

Preliminary communication

Best Archival Practice in the Regulation of Medicines: Work on the Guidelines for Agencies for Medicinal Products

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Summary

This paper announces the beginning of the work on the standardization of filing of electronic medicinal dossiers in agencies for medicinal products. Medicinal products electronic dossiers have to be preserved for the long-term because of the requirements for protection of patients' safety and standardization of archiving procedures.

Key words: common European best archival practice, electronic Common Technical Document, eCTD, Open Archival Information System

Introduction

Management and long-term preservation issues connected with the medicinal products' documentation became a very important topic since the end of 2009 – the year when the European agencies for medicinal products were supposed to switch from the paper-based records to the electronic records. Since the field of medicines' regulation and control is constantly being challenged for pharmacovigilance and legal reasons, it is of the utmost importance to standardise the procedures of management, storage and long-term preservation of electronic records in this domain.

Having all said in mind, a new subgroup with the mandate of creation of guidance for prescribing archival procedures for medicinal products' electronic submissions in the EU national agencies for medicinal products and the European medicines agency (EMA) is found by the Telematic Implementation Group on electronic submission (TIGes). Electronic submission denotes electronic medicinal products' documents, i.e. basic documentary resource for me-

dicinal products regulation and control. Although relevance of such guidance was emphasised before the foundation of the subgroup, now more and more European agencies for medicinal products are joining this initiative for preparing the guidance and proposing it to the TIGes.

TIGes is one of the telematic projects¹ that gather European agencies for medicinal products. TIGes' meetings are hosted by EMA in London. Telematic projects are way to implement common European strategy of working with electronic resources for regulation of medicines since 2003, and TIGes group is responsible for implementation of electronic submissions since 2000. Beside electronic submissions, telematic projects involve managing of common European database for clinical trials, manufacturing and manufacturers data, database of medicinal products for human on the European market, common human pharmacovigilance system, veterinary pharmacovigilance database, and managing infrastructure and referral projects, such are the system for safe exchange of data between agencies for medicinal products (EudraLink), secure European regulatory network of EMA and national agencies for medicinal products (EudraNet), European review system for assessments of electronic submissions (EURS), and telematics controlled terms repository (EUTCT).

TIGes group is in charge for production, approval, implementation and monitoring of all European standards and guidelines that support European and global specifications for electronic submission in the electronic common technical document format (eCTD) and guidelines for additional European non-eCTD electronic submission format. TIGes meets four times a year, the first day is reserved for meeting of regulatory delegates just from agencies for medicinal products, and second day is for meeting of regulatory delegates with pharmaceutical industry associations representatives and other invited guest, according to current topics and business needs that need to be discussed and solved. There was forty six meetings held until now and during this eleven years period various subgroups were established, such are subgroup for implementation of veterinary electronic submissions (TIGes Vet), subgroup for interlinking of various standards and their implementation (Interlinking), subgroup for implementation of European review system specification published by EMA and monitoring various vendors' tools (EURS), subgroup for development of central repository of electronic submissions received by EMA in centralised procedure, subgroup for development of common European portal for receiving electronic submissions for all agencies, subgroup for production of electronic application (submission) form (eAF), and subgroup for (medicinal) product information management (PIM). It can be stated that TIGes represents a contemporary dynamic work environment adaptable to implementation of telematic strategy and management of different projects, e.g. while further work of PIM and EURS sub-

¹ Introduction to the EU telematics programme, 19 May 2011, http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/05/WC500106712.pdf, June 2011.

groups remains uncertain because of closing of PIM project and change of EURS mandate, new subgroups like *ad-hoc* guidance group Best archiving practice guidance is being born.

