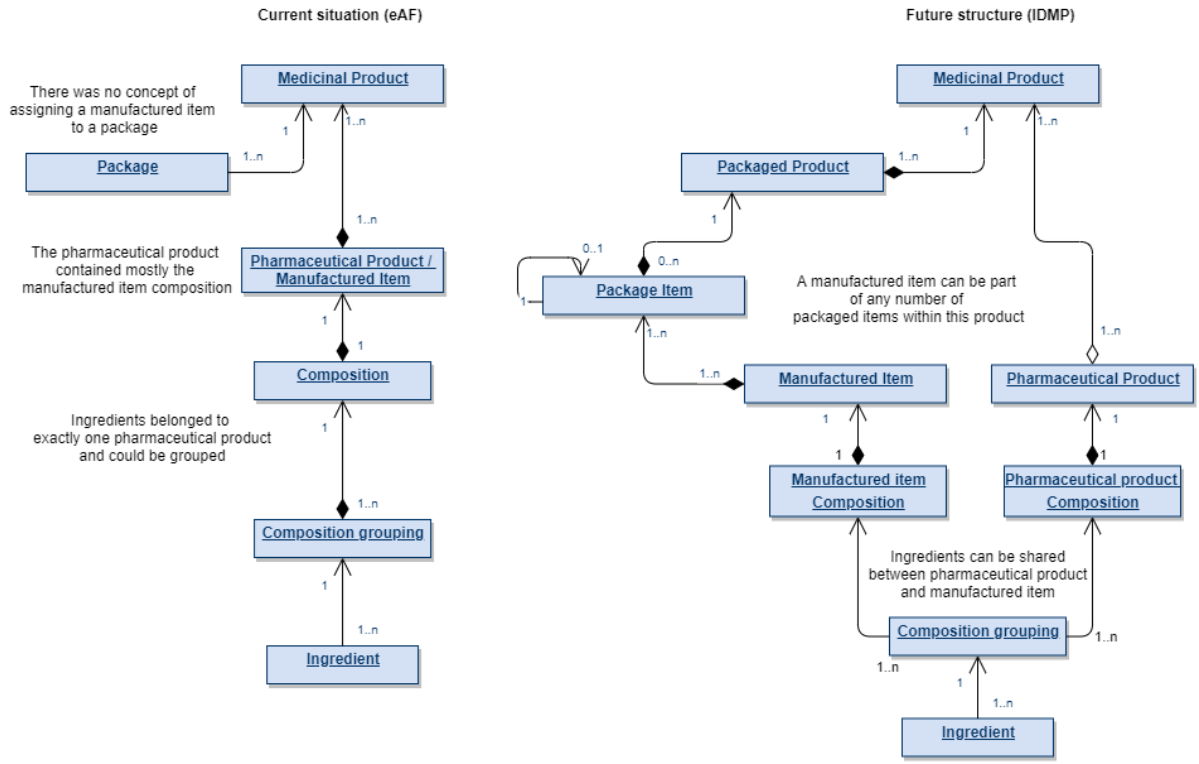

Figure 5: Composition comparison eAF / IDMP

4.2 Transformations in the content backbone

The content of the eAFs is stored in an electronic data format. This underlying technical structure is formatted in XML with a schema definition that is called “Data Exchange Structure (DES)”. This architecture allows regulators to consume the data content in an automatised way. The full eAF content can be provided to IT systems using a PDF native XML export. Applicants can utilise this technique and input data into the form by populating the XML backbone with data from applicants’ IT systems. The syntax of the XML validates against the DES that is being published by the eAF maintenance group on an EMA website.

Both the data format definition DES and the resulting XML export have the disadvantages of containing a lot of PDF specific and unnecessary elements, they do not always reflect the order of fields and have no continuous naming, - or structure convention.

To overcome these drawbacks the future tool will be based on a new underlying data structure. The new format will utilise the concept of FHIR resources and resource bundles. The resource definitions are published and documented extensively online on the FHIR website[8].

The new backbone design follows the decision made by EMA to use FHIR as an exchange standard in the EMRN. FHIR is being used for IDMP and SPOR implementations[9] and is therefore the logical consequence for the new application forms’ backbone.

