

**The new Clinical Trial Regulation and corresponding
new EU portal and database:
an opportunity to enhance standardisation and
interoperability in regulatory systems**

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LIST OF ABBREVIATIONS

ANSI	American National Standards Institute
CAP	Centrally Authorised Product
CEN	Comité Européen de Normalisation, European Committee for Standardisation
CENELEC	Comité Européen de Normalisation Électrotechnique, European Committee for Electrotechnical Standardisation
CSR	Clinical Study Report
CT	Clinical Trial
CTA	Clinical Trial Application
CTD	Common Technical Document
CTP	Clinical Trial Protocol
CTR	Clinical Trial Regulation
eAF	electronic Application Form
EC	European Commission
eCTD	electronic Common Technical Document
EDQM	European Directorate for the Quality of Medicines and Healthcare
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHR	Electronic Health Record
EMA	European Medicines Agency
EMB	EMA Management Board
ESTRI	Electronic Standards for the Transfer of Regulatory Information
ETSI	European Telecommunications Standards Institute
EU	European Union
EUCTR	EU Clinical Trials Register
EudraCT	European Union Drug Regulating Authorities Clinical Trials
EUNDB	European Union Network Data Board
EURECA	Enabling information re-Use by linking clinical REsearch and Care
EUTCT	European Union Telematics Controlled Terms
EVCTM	EudraVigilance Clinical Trial Module
FDA	Food and Drug Administration (US)
GInAS	Global Ingredient Archival System
HIMSS	Healthcare Information and Management Systems Society
HL7	Health Level 7
HMA	Heads of Medicines Agencies
IB	Investigator's Brochure
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMP	Identification of Medicinal Product
IEC	International Electrotechnical Commission
IHTSDO	International Health Terminology Standards Development Organisation
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug application
ISO	International Standards Organisation/International Organisation for Standardisation

IT	Information Technology
ITU	International Telecommunication Unit
IDMP	Identification of Medicinal Product
MAA	Marketing Authorisation Application
MDM	Master Data Management
MedDRA	Medical Dictionary for Regulatory Activities
MP	Medicinal Product
MPD	Medicinal Product Dictionary
NCATS	National Center for Advancing Translational Sciences
NeeS	Non-eCTD electronic Submission
NIH	National Institutes of Health
NMV	Next Major Version
RPS	Regulated Product Submission
SDO	Standards Developing Organisation
SPOR	Substances, Products, Organisations and Referential
SUSAR	Suspected Unexpected Serious Adverse Reaction
USA	United States of America
WHO	World Health Organisation
XEVMPD	Extended EudraVigilance Medicinal Product Dictionary
XML	Extensible Markup Language

1. INTRODUCTION

In 2004 Clinical Trial Directive 2001/20/EC [1] came into force to regulate the execution of clinical trials (CTs) in the European Union (EU).

The Directive was a big step forward in regulating the assessment, performance and recording of CTs but experience with the process over the last several years has indicated that a new approach is needed.

Therefore the new EU Clinical Trial Regulation 536/2014 (CTR) [2] was introduced in 2014 (but will not be applied until 2016).

The new Regulation, which replaces the Directive, defines a single submission process for CT applications with an overall streamlined assessment. The current clinical trials database EudraCT will be replaced in the long term by a new EU portal and database for submission and storage of data for clinical trials.

The new portal and database have to be set up as completely new IT systems by the European Medicines Agency (EMA). These systems will be used to collect data about planned and already performed clinical trials. Entry will be made directly via the portal by the sponsor, the Member States of the EU or the European Commission (EC). These data will be stored in the EU database and a great part of the contents of the database will also be made accessible to the public to improve the transparency of clinical trials.

1.1 AIMS AND OBJECTIVES

In light of the growing importance of standardisation and interoperability in the EU and worldwide due to the increase of complexity, the rising numbers of systems and the growing amount of data, this thesis analyses the role of EU regulatory initiatives in this field, such as different roadmaps, for the introduction of the new Regulation.

The thesis takes a closer look into the possibilities of where standards can and will be used in the implementation of the new Regulation.

It aims to demonstrate where and how the new systems, coming with the Regulation, can be enabled to interoperate with other systems in the European regulatory systems landscape.

1.2 METHODS

In order to demonstrate in general the impact of standardisation and interoperability in the EU and internationally, different ways of standardisation and available standards are described at the beginning of the thesis. Afterwards, some initiatives in the EU and worldwide to promote interoperability are presented.

This includes the presentation of several roadmaps initiated by the European Medicines Agency (EMA) which are relevant for the enhancement of interoperability for the different regulatory systems in the EU.

To obtain an impression of the major changes the new legislation will implement from a technical perspective, the current Directive and the new Regulation are briefly described in one section with regard to these aspects.

The functional specifications for the set-up of an EU portal and database developed by the EMA were reviewed regarding relevant important aspects for the use of standards. Technical requirements in connection with possible ways to use already existing standards in the portal and database are presented. The fields where the new database can interoperate with existing or future systems by the use of already introduced or coming standards (e.g. IDMP) are highlighted to demonstrate the possible enhancement of standardisation and interoperability.

2. STANDARDISATION AND INTEROPERABILITY

The regulatory landscape consists of many different regulatory computer systems which store, process and present data and information about medicinal products, regulatory activities and, for example, clinical trials. These systems are also used to exchange and analyse data (e.g. for pharmacovigilance).

The more frequent and complex regulatory systems become, the more it is essential to use standardised ways to describe information and to use standardised processes.

Good management of regulatory information is only possible when sensible standards are used.

Using the same standards across different systems and being able to exchange data is one of the prerequisites for the interoperability of regulatory systems.

2.1 STANDARDISATION

Standards help to structure information, processes and the exchange of data.

There are several different kinds of standards in information systems [3]; the important ones include:

- **Terminology standards:**

Standards for vocabularies and terminologies describe the meaning of words with codes for terminologies and classifications, e.g. EUTCT, ICD-10

- **Standards for structure:**

These standards enable computers to extract single pieces of information from a larger set of information, e.g. IDMP, MedDRA, CTD

- **Messaging standards:**

Standards to exchange/transport information from one system to another, e.g. xml standards, HL7, eCTD, eAF

2.1.1 Within systems

If standards for vocabularies/terminologies are used within one system, controlled entry and storage of data can be achieved.

On the other hand, if standardisation is disregarded and, for example, different terms are used for identical information, this can lead to duplicated or unstructured entries of information.

In its turn, this results in difficulties searching for information in a system if the precise term is not known. Hence, it is also problematic to perform a proper analysis of data because either a data set is used twice for the analysis (if the same entry is described using different expressions) or not at all because the analysis does not recognise the term in the respective context.

That means, important information for an analysis can get lost due to a different description of information or usage of terms and therefore the analysis remains incomplete and cannot give a reliable result. Especially in pharmacovigilance it is vital to avoid such situations; they can be avoided by using unique, unambiguous standardised terms.

Using integrated data dictionaries enables a user during entry of data to use standardised terms.

2.1.2 Across systems

Further, it is not only necessary to be able to retrieve and analyse data within one system. Analyses of data across systems are also a target that can be achieved if the same standards for terminology are used in the individual systems.

Another aspect is the re-use of information. If the same standards are used in different systems, it is possible to re-use already entered or submitted information from one system in other systems.

The prerequisite for this is the possibility to integrate or exchange data between systems.

Exchanging data between systems can be achieved with standardised exchange messages. This is only possible if proper standards for the exchange of data are available.

2.2 INTEROPERABILITY

As shown in the previous section, using standards and being able to exchange data between systems is the key and prerequisite for the interoperability of systems.

What exactly does interoperability mean?

According to the Oxford dictionary, computer systems or software are “interoperable” if they are “*able to exchange and make use of information*” [4].

The Healthcare Information and Management Systems Society (HIMSS) is even more accurate in the description of interoperability and defines it as “*the ability of different information technology systems and software applications to communicate with one another; exchange data accurately, effectively and consistently; and effectively use the data that has been exchanged*” [5].

These definitions show that exchanging information is not the sole issue, it is also important that the information can be used in other systems.

Taking this into account there are three aspects of interoperability [6]:

- Technical interoperability
- Semantic interoperability and
- Process interoperability

Technical or functional interoperability is given as soon as the data can be exchanged reliably from one system to another with standardised exchange messages (e.g. xml). They are usually platform independent. Technical interoperability does not include that the other system can understand the exchanged data.