Best archiving practice and guidance

Ad-hoc guidance group Best archiving practice is a subgroup of TIGes with the mandate of creation of common European best archiving practice document. The goal of long-term preservation attempts in this case is medicinal products' dossiers, so called "electronic submissions". An electronic submission consists of records on manufacturing a medicinal product and its characteristics, substances and ingredients. These records are compiled into parts I-IV according to an older format or into modules 1-5 according to the current Common Technical Document (CTD) format. *Ad-hoc* guidance group Best archiving practice was founded upon proposition of Cécile Lombard from French agency for medicinal products and Arian Rajh from Croatian counterpart-agency after the visit of Croatian delegation to the French colleagues in January 2011. Additional reason to found this particular subgroup lied in the results of an internal TIGes' survey on the EU agencies' archives. The 2010 TIGes' survey on archives showed that the EU agencies for medicinal products did not established coherent archival policies, processes and systems capable of long-term preservation of electronic submissions (or electronic medicinal products dossiers). The provisional idea of solving the problem of long-term preservation was presented to TIGes' delegates as a business case which has been translated into the mandate of the proposed *ad-hoc* guidance group in the later stage. *Ad-hoc* guidance group is chaired by the Cécile Lombard and current members are delegates from Poland, Denmark, France, Croatia, Hungary, Finland, Luxembourg, Malta, Austria, the Nederland, Greece, Slovenia and Estonia. It is expected that the delegates from Sweden and EMA join the *ad-hoc* guidance group. EMA ensures support and logistic for web-conferences of this *ad-hoc* group.

Guidance should include mutually recognised requirements for all agencies and their information systems, and recommendations for establishment of national and organisation-specific solutions for long-term archiving of electronic submissions. These mutually recognised requirements and organisation or nationally-oriented recommendations should enhance long-term preservation framework. The future guidance will refer to the following existing specifications, guidelines and standards:

- European specification for administrative module of electronic eSubmissions (current version is 1.4. from 2009)
- Modules 2-5 of electronic submissions global specification (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH)

- Electronic submission guidelines for eCTD in NeeS format issued by TIGes
- General International Standard Archival Description standard ISAD(G) and International standard archival authority record for corporate bodies, persons and families ISAAR(CPF)
- ISO 14721:2003 Space data and information transfer systems – Open archival information system – Reference model
- ISO 15489-1:2001 Information and documentation – Records management – Part 1 and Part 2
- ISO 23081 Information and documentation – Records management processes – Metadata for records – Part 1 and Part 2
- Model Requirements for Electronic Records Management specification

OAIS and the referent framework of the guidance

The referent framework for archiving electronic submission in eCTD format and records submitted to the agencies in support of regulation of medicines should include mutual requirements, stated by all agencies, and more-loose recommendations that could fit in the broader national and organisational practices. An information model provided in ISO standard for Open Archival Information System (OAIS) should be used as the foundation of such highly productive referent framework.

Open Archival Information System is a standardised reference model of an archive, made of human organisation and systems, capable of accepting responsibility for preserving information and for making it available for designated community. In this case openness means possibility of various implementations of the information model, not unlimited access.² OAIS is also the reference model for information systems capable for long-term preservation of digital contents. OAIS prescribes information and functional model. Fundamental entity of OAIS information model is information object. Information is defined in OAIS standard as a combination of set of bits and their representation. Information object is compiled as data object and representation information which makes possible to interpret set of bits of the data object. We are referring to the digital data objects, although the reference model encompasses physical objects, too. Representation information ensures interpretation of digital data object by providing its meaning. There are several types of representation information: structure information, semantic information or representational network. Information objects are divided to content information, created when representation information interprets content data object, preservation description information, packaging information or descriptive information. Basic information objects and primary goal of preservation is the content information. In order to preserve

² ISO 14721:2003, 1-11.

it the system generates archival information package. Packaging information aims to bond content information, preservation description information and descriptive information. These information are rapt together into information package which can be archival (AIP), dissemination (DIP) or submission information package (SIP). Submission information package is input into OASIS system and disseminated package is part of the content provided for users. ISO OASIS standard also defines basic functions of the OASIS system/archive. These functions should be implemented by Best archival practice for electronic submissions and they should deal with execution of complex verifications of packages due to the risk of content obsolescence and preparation for migrations.