[8] See http://build.fhir.org/ (draft version)

[9] See SPOR API under https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/substances-products-organisations-referentials-spor-spor-api-v2-specification_en.pdf

The next table compares the future FHIR based structure with the legacy DES backbone:

FHIR based backbone	DES based backbone
• International standard supported by a wide community • It is easy to present information in an IDMP compatible structure • FHIR has a resource relational concept which allows for reusing identical information • FHIR is used across business domains • Publicly available FHIR servers for training and testing purposes • FHIR allows for extensions, but they are only known within the specific business domain • New data elements to the standard require time consuming ballots and can be rejected • FHIR foresees key/value pair concepts for attributes and lists, but having different lists for the same field can make automatic data extraction complex • A code able concept or a reference can contain different elements only known at runtime making automatic data extraction complex • Lose coupling of data standard and user interface • FHIR supports validation against publicly known schemas and project specific profiles •	• Proprietary standard for application forms, based on PDF specifics • Applicable only in Europe, no community forums to support implementers • Not compatible with IDMP standards • The standard doesn't support relational concepts[10] • The user interface of the application form needs to copy identical data across sections • DES contains duplicate elements because the PDF User interface requires it • No standalone validation methods are available for IT systems, validation is possible within the PDF user interface • DES is only used within regulatory activities within authorisation and lifecycle management of medicinal products

Table 4: Comparison FHIR / DES based backbones

[10] (e.g. For centralized products, when several products are populated in the form, it is not possible to determine which packages are associated with each product)

4.3 Possible content extensions derived from additional business cases

As described above the content of eAFs is defined by legal and regulatory needs under the responsibility of NtA based at the European Commission. Content extensions can only be made with NtA agreements.

However, since the new tool is also intended to support additional business cases the challenge is to find a way to both comply with this restriction and to make an extension technically possible.

The current business cases are the following:

- Initial applications for marketing authorisations
- Variations of marketing authorisations
- Renewal of marketing authorisations

Future potential business cases might extend the current usage of the web forms and underlying data backbone:

- Utilise the data content to also populate SPOR PMS, Article 57[11]. and the Union Product Databases (veterinary domain) The SPOR Taskforce has published a stepwise approach to replace the current XEVMP format by the eAF data backbone[12].
- Further Post-Marketing data related activities (e.g. availability reporting, MAH transfer,…)

Supporting “electronic Product Information ePI”

It is out of scope of UNICOM to realise the support for further business case but the fundamental architectural concepts will consider the future needs. The implementation will be organised by separate projects driven by business needs and the EMRN strategy.

4.3.1 Potential extensions

The following business cases will trigger extensions of the defined eAF context

Potential extensions in the context of Article 57(2) of Regulation (EC) No. 726/2004

EMA plans to replace the XEVMPR format with a FHIR based messaging. Additional data elements for the Art. 57 (2) are necessary compared to the eAF relevant scope like

- Indications are currently not in scope of the electronic application forms. At the moment indications are only contained in SMPCs and national texts. They are also part of the Art. 57 database, in accordance with Article 57(2) of Regulation (EC) No. 726/2004.

- Marketing authorisation holder's contact email address and telephone number for pharmacovigilance enquiries.

Context of the implementation of the Veterinary Medicinal Product Regulation (EU) 2019)

Although the veterinary domain is not directly included in the UNICOM project synergies with the human domain were identified and if possible, will be implemented. The veterinary domain will also utilise the new tool with additional data elements.

[11] This database is defined by Article 57(2) of Regulation (EU) 726/2004. See also https://www.ema.europa.eu/en/human-regulatory/post-authorisation/data-medicines-iso-idmp-standards/data-submission-authorised-medicines-article-57

[12] https://www.ema.europa.eu/en/human-regulatory/research-development/data-medicines-iso-idmp-standards/spor-master-data/substance-product-data-management-services#eu-idmp-implementation-guide---version-2.0-section

4.3.2 Technical approaches to consider extensions

This section describes how extensions are made possible under the condition that the official eAF is conserved in its current format.