This is the difference from **semantic or data interoperability**. With semantic interoperability, systems which exchange data with other systems are able to understand the meaning of the exchanged data. The systems understand the data in the same way [6] and the effective use of the exchanged data is possible.

This can be achieved for example by using the same terminology standards (e.g. data dictionaries or classifications) [7].

Process interoperability goes even further. People who are involved in the different processes have to share a common understanding of processes to enable the relevant computer

systems to work together [8]. Work processes have to be coordinated [6]. Only then can process interoperability, i.e., sharing business processes across a network, be achieved.

“For example, healthcare professionals must standardise business rules to ensure that health information is recorded in a uniform and timely manner such that the transfer of information between systems is consistent and complete.” [8].

2.3 EUROPEAN AND INTERNATIONAL INITIATIVES

There are many initiatives on a European and international level to develop standards and their use and hence also enhance interoperability.

As so many different initiatives are available, only a selection is mentioned in this section to give a general impression of the diversity of this field. The main areas mentioned here are initiatives in connection with eHealth and pharmaceuticals regulation.

In general, when industry or other groups see the need for a new standard, a proposal for possible standards can be given to a standards developing organisation (SDO, e.g. CEN, ISO, HL7). In these organisations, experts from different fields and regions develop and discuss the proposal further and as the final step the standard is approved by a positive ballot.

It is also possible to develop standards independently of SDOs if the need for standardisation is detected in a special field. An accepted central committee or board for the respective field evaluates and recommends such standards and usually also communicates the approval steps of the standard to the concerned stakeholders (e.g. ICH for eCTD 3.2.2, the European Union Network Data Board (EUNDB) or the European Directorate for the Quality of Medicines and Healthcare (EDQM)).

2.3.1 Europe

In the context of the “Digital Agenda for Europe” the European Commission has developed the “Europe 2020 strategy”. One of the pillars of this strategy is entitled “Interoperability and standards”.

The goal of this pillar for Europe is to ensure *“that new IT devices, applications, data repositories and services interact seamlessly anywhere”* [9].

According to the Digital Agenda the way to achieve this is the improvement of standard-setting procedures and the increase of interoperability [9].

The European Union has also released a regulation dealing with European standardisation (Regulation (EU) No. 1025/2012 [10]). This regulation describes in general what standards are and how they are handled in the EU.

According to the regulation the fundamental principles for European standardisation are coherence, transparency, openness, consensus, voluntary application, independence from special interests and efficiency.

It is not mandatory to use standards if not explicitly mentioned in the legislation, but having accepted standards available in Europe provides the opportunity to use them where appropriate and helpful.

Using given accepted standards properly makes it easier for people to work together across fields. Processes can be more efficient and transparent.

The downside of using standards can be that flexibility is restricted because as standards have to be able to fit different circumstances (which is the nature of standards) they are limited to some extent.

2.3.1.1 eHealth

One of the main areas for application of the Digital Agenda is **eHealth** ([11], [12]).

In this context projects for standardisation and interoperability which also lie in the area of clinical research are ongoing or have already finished, e.g. EURECA, Linked2Safety, GRANATUM, Salus, SemanticHealthNet, TRANSFoRm [13].

All of these projects are linked to clinical research and data gathered there and the connection to other data such as Electronic Health Records (EHRs). The overall aim is to facilitate and improve clinical research.

2.3.1.2 Pharmaceuticals regulatory area

Much more relevant for this master thesis are the initiatives directly related to the **pharmaceuticals regulatory** field:

In this field, the European Medicines Agency (EMA) is responsible for implementing the EU Telematics Strategy 2014-16 [14] (and, while this thesis was being prepared, the Telematics Strategy 2015-17 [15] has already been drafted). This strategy has been developed by the European Medicines Regulatory Network (represented by the Heads of Medicines Agencies (HMA), the EMA and the EC).

To ensure that the Telematics strategy is applied in the EU, an advisory body, the European Union Network Data Board (EUNDB) has been created. The EUNDB proposes standards, for example, and tries to support the best use of the Telematics strategy in the EU and the European Economic Area (EEA) [16].

The Vision for EU Telematics is described as:

“A European IT collaboration that will deliver a broad range of cost-effective, efficient and inter-operable services to the European Medicines Regulatory Network and to its stakeholders that improve the quality and effectiveness of their business activities.” [14]

The strategy paper clearly states that one of the strategic business goals of the strategy is the optimisation of interoperability of IT solutions in the EU. This includes the creation of best practices for application development and the introduction of commonly used standards for database creation and data repositories.

Part of this strategy is also the technical support of the new legislation for clinical trials (CTR) and an eSubmission strategy that is developed and presented in an eSubmission roadmap [17]. The **eSubmission roadmap** states that *“interoperability of systems has become the key for efficient use of data and resource”*.

The EMA has also released a new **Master Data Management (MDM) Roadmap** [18] for the use of medicinal product data related to Substance, Product, Organisation and Referential (SPOR) data.

This MDM solution aims to deliver ISO IDMP (Identification of Medicinal Product) standards-compliant master data. ISO IDMP is a set of international ISO standards which are used to describe a medicinal product (for more information on IDMP, see section 4.3).

With these structured and standardised master data coming with the MDM, the exchange of medicinal product data between the different EMA systems will be improved. This will result in more efficiency, better data quality and simplified implementation of new systems.

MDM services will be introduced by the EMA using a staggered approach. The first data services which will be delivered are the Referentials. The implementation of the other parts of the MDM, such as substance, product and organisation will follow at a later stage [18].

The main basis for the Referentials will initially be the current European Union Telematics Controlled Terms (EUTCT) system with subsequent iterative adaptations of the controlled vocabularies to meet ISO IDMP specifications.

EUTCT is the current “*Community repository and provider of controlled terms in multiple languages for the ongoing exchange of data between information systems and applications throughout the European Medicines Regulatory network (EMRN)*” (extract from EUTCT website [19]). The controlled term lists are not only managed and maintained by EUTCT but also by external providers, such as the EDQM. The EDQM provides standard terms for dosage forms, routes of administration or containers.

EUTCT will be migrated to the future MDM (Referentials) [15].

2.3.2 International

2.3.2.1 eHealth

On an international level the World Health Organisation (WHO) is very active in eHealth projects relating to standardisation and interoperability.

A forum is held regularly with participants from different fields including SDOs, standards maintenance organisations, delegates from different states, industry and others. In this forum topics regarding standardisation and interoperability in eHealth are discussed by different stakeholders [20].

To get international health standards which are globally used and adopted, it is necessary that the creation and introduction of these standards are coordinated globally. The WHO plays an important role in doing this and collaborates with different SDOs such as the International Health Terminology Standards Development Organisation (IHTSDO - development of

SNOMED-CT and ICD), Health Level 7 (HL7) or the International Standards Organisation (ISO) [20] (see also section 2.3.3).

2.3.2.2 Pharmaceuticals regulatory area

In this area the International Conference on Harmonisation (ICH) has to be mentioned.

ICH represents mainly the regions of Europe, Japan, the United States, Canada and Switzerland but many other regions worldwide try to adopt the processes developed by this institution.

The ICH has established a working group which evaluates and recommends standards for electronic exchange of data (Electronic Standards for the Transfer of Regulatory Information (ESTRI) [21]).

The ICH working groups are involved in many initiatives regarding standardisation and are in close cooperation with SDOs.

One example for initiatives of the ICH is the standard E2B (R3) for the electronic submission of Individual Case Safety Reports (ICSRs). In this context the need for a harmonised product information and description was identified and the development of five International Standards for Identification of Medicinal Products (IDMP) has been finalised. ISO IDMP (see section 2.3.1.2 and 4.3) is an internationally developed standard to uniquely identify medicinal products.

ICH (ESTRI) has also developed the eCTD (electronic Common Technical Document) as an electronic exchange standard for submissions [22] (see Section 4.4) and the Medical Dictionary for Regulatory Activities (MedDRA) [23]. This dictionary contains standardised medicinal terminology which is used for registration, documentation and safety monitoring of medicinal products in human use. MedDRA improves sharing regulatory information for such products on an international level.

For substances, a global system named Global Ingredient Archival System (GInAS) was developed, and is maintained and distributed by the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH) in the US. GInAS provides a common unambiguous identifier for all substances used in medicinal products and is consistent with the ISO 11238 standard for substances.