Problems related to electronic submissions

Each part or module contains particular medicinal product information. It can be administrative information, (pharmaceutical-chemical) quality related information, nonclinical and clinical information. Quality information is used for assessment and testing of quality of medicines, nonclinical information for efficacy and clinical information for approving of safety of medicines. Nonclinical documents contain information provided by the medicinal product's manufacturer and scientists conducting approbation of pharmacological profile of the product, and pharmacokinetics, pharmacodynamics and toxicology tests. Common technical document (CTD) paper format, dividing dossiers into modules, have one additional module – module 2 or summary of the dossier. CTD format has also electronic version – electronic Common technical documents format (eCTD). eCTD dossier contains PDF files within structured folders. For lifecycle of the dossier there is XML DTD in “util” folder of the dossier. Each dossier is published by the medicinal product manufacturer and submitted to the medicinal product agency as a sequence, so dossier can be seen as a set of sequences counting from 0000 onwards. Granulation of folders and filenames in sequences are strictly specified. Metadata is extracted from XML and used by the review systems or applications for representation of eCTD dossiers. That is how assessment of medicinal products is facilitated because assessors can retrieve the data effectively. New, appended, deleted or replaced documents are emphasised in the review tool with different colour. In Reykjavik in February 2005 Heads of the European medicines agencies set out the end of 2009 as the target date for shifting from the paper based format to eCTD. Today most of the medicinal products agencies work with eCTD but they still have not established filling policies and procedures. Proactive approach for long-term preservation of eCTD dossiers on the European level is something that should be established. The basic problem in working with medicinal product dossiers is complexity of relations between dossier, case and regulatory procedure. That problem exists regardless of format of the dossier, either being paper or electronic. But if an organisation wants effective control of eCTDs and electronic documents in general, it is obligatory to carefully design the organisation's business processes

that use electronic documentation as resource. Misplaced paper files can be found eventually, but maintenance and management of complex digital objects is much more demanding.

What are relations between dossier, cases and regulatory procedures? One dossier can be business resource for many medicinal products (cases), i.e. for capsules and suspension, which can be divided into two separate medicine products sharing same active substance. One dossier can be resource for control of many medicinal products, i.e. when submitted as a dossier for group variation. Regulatory procedures that use dossiers are procedures of registration, renewal of registration and variation of approval. There are several types of regulatory procedures, because medicinal products could be regulated either by the European medicines agency in a centralised procedure or by national agencies for multiple markets (mutual recognition procedure or decentralised procedure) or for their own national markets (national procedure). The same dossier can be resource in more than one procedure, i.e. for variation of solution and for registration of capsules which are new on some national market. Or, dossier once used for registration of medicinal product on common EU market could be used for registration of the same product outside EU. In conclusion, national agencies' for medicinal products function is national administrations and they are obligated to follow registration offices' procedures which distinguish medicinal products, cases and regulation procedures.

The fundamental question in the preparatory work on Best archiving guidance is – what to preserve? In addition to preservation of dossiers, submitted by manufacturers of medicinal products, there is a need to preserve additionally submitted medicinal products-related documents, that do not fit eCTD specification and therefore they are placed outside of the eCTD record, then records created by agencies for medicinal products during assessments, as well as the final version of documents for medicinal personnel and patients.

Conclusion

Creation of the Best archiving practice guidance will be very demanding due to the complexity of structure and relation of digital objects that we want to preserve over long term. One of the most useful experiences that can facilitate that attempt is a prototype application for packaging eCTD dossiers and other records into OAIS-compliant archival information packages, presented to the public on eTELEMED 2011³ international conference. The prototype showed possibilities of extracting metadata from the content, adding preservation metadata, mapping different metadata schemes, packaging content, protection of packages, and analysis of potentially obsolete parts of the content.

³ Stančić, Hrvoje, Rajh, Arian, Pavlina, Krešimir. Long-term Preservation Solution for Complex Digital Objects Preserved as Archival Information Packages. eTELEMED 2011, 23-28.02. 2011., Gosier, Guadeloupe, France.

Once the creation process of the Best archiving practice starts, it will be important to define critical components of archival information packages and logical connections between them. Furthermore, it can be assumed that versioning of packages could be an issue and protection of every version could be yet another requirement. It should be defined which metadata to preserve and how to structure them. It will also be necessary to test packages periodically in order to detect possible obsolescence of content or file formats contained in packages, to analyse components, to prepare packages for migrations, to version packages with the preservation-related changes and to protect that new versions. The final goal should be to have the possibility to retrieve and use archival information packages for particular medicinal product or products that have been sold on particular market in a particular time period.

Beside the expected usage of the Best archiving practice by agencies for medicinal products it could also be used by pharmaceutical companies. The pharmaceutical companies have difficulties to answer questions like: “Which dossier was submitted to which agency?”, “Which documents were valid in which time?” etc. because of the rising amounts of dossiers, number of agencies that regulate their medicines, and complexity of regulation procedures. These questions are usually asked for pharmacovigilance and legal reasons, and agencies must be able to answer them quickly and correctly as well as be able to prove the authenticity, integrity and usability of the preserved electronic records at the same time making no room for questioning their trustworthiness.

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