User experience

The user interface will enable the applicant to enter additional data needed for further use cases. These data elements will be marked and special business rules will apply.

Technical backbone

The technical data structure of the eAF message can evolve in future releases to include additional FHIR resources needed to carry information for other data consumer e.g. PMS or Art.57.

eAF representation used for submissions in regulatory submissions

The official eAF representation in human readable PDF used for submission in regulatory submissions will only include data content as defined by NtA.

4.3.3 Indications

Indications are currently not in scope of the electronic application forms. At the moment indications are only contained in SMPCs and national texts. They are also part of the Art. 57 database, in accordance with Article 57(2) of Regulation (EC) No. 726/2004.

EU Implementation Guide v2	Mandatory (at least one language)
FHIR R5	Optional
eAF content	Not available

Conclusion:

As this is foreseen as a major change it is not part of the first implementation of the new IDMP/FHIR-based application forms.

5 Data authoring process

5.1 General AS-IS process

Application forms are currently available for download via the EMAs website[13]. Applicants have to make sure that the latest versions are used After entering application data into the application form (eAF) the authoring process will be “finalised” by adding a signature scan (picture) into the PDF.

The applicant has to include the eAF in the relevant dossier for submission, either inside eCTD module 1.2 (human) or inside the vNeeS dossier (veterinary).

The following section describes the AS-IS process and the planned process changes when entering data.

5.2 General TO-BE process

In the future scenario all application forms will be replaced by online web forms[14].

These web forms will only be accessible by a unified application platform provided by EMA. This platform requires personalised user credentials which can be acquired with EMAs identity management system. The underlying registration and access process is harmonised and in line with other existing similar use cases.

Once the user is logged in to the application platform, they can select the appropriate application dataset type and create new or continue with existing datasets.

The submission of the PDF representation of the finalised dataset within dossiers is the same as the AS-IS process.

5.2.1 Details Variation Forms AS-IS

The current variation form is split into four parts:

1. procedural information,
2. basic product masterdata
3. product changes (variation classification and product changes)
4. section about paediatrics and orphan

The information given in the “**procedural information”** section defines the type and classification of the variation and limits the selections that can be made in the “product changes” section.

The variation classification defines the scope of the changes and is based on the classification guidance[15].

The “**basic product masterdata**” section contains the main attributes of the concerned products of the variation. Key values are used by data importing tools at regulator level to automatically identify products, which are relevant in this variation. Additional attributes are mainly used for plausibility checks, to ensure that the correct products are included in the variation application.

The “**product changes**” section allows for the input of the current product masterdata values and the input of the proposed value of a change (present and proposed concept). These values are free text with one exception. It is possible to select an organisation from SPOR OMS or even add a graphical information.

[13] http://esubmission.ema.europa.eu/eaf/index.html

[14] The result is a FHIR message. The definition will be published to enable creation by IT systems (e.g. RIM from applicants).

[15] https://ec.europa.eu/health/sites/health/files/files/betterreg/pharmacos/classification_guideline_adopted.pdf

In case of groupings, the change is described once and is then relevant for all products mentioned in application form.

The last section “about paediatrics and orphan” is only available for type II of IB variations.

5.2.2 Details Variations Form TO-BE

In the future the applicant will be guided through the form to:

- **First,** select the concerned products. The section “basic product masterdata” will no longer be asking for manual input of product data, but prompt to select the concerned products from the product management repository, SPOR PMS, and automatically depict its masterdata. There may be restrictions on who can select which product, so the login credentials would be forwarded to the SPOR system, and the product list may be limited accordingly. The selection of the products will also have an impact on the change section.

- **Second,** specify the changes by selecting the variation classification and their respective variation types. This selection of the variation classification will set the context of further steps and will dynamically define relevant product data elements, which have to entered. The selection of the variation classification will limit the number of product fields shown and display only the relevant data input and its context

- **Third,** the system will be able to derive the procedure type, the domain and the grouping/worksharing information based on the selected products and variation classifications

- **Finally,** the user will describe the changes to the products or the marketing authorisation This section will no longer only have free text fields for present and proposed data, but will reuse the official product information from SPOR PMS and display it if it is available. This data will be changeable in a structured format to indicate the proposed value.