International and European initiatives are in close collaboration to establish a global approach:

One example is the eSubmission Change Management Board (CMB) in Europe as part of the change management structure of EU Telematics which works closely together with the European delegation of the ICH M8 Expert Working Group responsible for the ICH eCTD Specification as well as the ICH M2 Expert Working Group responsible for ESTRIM [24].

The same applies to the ICH and WHO initiatives (e.g. MedDRA is mapped to the WHO system [23]).

2.3.3 Standards developing organisations (SDOs)

The development of accepted and known standards is only possible if this is coordinated and published by accepted organisations.

Several different SDOs exist depending on the subject and region. Only the most important ones can be mentioned in this section.

In Europe, standards are developed, for example, under the responsibility of three independent European organisations, the European Committee for Standardisation (CEN), the European Committee for Electrotechnical Standardisation (CENELEC) and the European Telecommunications Standards Institute (ETSI).

In the United States of America (USA), the American National Standards Institute (ANSI) develops standards and coordinates US standards with internationally developed standards.

On an international level the largest organisations are the International Organisation for Standardisation (ISO), the International Electrotechnical Commission (IEC) and the International Telecommunication Union (ITU).

The major SDO for electronic health information is the Health Level Seven International (HL7) organisation.

The most relevant organisations in the medical field are the CEN, the ISO and HL7.

3. CLINICAL TRIALS AUTHORISATION IN THE EU

3.1 CLINICAL TRIALS DIRECTIVE – STATUS QUO

In 2004 Clinical Trial Directive 2001/20/EC (CTD) [1] was implemented and together with corresponding guidelines governs what has to be done to perform a clinical trial in the Member States of the EU.

Because Directive 2001/20/EC is a directive, it was necessary to transform the information given in the document into national law in every single Member State in the EU.

As there is always room of interpretation in this process of transformation, this resulted in a number of different national requirements in the individual European countries.

These differences make it quite complex and time-consuming for sponsors of clinical trials to get permission for multinational trials from the individual national authorities and the favourable opinion of the related ethics committees.

The sponsors have to submit a single Clinical Trial Application (CTA) to all the Member States in the EU where they want to request permission to perform the clinical trial.

These multiple submissions for one clinical trial include much identical information but many countries also request country-specific documents, have their own questions and require their own modifications.

There is no single coordinated assessment and decision from the European countries to grant permission to perform the trial. The single countries themselves assess if the trial is acceptable before granting the approval for the trial in that country.

This leads to a great deal of effort for sponsors to coordinate the different national CTAs and causes uncertainty in the planning of timelines for clinical trials.

3.1.1 EudraCT

The EudraCT (European Union Drug Regulating Authorities Clinical Trials) is the current European database for all interventional clinical trials of medicinal products in Europe.

The database was established in accordance with Directive 2001/20/EC [1] in 2004. Since then, all data regarding clinical trials have been stored in this database. Some of the data are publicly available (EU Clinical Trials Register (EUCTR)).

A subset of the data from the requests for clinical trial authorisation is entered into the database to deliver an overview of clinical trials conducted in the EU.

The database is linked to the EudraVigilance Clinical Trial Module and shares common key fields with the CT Module [25]. The CT Module contains all Suspected Unexpected Serious Adverse Reactions (SUSARs) recorded for clinical trials in the EU.

Entry of data into EudraCT and the EudraVigilance CT Module is only possible for competent authorities of the Member States, the EMA and the EC. Sponsors do not have write access to these databases. This data entry will be made on the basis of the data provided in the application form filled in by the sponsor.

Since 21 July 2014 sponsors have been obliged to post clinical trial results in EudraCT.

3.1.2 Process for Clinical Trial Application according to the Directive

Currently an application form is used for CTAs submitted in compliance with the Directive. The first step is to request a EudraCT number for the clinical trial via the EudraCT website. As soon as the number has been received, the application form can be filled in with all the requested information. Subsequently an xml file is created with the information provided. This xml file has to be sent to the authorities together with all the other documents which have to be provided for the CTA.

3.2 NEW CLINICAL TRIAL REGULATION

In 2009, the European Commission initiated an “Assessment of the functioning of the ‘Clinical Trials Directive 2001/20/EC’ with the publication of a public consultation paper [26].

According to the European Commission the number of clinical trial applications in Europe fell by 25% from 2007 to 2011 after introduction of the Directive.

In one of the recitals at the beginning of the Regulation (recital (4)) it is mentioned that the Directive did not lead to a harmonised approach to obtain approval for a clinical trial in Europe.

As a consequence of this assessment Directive 2001/20/EC will be repealed by the new Clinical Trial Regulation No 536/2014 [2].

The performance of studies in Europe decreased as a result of the complex process for CTAs defined in the Directive and it is hoped that with a single application and assessment for a clinical trial in Europe the number of studies in Europe will increase again.

As the new CTR is a regulation, it is not necessary to transform it into national law and it is directly binding on the Member States of the EU.

The Regulation was adopted on 16 April 2014 and came into force on 16 June 2014 but will not apply until 28 May 2016.

The CTR can only be applied when a positive audit for a new EU portal and EU database has been performed and portal and database have achieved full functionality and meet the functional specifications.

There is a transition period of one year after the Regulation becomes applicable in which clinical trials can still be authorised according to the Directive. Trials which have been authorised under the Directive can continue to follow the Directive until 3 years after the Regulation applies (see Article 98 of the Regulation).

The main characteristics coming with the new Regulation are the following [27]:

- Clinical trial applications will only be submitted via a single entry point, the EU portal, no matter whether the trial is multinational or national. The submission of an application to every single Member State where the trial will be performed is no longer necessary.
- Only one single set of documents has to be submitted for the application (as given in Annex I of the Regulation).
- The dossier exists of two parts – a general part (part I) and a national part (part II). Part I of the application is assessed in a harmonised procedure with strict timelines (including ethics committee). Part II is assessed separately by each Member State concerned.
- Tacit approval applies if no objection to the trial is expressed by the authority within the given timelines
- Increased transparency regarding clinical trial data
- The Union is in control in Member States and third countries for supervision and enforcement of rules

- Clinical trials which are referred to in a CTA in the EU but conducted outside the EU have to fulfill EU regulatory requirements

3.2.1 Clinical Trial Application (CTA)

As mentioned before, it is necessary to submit a Clinical Trial Application (CTA) to the authorities via the EU portal to get the permission to perform the trial. The data submitted via the EU portal is automatically stored in the EU database.

The CTA consists of many different documents. These include administrative documents (e.g. an application form) as well as documents which describe the planned clinical trial and the medicinal product used in the clinical trial, e.g. the Investigational Medicinal Product Dossier (IMPD), the Clinical Trial Protocol (CTP) and the Investigator's Brochure (IB).

Annex I of the Regulation contains a comprehensive list of documents that need to be included in the CTA as soon as the new CTR applies.

3.2.2 EU Portal and Database

The introduction of the new EU portal and new EU database is described in Articles 80 and 81 of the new Regulation.

In future all data for clinical trials should be submitted via the portal (entry point) and stored in the database (repository). The entire communication between applicant and Member States will also be done via the portal.

The new EU portal and database will be set up and maintained by the European Medicines Agency (EMA).

The release of the portal and database is the prerequisite for the application of the Regulation. Before they can be used, the performance of an audit and validation is required. As soon as this is done, the Regulation can be applied; this is not expected to be before 2016.

It is clearly stated in the respective articles of the Regulation that the portal has to be technically advanced and user-friendly. For the set-up of the database duplicated entries for the EU database and other databases like EudraCT and EudraVigilance databases should be avoided.

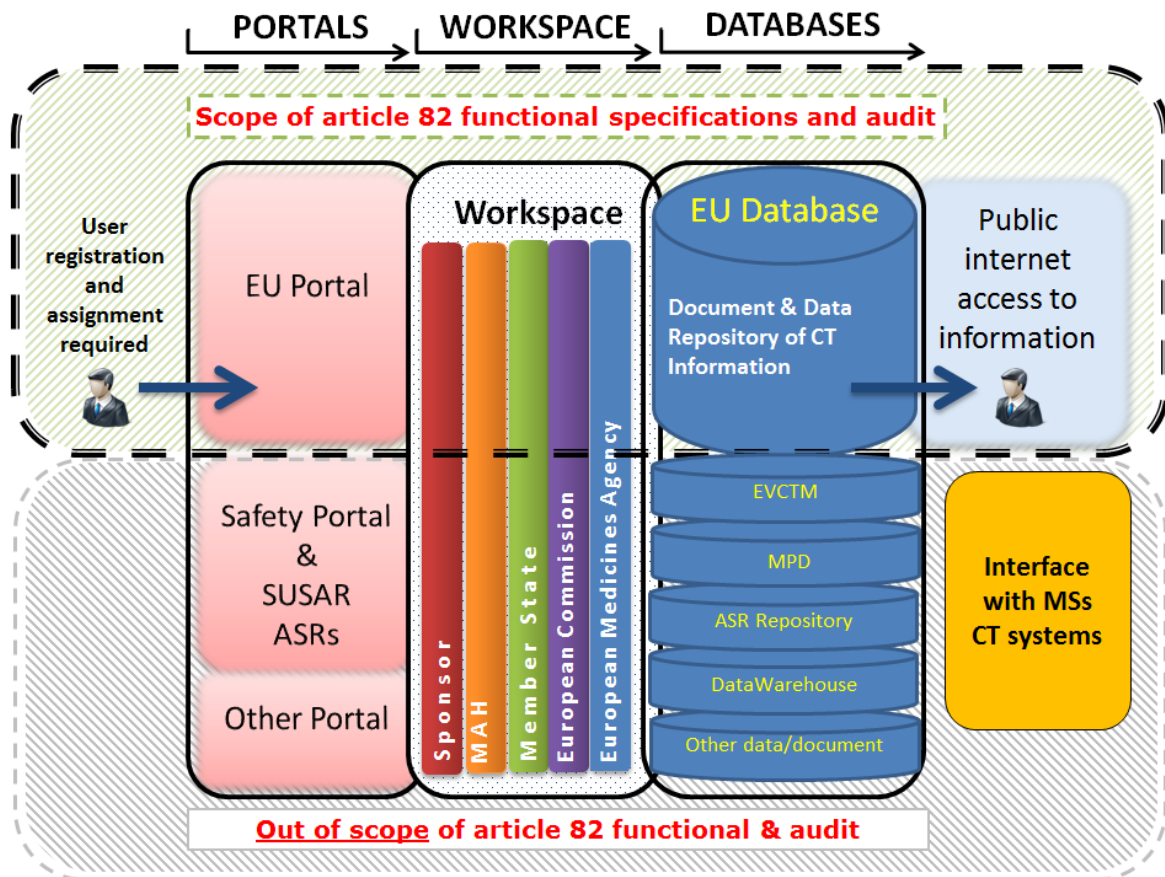
3.2.2.1 Functional specifications for the EU portal and EU database (EMA)

The EMA has already released functional specifications [28] for portal and database as requested in Article 82 of the Regulation.

These functional specifications describe the aspects of the portal and database which need to be audited before the CTR can be applied. A successful audit will guarantee the full functionality of the new system.

In the scope section, the document gives a clear overview of the clinical trial systems (see Figure 3.2.2.1: 1) and the position of portal and database in this environment.

In addition to the portal and database a workspace will be created which enables all stakeholders, e.g. Member States or sponsors, to prepare, track or control applications or reports before they are submitted to the database via the portal.



source: EMA functional specifications for EU portal and EU database [28]

Figure 3.2.2.1: 1 High level overview of the clinical trial systems

A dossier builder will be available in the workspace to allow sponsors to prepare application dossiers (functional specification no. 3.2).

A relevant aspect of the functional specifications is the necessity to request a unique EU clinical trial number (corresponding to the previous EudraCT number) which makes it possible to group together related information or to request an EU medicinal product (MP) number from the medicinal product dictionary (functional specification no 2.1 for the EU portal in [28]). This is relevant because the number is unambiguous and can be used to interconnect data for clinical trials and medicinal products in different systems.

Also relevant is the opportunity for sponsors to prepare a CT application form in the workspace. With a dossier builder the sponsor can also build a dossier in the workspace (functional specification no. 3.2). Both, application form and dossier will be submitted via the portal to the database.

For the workspace it is stated that the different submissions of a CTA for one clinical trial should be assigned a sequential number to track the life cycle of a clinical trial (also functional specification no 3.2). The EU CT number is needed here again to be able to uniquely identify the clinical trial throughout the whole life of the trial.

The functional specifications for the portal also mention, that duplication of entries has to be avoided and data which are already stored in other EMA systems should be re-used and be available for selection in the portal (functional specification no. 2.7 for the portal).

This includes the requirement that the new system is able to deal with the transition from current master data systems (e.g. EUTCT) to future master data systems.

A big difference between the previous EudraCT and the new EU database is the obligation to submit the clinical study report (CSR) for trials which are used for a Marketing Authorisation Application (MAA) (Article 37(4) of the Regulation). This obligation is reflected in requirement no. 9 of the functional specifications.

It is also mandatory to submit summaries of clinical trial results (including lay summaries) for all trials (Article 37(4) and requirement no. 7 in the functional specifications).

These obligations are intended to make the new portal and database the key instrument for transparency for clinical trials in the EU [29].

The part of the CSR to be provided to the EU database that will be available for the public has to be redacted to eliminate confidential information from the contents [30].

The proposed and final redacted version of the CSR also has to be submitted in separate eCTD sequences of the MAA via the EMA gateway to the authorities [31].

4. RESULTS - STANDARDISATION AND INTEROPERABILITY – NEW CLINICAL TRIAL REGULATION

Data standards (Article 81, CTR) or standards for forms (Article 40(2), CTR) are mentioned in the Regulation but were not defined in the Directive. During development of the Regulation it was taken into account that since the implementation of the Directive, standardisation is becoming increasingly important for the storage and exchange of data.

Where exactly can the massive change coming with the Regulation be taken as a chance to implement standards? Where can exchange between systems – even if not yet in place - be driven forward?

Some of the major areas where there is room for possible use of standards and hence improvement of interoperability in the set-up of EU portal and database are presented in the next sections.

4.1 ELECTRONIC APPLICATION FORM (eAF)

The Clinical Trial Application which is submitted via the portal to the database must contain an EU application form (see Annex I of the CTR) which has to be filled in with information about the MPs that will be used and other information about the planned clinical trial.

According to the functional specifications (No. 4.3 in [28]) some questions in the application form are also planned to be used as a trigger for publication of the trial data.

The information in the application form is very important. It reflects the nature and properties of the clinical trial and the medicinal product used. The information provided in the AF is written into the database. If the information submitted in the application form is not filled in

accurately, either the information stored in the database is not correct or a lot of effort is needed to retrospectively correct data which was not submitted correctly.

In the current application form which has been created in accordance with the Directive many entries have to be created manually and are not completely controlled by integrated dictionaries. This can lead to inaccurate or inconsistent information for the application of the clinical trial and subsequently to incorrect information in the database.

One of the possibilities to enhance standardisation with the new CTR would be to optimise the application form and use a structured electronic application form (eAF) for the CTA.

Structured electronic application forms have many advantages:

In structured eAFs it is possible to integrate dynamic lists of standardised controlled terminology (online access) which can be used to fill in the form.

Offering the possibility for the applicant to choose terms from existing standardised dictionaries in a provided eAF template helps to improve the consistency of data and hence improves data quality during data entry.

Even adjusted language settings could be used if the dictionaries are maintained in different languages.

The best way to achieve this enhanced data quality and consistency is to use defined master data for the application form for clinical trials.

As mentioned in a previous section (see section 2.3.1.2), the EMA is currently developing a master data management concept which will include information about substances, products, organisations and referentials (SPOR data) [18]. This master data concept will deliver standards compliant master data.

It is planned to use these master data in many other systems in the European regulatory environment. If these structured and controlled master data are also used in the electronic application form for clinical trials, the data delivered are of a high quality and can be re-used where necessary and applicable.

In structured electronic application forms it is also possible to import and export electronic data and to auto-populate data within the form (depending on previous entries).

Plausibility checks and validation which will be performed during creation of the eAF can be included. This also leads to improvement of quality and consistency of data and avoids errors.

The delivered structured and controlled data can be easily written into the database and if the forms use xml as data exchange standard (see functional specification no. 3.2) these data can possibly be exchanged with other systems and even be understood if the same dictionaries are used.