In summary the following will be implied:

- Rather than free text there will be structured data input elements for text, numbers, dates, RMS controlled term list select choices and OMS/SMS/PMS based master data.

- As PMS is a system that is being developed stepwise, there will be free text changes in the variation form in the beginning, which will be replaced with explicit data fields once they become available in PMS.

- Legacy data from SPOR PMS will show current data in variation forms with all impurities that exist today. If these are not cleaned before utilised in variation process, they could very likely be changed within the variation, changing more information than initially intended. This will be a challenge with variation classifications and fees, but will ultimately clean the legacy data of the Article 57 EMA / MAH database, which is the source for PMS.

- There will be separate data input elements per change for each selected product. This is in contrast to having one shared input element for all products per selected variation topic in the current form. Currently the data propagation to each product is done manually at the receiving end, at regulator level.

  The future process will shift this to the applicant side, minimising errors due to misunderstanding and ensuring that the application form contains all data already propagated correctly. This means that the relationship between the requested data change and the product is already specified during input. For example, changing a package size for two products will show all packages for both products and the applicant will update the relevant content for both products. There may be sections where the change can be propagated automatically but in most cases

the applicant has the duty, but also the ability to indicate the exact location of the change for every product.

- A delta view on the data elements subject to change and their present information will be generated for the regulators to indicate what has been updated for which products.

- The variation form content can be used to maintain SPOR PMS content with the MAH applicants providing the application dataset and NCAs validating and assessing the submitted content. Starting the variation procedure, products will be selected directly from SPOR PMS and once the application form is validated, this information can be used to update all information systems. This would substantially improve data quality for EMA and the network.

- Finally, the time it takes to fill in the form will be substantially decreased due to
  - Seeing mandatory fields right away with online validation on leaving a field
  - 3rd party tools like auto complete for forms
  - A generally leaner structure to enter data
  - Improved performance to open and manipulate the forms

5.2.3 Details Initial Marketing Authorisation and Renewal Form TO-BE

The MAA form today is a rather large PDF form containing several hundred fields. Due to the change in technology to a web frontend, there are some aspects on validation and performance, which will improve the productivity of filling in the form.

In the future, the MAA, renewal and the variation forms will share the section describing the medicinal products (basic product masterdata).

The future MAA and renewal forms will also benefit from selection from PMS to include reference products

5.2.4 Line Extensions

Currently there is no plan to rework the process of line extensions in the first release of the project although we are discussing an improvement to the data authoring process. The suggestion is to split the different types of line extensions into two groups:

1. Line extensions that change an existing product (e.g. adding a route of administration)
2. Line extensions that create a new product (e.g. adding a strength)

Ideally the first group what use the variation form to provide the suggested updates to the product and the second group would use the MAA form to specify the details of the new product.

5.3 Utilising RIM systems to create application datasets

As some pharmaceutical companies have all the necessary information for an application dataset in their respective IT-systems, the data does not have to be manually drafted in the new web form.

Applicants will be able to reuse data from their respective IT-System to create FHIR compatible data.

To provide applicants with the means of validating against business rules and creating the human readable PDF representation a tool will be provided that follows the same validation rules as the online webform.

6 Requirements Analysis

The requirements analysis was organised by a dedicated topic group. The first phase included a series of workshops with representatives of the various stakeholders (WP3 partners, EMA, industry) and the review of the EU implementation guide v2. The work was structured into a number of topics and results are documented in the AGES confluence[16].

- A list of "epics" – large use cases – that describe the functionality of the system
- A list of data fields and their business rules
- A mapping to FHIR and a list of open issues on difficult mappings

6.1 Document functional requirements

The initial draft use case diagrams specifies a baseline of the main use cases and a list of epics describes the general functionalities of the system.