Hence, using these electronic forms enable systems to re-use the data provided with the form. eAFs are mandatory for the submission of eCTDs for centralised procedures in Europe as of 01 July 2015 and as of 01 January 2016 for all procedures [32].

It would be a step forward to use the introduction of the new CTR to adjust the format for the application form for CTAs in the same way as has already been done for eAFs for the submission of eCTDs. Harmonising the entry of data for these forms offers the opportunity to streamline the processes and maybe even to re-use the entered data for the CTAs for the upcoming submission of an eCTD at a later stage in the life cycle of a product (depending on the future repositories for these submissions).

The direct integration of the eAF into the portal and an interface to the MDM services will optimise this process.

4.2 INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER (IMPD)

A very important part of the CTA is the Investigational Medicinal Product Dossier (IMPD). The IMPD “*shall give information on the quality of any investigational medicinal product, the manufacture and control of the investigational medicinal product, and data from non-clinical studies and from its clinical use.*” (Annex I, part G of the CTR).

The IMPD is also part of the CTA for applications submitted in compliance with the Directive.

Both, the Directive (in a corresponding guideline [33], section 2.7) and the new Regulation (in Annex I) state that the IMPD for non-clinical and clinical data should be submitted in a logical structure corresponding to the structure of module 4 and 5 of the ICH Common Technical Document (CTD).

The Regulation also states this for the quality part. However, the Directive refers to another guideline [34] for the structure of the quality data.

So far, the numbering in the IMPD does not completely correspond to the numbering of the eCTD. The IMPD is created as one single document and the information is not submitted in a defined structure. Therefore it is not possible to re-use information from IMPDs already submitted for other CTAs or other applications.

With the new Regulation, the structure of the IMPD will completely follow the eCTD structure for Module 3, 4 and 5.

In chapter 4.4 a description is given of an eCTD and what will be changed in future with the new version of the eCTD (version 4.0, Regulated Product Submission (RPS)). The analogy of the two structures of IMPD and eCTD could be a possibility to create IMPDs in future in a similar way as eCTDs have been created:

As a structured output with several single documents and an xml exchange message file that can also be delivered with lifecycle operators which display changes during the lifecycle of the drug in development.

This could enable authorities, sponsors and marketing authorisation applicants to use the same tools for the creation, viewing and validation of IMPDs and eCTDs.

In the USA a similar approach was followed in the past with the creation of Investigational New Drug applications (INDs).

This approach could help to re-use information given in the IMPD for other CTA submissions or an upcoming eCTD submission if the same structure/format and tools are already used. Especially with RPS, where document IDs and keywords determine the use of a file, this approach is imaginable (also depending on possibly available future repositories for the different submissions).

The content of an IMPD cannot be completely identical to the MAA because the product in development has to be presented with another focus (risk aspects, state of development) but the structure can be adjusted and metadata/master data which has been used for the IMPD could be inherited or re-used for eCTDs if appropriate (and also depending on future common repositories). With this the duplication of entries can be avoided in future.

The functional specifications [28] no. 4.3 specify that the IMPD should be structured in a way that each section in the IMPD (efficacy, safety and quality) can be handled as a separate

section. This is necessary to be able to apply different publication rules to the different sections. This request would also be in compliance with the proposed new structure.

The prerequisite to tread this path is a system that accepts submissions in this structure.

4.3 XEVMPD/ISO-IDMP AND SAFETY REPORTING

Article 81(3) of the CTR mentions that the EU database “*shall support the recording and submission to the Medicinal Product Dictionary, contained in the Eudravigilance database*”.

The Medicinal Product Dictionary (MPD) was implemented according to Article 57(2) of Regulation No. 726/2004/EC [35] and the amending pharmacovigilance Regulation (EC) No. 1235/2010 [36]. The dictionary is also requested by Directive 2010/84/EC [37] which amends Directive 2001/83/EC [38], with respect to pharmacovigilance.

Marketing authorisation holders have to electronically submit any information on medicinal products for human use of which they are aware. This has been introduced to be able to perform proper pharmacovigilance activities.

The information has to be submitted to a component of the EudraVigilance database, the Extended Medicinal Product Dictionary (XEVMPD) using, for example, EUTCT.

According to the currently valid ‘Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (‘CT-3’)’ [39] (section 7.9) the information for Investigational Medicinal Products (IMPs) has to be provided to and registered in the Extended EudraVigilance Investigational Medicinal Product Dictionary (XEVIMPD) before the application form for clinical trials can be completed.

Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during a clinical trial have to be reported to the EudraVigilance Clinical Trial Module (EVCTM).

In future (beginning on 01 July 2016) XEVMPD/XEVIMPD will be replaced by the international standard for the unique description of medicinal products ISO-IDMP (Identification of Medicinal Product) to achieve a greater standardisation of product information. This is a requirement of the Commission Implementing Regulation (EU) No. 520/2012 (Articles 25, 26 and 40) [40].

IDMP has been developed by the International Standards Organisation (ISO) and exists of 5 ISO standards to describe a medicinal product. These are the following (see also Figure 4.3: 1):

- **ISO 11615**, Health informatics – Identification of medicinal products – Data elements and structures for the unique identification and exchange of regulated **medicinal product** information (**Drug Dictionaries (MPID)**).
- **ISO 11616**, Health informatics – Identification of medicinal products – Data elements and structures for the unique identification and exchange of regulated **pharmaceutical product** information (**Pharmaceutical Product Identifiers (PhPIDs)**).
- **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**, Health informatics – Identification of medicinal products – Data elements and structures for the unique identification and exchange of **units of measurement**

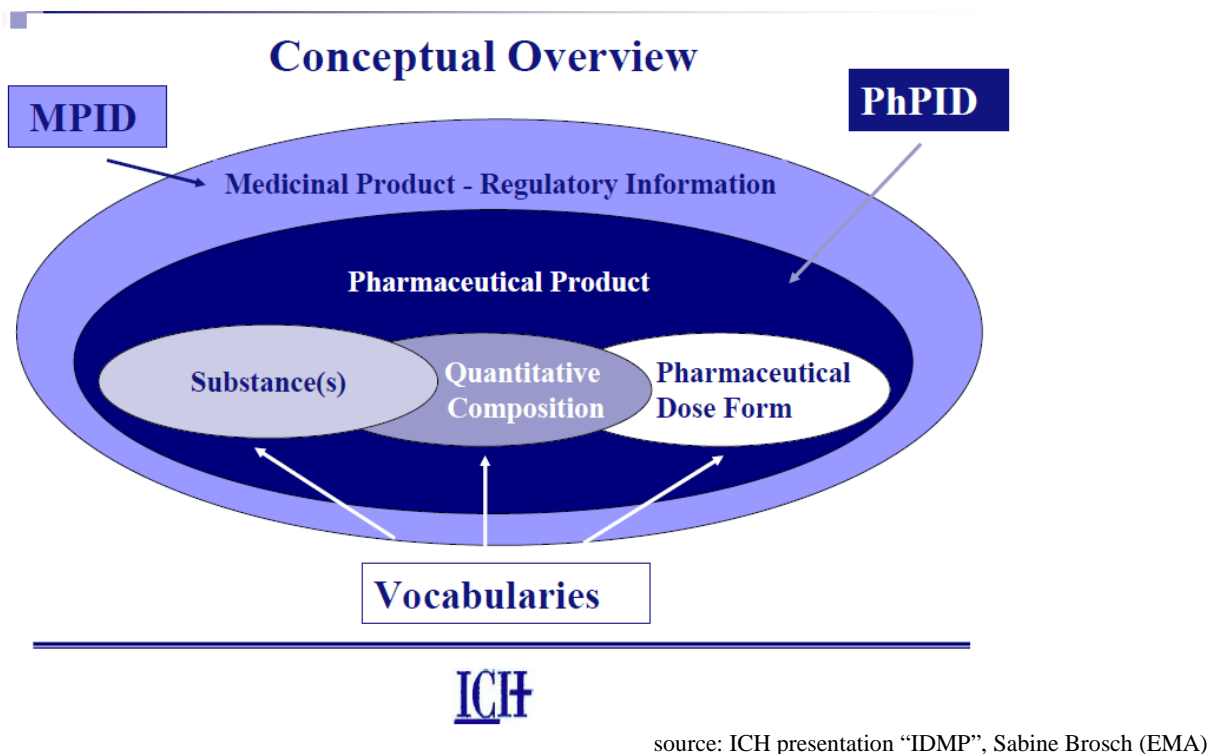
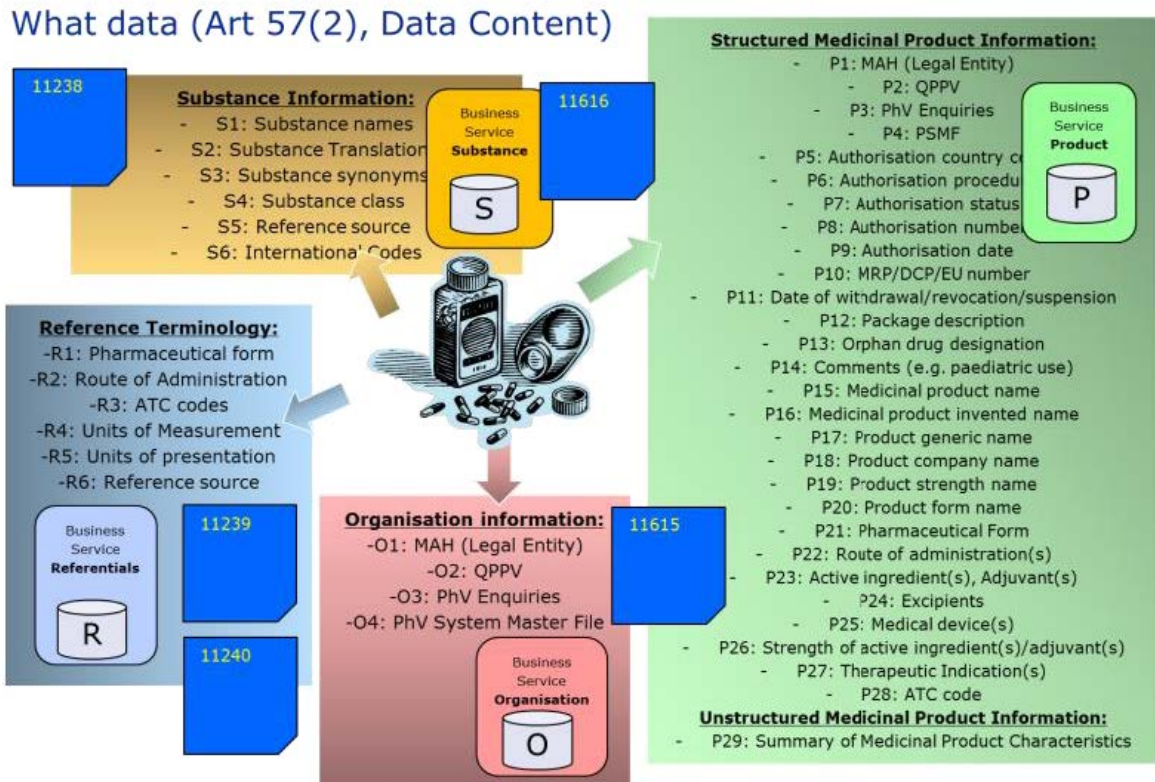


Figure 4.3: 1 Conceptual overview IDMP

ISO-IDMP has a lot of data elements that can be used to describe a medicinal product and has a much broader scope than XEVMPD.

Implementation guides for the introduction of IDMP in the EU are under development. The EMA has to define which elements have to be used for submission of the product data to the medicinal product dictionary.

The authorities are in the process of determining which IDMP-compliant SPOR data have to be included in the message for the MPD. The current proposal for the contents of the message is displayed in Figure 4.3: 2.



source: International activities and IDMP, 2nd EU ISO IDMP Task Force Meeting [41]

Figure 4.3: 2 Work in Progress: SPOR data and IDMP

The main purpose of IDMP in the long term is the exchange of information about medicinal products across the world. To achieve this it is therefore essential to develop controlled vocabularies.

As the introduction of ISO IDMP and the new EU database is expected around the same time, it is important to set up the EU portal and database in such a way that data which will be recorded and submitted with the CTA to the medicinal product dictionary are already IDMP compliant. In addition, it is essential to integrate the data of the medicinal product dictionary in the EU portal and database to be able to select products which are already recorded in the product dictionary.

This is also the prerequisite for the functional specifications nos. 1.1, 2.1, 2.7 and 4.9 for portal and database.

The “Annex to the European Medicines Agency (EMA) Master Data Management Roadmap” [42] states that “*Newly implemented applications will be designed to natively work with the MDM solution.*”

Especially the use of future master data compliant with IDMP and their integration in the EU portal/database for unique identification of the medicinal product brings a lot of benefits as the new master data management system and IDMP standards are also planned to be introduced in other systems in the EU and in international systems (IDMP).

It is likely that the U.S Food and Drug Administration (FDA) will also adopt these standards in the near future (presumably using HL7 Structured Product Labeling (SPL) Release 7 which includes all ISO IDMP elements [41]).

For safety reporting it is mentioned in the CTR (Article 40(2)) that a standard web-based structured form should be used by the sponsors to report SUSARs directly to the EudraVigilance database. For safety reporting according to Article 17 of the Directive, SUSARs are reported by the sponsors to the authorities and the authorities enter the reported SUSARs into the database.

For the new web-based form it would also be advisable to integrate the master data provided with the new concept of master data management.

4.4 RPS / ECTD 4.0

Applications for marketing authorisation and variations thereof consist of metadata and many individual documents to demonstrate the quality, safety and efficacy of a medicinal product.

At the moment the electronic Common Technical Document (eCTD) version 3.2.2 is the valid standard in the ICH countries (and others) to submit an electronic application for marketing authorisation to the authorities (in the EU depending on the procedure used).

eCTD 3.2.2 has been used for several years and it is planned to introduce eCTD version 4.0 (eCTD Next Major Version (NMV)) in the coming years. This new standard can be used for all types of regulatory submissions, offers much more flexibility and is in line with international standards.

eCTD 4.0 is based on an HL7 xml message standard named Regulated Product Submission (RPS) and has been developed in close collaboration with the ICH to be used for the submission of any regulated product. RPS is also expected to be approved as an ISO standard. The update from eCTD version 3.2.2 to 4.0 contains a number of changes:

With RPS, in contrast to eCTD v3.2.2, it is possible to re-use already submitted documents for other products or applications which makes grouping and worksharing of submissions easier and prevents the submission of the same document to the agency several times.

This will be achieved with the use of unique ID tags (document elements) and a combination of keywords which describe the context of the use of the file (contextOfUse element). For some of the keywords, controlled vocabularies are necessary (will be defined by the implementation guides) [43].

Only one xml-file (submissionunit.xml) will be created for common and regional information (for the current version of eCTD several xml-files have to be created).

Two-way communication between agency and applicant, which is not possible with eCTD 3.2.2 is an option with RPS.

As the xml message for RPS is more complex than for eCTD 3.2.2 (and without a style sheet), it is necessary to have special dedicated viewer tools to review applications submitted in the RPS format. Full access to the controlled vocabularies provided by ICH or EUTCT has to be guaranteed in these viewing tools so that they are capable of displaying the content [43].

Using these controlled vocabularies avoids creating data inconsistencies and supports the automated extraction of information into databases.

With the concept of ID tags and keywords for the context of use, RPS delivers flexibility regarding the structure of submissions that is not possible with eCTD 3.2.2. This flexibility also opens the option to use RPS for other regulatory submissions such as CTAs.

As already described in section 4.2, the same tools for creation of these submissions can be used with adjusted, or even the same controlled vocabularies, where applicable.

The prerequisite for using RPS for CTAs is that the portal and database are able to accept information submitted in this way.

Going even further, if the same repository is used for the different submission types such as CTAs and eCTDs, it would even be possible to re-use already submitted documents in the whole lifecycle of a medicinal product.

5. DISCUSSION

5.1 STANDARDISATION AND INTEROPERABILITY

Regulatory information can only be used effectively and efficiently if appropriate standards are available and used, either for the data itself, or for the exchange and processing of data.

Adhering to standards guarantees better quality of data and improved methods to exchange and integrate data.

Data which are entered and stored in standardised form are much easier to retrieve and analyses of such data within and across systems are much more reliable and reproducible.

If stakeholders can agree on using the same standards, this goes – in the long term - along with lower costs of implementation. It is not necessary to re-invent the wheel during development of systems and processes when data descriptions and exchange messages are already available.