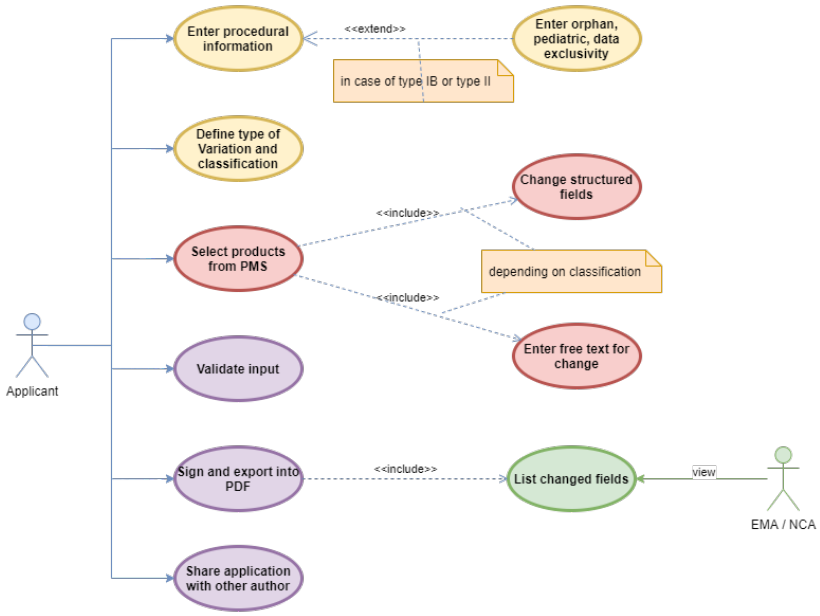

Figure 6: Use Case diagram (web form) As an applicant I want to enter procedural information

- As an applicant I want to define the type of variation and chose the possible classifications associated
- As an applicant I want to select the products concerned by this variation from PMS
- As an applicant I want to see the fields I can change in accordance to the variation classification
- As an applicant I want to enter free text for the non PMS fields concerned by my classification
- As an applicant I want to enter orphan, pediatric and data exclusivity information for IB and type II variations
- As an applicant I want to validate the entered information against the FHIR profile
- As an NCA I want to see the fields that have been changed
- As an applicant I want to export my application into a signed and validated PDF with a FHIR XML attachment

[16] https://confluence.ages.at/display/UIMPH2H/TO2+Requirements+Analysis

- As an applicant I want to share my application for other authors to contribute

6.2 Document Business Rules for Variation form

The main focus of the requirements was on defining the data fields and their business rules. This includes a mapping between eAF and FHIR and a restructuring of the content to be IDMP compatible. The results can be downloaded as excel in the detailed specification.

6.3 Create FHIR Resources

Steps to create the FHIR message

1. Identify all fields necessary in a product variation already included in the MAA
2. Identify missing fields from the MAA that are needed for a variation
3. Identify all fields concerning the PMS product outside of section 2 of the MAA and move them into section 2
4. Identify all fields missing in section 2 but needed to submit a PMS product
5. Augment FHIR ressources with the remaining attributes from the procedural information
6. Create a 2 part FHIR message including product and procedural information
7. Create a FHIR profile that validates variation form rules

During the mapping to FHIR it was decided to not introduce new FHIR resources, but to use existing resources as much as possible. The resources defining the medicinal product and its satellites need a few minor changes to accommodate the data.

The resources names “Questionnaire” and QuestionnaireResponse” might be able to handle procedure data. It is currently under discussion if this is a viable option.

6.3.1 Differences between EU IG, FHIR and eAF

While mapping fields between the eAF, EU IG and FHIR over 100 issues were identified. Gaps that were found between the application forms and the EU implementation Guide were submitted to EMA as part of the consultation phase for the version 2 of the document. Other gaps are being discussed as part of the detailed requirements analysis.

While encountering mapping issues a standard methodology was agreed upon depending on the nature of the issue:

I a) Data elements are listed in IDMP standards but are not in scope of the current eAF version and would need NTA decisions to include them.

e.g. indication

--> such elements will not be added, but noted and taken to a list for NTA for future releases

I b) Data elements are listed in IDMP standards but are not in scope of the current eAF version; CMDx or the regulatory group can decide about this content change

e.g. effective date of manufacturing business operation, paediatric business indicator

--> such elements might be added, if decisions are done according to our timelines

II) Existing eAF data elements have to be changed due to the new concepts (FHIR, IDMP, EU IG):

e.g. package, manufacturing item

--> as long as the content of the eAF is not changed this structural amendment will be implemented; Strategy listed in Ia, Ib will be considered.