This also reduces effort and time which is in the interest of authorities and other stakeholders such as sponsors of clinical trials or applicants for marketing authorisations.

Developing standards is a good thing as long as the development and implementation is coordinated. However, if too many different standards are developed and used this is counterproductive.

In the short term it has to be taken into account that resources are needed to develop and implement standards. But in the long-term this effort is neutralised and indeed transformed to a positive effect.

The following bullet points list the advantages and possible disadvantages of using standards:

Advantages:

- Analysis of data easier and more reliable
- Better quality which also leads to improved safety
- Reduction in duplication of data entry
- Development of software faster, more structured
- More efficiency, interoperability enabled
- Lower costs in the long term

Disadvantages:

- Investment for development
- Investment for implementation - change management necessary (introduction of new standards bring out changes in processes and operations, training, education of users for new processes and methods of recording)
- Higher costs for early developers
- Standardisation can reduce the autonomy and independence of providers [8]

The interoperability of systems is directly linked with standardisation. As shown in the previous sections this is a very important achievement. It enables systems to re-use data which have already been submitted and avoids duplication of entries.

Especially the use of integrated standardised master data in systems (as will be introduced with the SPOR concept by the EMA) permits consistent master data management in the growing number of regulatory systems and is a major step towards improving efficiency.

5.2 EU PORTAL AND DATABASE

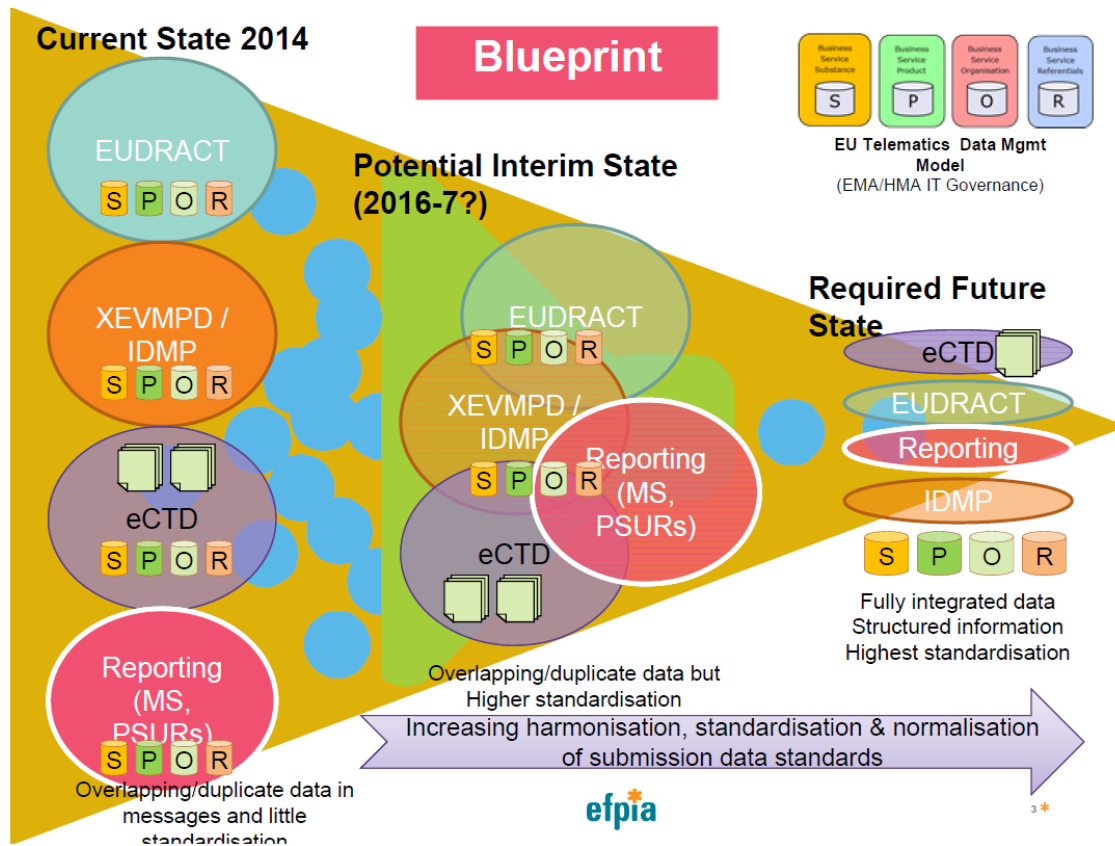
If we want to analyse where standardisation can be taken into account during the new set-up for portal and database, it is necessary to take a look at the regulatory systems landscape.

The question is where we have a connection of the data submitted to the new database and other systems and where we can now grasp the opportunity to improve the interaction between the systems.

The previous sections have highlighted some of the fields where structured standards can play a role in improving interoperability for the EU portal and database and which standards can be used (eAF, structured IMPD, IDMP, RPS).

Figure 5.2: 1 shows an overview of the present status of standardisation as seen by the EFPIA (in 2014/15) and what we want to achieve in future.

Currently we have still many systems in parallel which do not use enough standardised data to be able to interoperate to an extent that would be desirable or which manage data in isolation so far.



source: presentation Angelika Joos, AGAH, 5 December 2014, EFPIA views CT Portal and Database [44]

Figure 5.2: 1 Harmonisation of submission data standards

But the figure also shows that there is a chance in future to achieve more and more harmonisation of standards which can be used in systems and messages and enables the systems to interoperate not only technically but also semantically.

The figure reveals that the master data management information (SPOR) which is in compliance with ISO IDMP plays a leading role in bringing forward the idea of standardisation and harmonisation in different systems.

As mentioned in section 2.3.1.2 of this thesis the EU Telematics strategy ([14], [15]) and the different roadmaps in this strategy such as the EMA Master Data roadmap [18] or the HMA eSubmission roadmap [17] support this approach because the vision is that all stakeholders will “be able to more effectively exchange data and simplify processes facilitating improved operational efficiency” [18].

The EU portal and database have to be set up completely from scratch. Here lies a possibility to improve the operational efficiency discussed above by using existing or new standards and enforce the possibility of interoperability with other existing systems.

In order to achieve this overall goal, the implementation of the CTR is one of the main objectives of the EU Telematics Strategy. In the strategy the development of solutions to support the implementation of the new CTR is mentioned (see Objective 2 in strategy 2014-2016 [14] and Programme 2 in strategy 2015-17 [15]).

Making the implementation of the CTR part of the European strategy should enforce the overall connection to other systems and should help to maintain an overview in the implementation of different new systems and processes.

The development of the EU portal and database aligned with other objectives of EU Telematics such as Objective 5 (data strategy) [14] and Programme 4 (data integration) [15], where interoperability through implementation of appropriate data standards (e.g. ISO-IDMP/SPOR) is enforced, can lead to a result which supports the strategic business goals of the EU Telematics strategy, such as efficiency or optimal usage of resources.

5.2.1 Master data - IDMP

One goal of the Master Data roadmap is the definition of how business applications will interact with the MDM solution. In the functional specifications for EU portal and database nos 2.7, 3.1.2 and 4.9 it is made clear that the master data (SPOR) should be available for selection in the workspace, portal and database to avoid duplication of entry. This emphasises the important role played by the management of master data again.

The objective of SPOR data is to be the “one source of truth” for master data in the EU [15]. It is important to define these data carefully and with foresight.

For the development of the dictionaries for the master data it is important to adopt - wherever possible - a global approach to avoid introducing additional dictionaries in isolation. Consideration needs to be given to using global IDMP-compliant dictionaries if they already exist or are in development, such as the global system GInAS for substances (in line with ISO IDMP).

5.2.2 eAF

MDM services compliant with IDMP also have to be integrated in a dynamic eAF as described in section 4.1 to be able to choose data from the dictionaries and to improve the quality and consistency of the submitted data.

The integration of the medicinal product dictionary in the eAF enables the applicant to insert a medicinal product number (ISO IDMP code) for products already registered in the MPD. The data available in the dictionary for these medicinal products can automatically be populated in the eAF after filling in the code.

According to the eSubmission roadmap [45], it is planned for the future (2018) to integrate eAFs for all submission types with the single submission portal for electronic applications so that information that is already held by regulators does not need to be submitted again [15].

This solution also has to be taken into account for CT application forms in the EU portal, to enable applicants to re-use already submitted data.

Another interesting solution for the future is imaginable: having one submission portal for CTAs and for MAAs with integrated eAFs. This would facilitate the creation of the eAFs tremendously because re-use of data would be possible and applications could be linked and interconnected via master data. This approach could offer the full use of the advantages provided with electronic structured application forms.

It has to be awaited what challenges the implementation of the new CTR with the planned processes may bring. As soon as the new processes have been established and reviewed, such future solutions can be taken into account.

5.2.3 CTA and RPS

With regard to the possibility of the creation of CTAs and IMPDs in a similar way as the eCTDs using the same metadata and tools, RPS provides much more flexibility than eCTD 3.2.2.

As RPS is more flexible regarding structures and uses fewer fixed folders, it is much easier to use this standard for the creation of submission structures other than the eCTD, such as CTAs. If the RPS standard is used for CTAs as it is used for eCTDs, the same tools for creation, validation and viewing of the submissions can be used. The same master data also need to be

applied; this should be done automatically using RPS for both (assuming that IDMP-compliant master data is used).

The interconnection of the CTAs can be enhanced as RPS makes it possible to re-use already submitted documents independently of a special product or application.

Even a common repository for CTAs and other submissions is imaginable for the future. This would offer a way to re-use the documents already submitted for the CTA for the later MAA (where applicable) and would avoid submitting the same documents to the authorities several times in the lifecycle of a medicinal product.

However, the prerequisite would be the introduction of both, an RPS standard for creation of electronic submissions and a common repository.

So far RPS has not been introduced. A common repository for all eCTDs submitted for Centrally Authorised Products (CAPs) is available and it is planned to further enhance the repository for all other EMA-run procedures [15]. Anyway, the set-up of a common repository for CTAs and other submissions is not likely for the coming years but could be a further step for planning submission strategies in the future. This will be a greater change and challenge.

Keeping the introduction of RPS in mind (even without a common repository) it has to be taken into account that the set-up of the new EU database is flexible enough to be able to receive CTA submissions in the RPS format.

However, the creation of submissions in RPS format is technically advanced and requires special skills and tools. This could be a limiting factor for using RPS.

It could be a problem for the authorities of smaller countries having the technical tools available for RPS, for example a viewer tool.

The same applies to small companies or small affiliates: special requirements have to be fulfilled for the creation of submissions with RPS which demands additional skills, resources and costs. Not all of the applicants have the resources to support this approach.

It has to be considered if RPS is too complicated for CTAs and if simpler solutions may be more feasible.

Even the fact that eCTD 3.2.2 was introduced years ago for centralised procedures, many national MAAs are still created using a much simpler technical format than eCTD, the Non-

eCTD electronic Submission (NeeS). This demonstrates how difficult it is to achieve acceptance for technically advanced solutions.

It will be interesting to see what will be changed and achieved with the introduction of RPS in the coming years. This is a further milestone for regulatory product submissions and opens channels for flexible solutions. But where it is feasible and where it will actually be used remains to be seen.

5.3 TIMELINES AND CHALLENGES

The implementation of new legislation always brings challenges, especially if the changes are as extensive as they will be with the new CTR.

No special timelines have been defined for the availability of the new EU portal and database but there are valid reasons for the fast replacement of the Directive (e.g. harmonisation, streamlined assessment). Therefore the application of the new Regulation should be introduced within a reasonable timeframe.

As the application of the Regulation is conditional to the availability of the audit for portal and database, confirming that they meet the functional specifications, the EMA has already published the specifications [28] and the appendix on data transparency [29] followed by a public consultation phase.

It was clear from the beginning that the application of the CTR cannot take place earlier than 28 May 2016 given that, before the Regulation becomes applicable, a positive audit must be finished and the EC is obliged to publish the results in the Official Journal of the European Union (Article 82 of the CTR).

In the meantime, a later date in 2016 or even a date in 2017 is considered more realistic for the application of the Regulation. It will take some time to set up the new IT systems and as they need to have full functionality before they can be used, it is also essential to take the time to obtain the input of different stakeholders for the set-up to achieve a result that is acceptable and feasible for all needs.

Timelines are also an issue for the introduction of the IDMP standard for the medicinal product dictionary.

The Commission Implementing Regulation (EU) No. 520/2012 (Article 40) [40] states clearly that the IDMP standard will become applicable as of 1 July 2016.

Implementing this in time presents a challenge for all stakeholders. The authorities have to deliver appropriate guidance and define which data are necessary for the submission to the MPD. International collaboration with other authorities is desirable to achieve a global approach, for example for controlled dictionaries. The transition from current controlled vocabularies, for example EUTCT, to IDMP-compliant dictionaries has to be considered. All this needs to be coordinated.

For pharmaceutical companies it is a major task to collect the mandatory data for IDMP (which are much more extensive than the data necessary for EVMPD/EVIMPD) from different sources in the company and to find an efficient way to manage the collection and delivery of reliable data.

For all new processes, such as the new process for clinical trials as described in the new Regulation, it is necessary for the authorities and for applicants to adjust to the new procedures.

According to a position paper of the EFPIA for the development of the EU portal and database [46] 48% of the activities necessary in the EU portal and database have to be carried out by the sponsors, with less than 40% of these being currently reflected in EudraCT. This means, internal processes for sponsors and authorities have to be adapted to the new situation and new guidance documents need to be written. Especially with limited resources and the tight timelines involved, this is a challenge.

During a transition period both systems – EudraCT and EU database – can be used and both processes are valid in parallel (Article 98 CTR). After the transition period, when new data is no longer accepted in EudraCT, the EMA has to find a solution for the handling of the legacy data from EudraCT and the EUCTR. This challenging task is also part of the EU Telematics Strategy included in Programme 2 for Clinical Trials [15].

6. CONCLUSION AND OUTLOOK

What has been made clear in the previous sections: standardisation and interoperability are concepts which can no longer be ignored in the regulatory landscape in the future.

Of course these are not new concepts, and standardisation is a topic which has been discussed and brought forward in this area for years.

It takes some time to introduce such improvements which influence - in the ideal case - many different systems. It takes a large amount of effort and efficient coordination of many experienced stakeholders to find the appropriate solutions.

Many different standards are already available in various fields and it has to be decided and agreed on by all parties or decision makers concerned, which standards can be used. It has to be decided which standards make sense in special areas, and which ones are feasible and usable.

The development of new processes and new technical systems and requirements offer a chance for reflection and a possibility for major changes as in the case of the new Clinical Trial Regulation.

The CTR is valid for the European Union but in the long term the aim is to achieve a global approach and to take into account what is planned internationally.

Globally applicable and developed standards should be used as much as possible as will happen with, e.g. RPS or ISO-IDMP, strongly supported by the implementation of the MDM concept by the EMA.

This leads to international harmonisation which offers a global overview and transparency for data and much better results for data analysis, e.g. for pharmacovigilance purposes because the amount of data is bigger and more representative.

The new EU portal and database can be set up in this way and even if not everything is used in this light yet, the set-up should be flexible and open enough to allow such global concepts for future use.

It will be necessary to monitor the implementation and utilisation of standards permanently and it would be advisable to react with flexible solutions if it turns out that the implemented approach does not achieve the expected benefits.

The aim is to simplify and harmonise processes, to achieve more transparency and efficiency with resultant lower costs and to generate high quality of data.

The final goal is to generate data that are reliable and robust and to optimise the retrieval and analysis of the available data. This helps all stakeholders to come to correct decisions based on reliable analyses (e.g. in pharmacovigilance).

In the end, this will improve patient well-being and help to bring forward innovative solutions.

7. SUMMARY

In summary, the introduction of the new Clinical Trials Regulation repealing the Clinical Trials Directive involves many changes and opportunities.

Only if successful existing and planned standards are used in the new systems can harmonisation through standardisation and following interoperability with other systems be achieved.

The EU portal and database should be implemented in the light of the current Telematics strategy and keeping the ongoing initiatives such as the MDM roadmap and the eSubmission roadmap (with the introduction of international standards, such as IDMP and RPS) in mind. This is the prerequisite for achieving globally feasible systems and solutions.

The result is the effective, safe and efficient planning and reporting of clinical trials and the improvement of processes in the life cycle of a medicinal product in the EU.

As the regulatory systems landscape is always in a continual development process, flexible, efficient solutions and willingness for change are necessary.

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Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

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