III) Data elements exist in FHIR but are not in scope of the existing eAF

IIIa) → will be populated if it can be automatically derived *(e.g. confidentiality indicator)*

IIIb) → if no automatism is possible no there is no implementation

IV) Data elements in the EU IG but not in FHIR

→ Request to EMA is sent and the implementation commences once it is added to FHIR

V) Data elements in FHIR but not in the EU IG

→ Usually, a field that will be added to the IG in the future and will not be implemented now

VI) Data elements in eAF but not in the EU IG or FHIR

→ A FHIR extension is created and submitted for approval to EMA and ISO; information to WP 1 and probably the FDA

6.4 Set up requirements processes

A process was established where data structure and epics were described utilising the knowledge from predecessor projects, the UNICOM WP3 members and the eAF maintenance group. The results are documented in the confluence wiki mentioned above. These results are presented to the development team from EMA and are being transformed into the DADI requirements process using ADO (Azure Devops).

7 Development

The Development will now be based on the PowerApps platform of EMA and will follow the methodology defined by the underlying EMA software development methodology. The PowerApps platform is also used for other application forms and can therefor benefit from existing integration with IAM and SPOR systems. The initial approach to reuse Angular based technology from CESSP Phase I was discarded due to the recommendation from EMA to follow the unified application forms development approach.

7.1 Originally planned architecture concept for a PowerApps approach

Starting from FHIR datasets implemented by EMA, the UNICOM WP3 Team will develop the pdf files corresponding to these application forms, including also the validation of the FHIR messages against a defined set of business rules. Each generated pdf file will have enclosed its corresponding FHIR message. The automated import of data from these FHIR messages, once extracted from the pdfs by Competent Authorities, will reduce administrative tasks in all NCAs avoiding errors caused by manual handling.

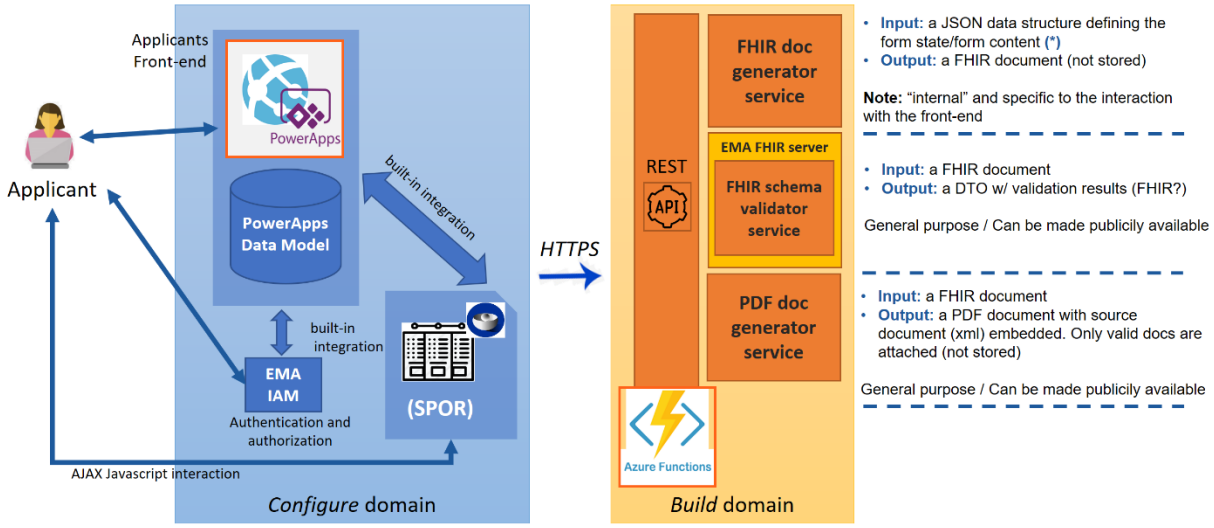

Figure 7: Originally planned PowerApps Architecture