EMA's Product Information Management (PIM) project halted – Impact from the perspective of biotech companies on strategies for structured product information management

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LIST OF ABBREVIATIONS

ANSI	American National Standards Institute
AR	Assessment report
CAPs	Centrally authorised products
CBER	Center for Biologics Evaluation and Research
CC	Country code
CCDS	Company core data sheet
CCM	Component content management
CCSI	Company core safety information
CDER	Center for Drug Evaluation and Research
CEN	European Committee for Standardization
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CIOMS	Council for International Organizations of Medical Sciences
CP	Centralized procedure
CRO	Contract research organisation
DCP	Decentralised procedure
DES	Data Exchange Standard
DITA	Darwin Information Typing Architecture
DRLS	Drug Registration and Listing System
EC	European Commission
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EN	English
EPAR	European public assessment report
EU	European Union
FDA	US Food and Drug Administration
FTE	Full time equivalent
GMP	Good Manufacturing Practice
HA	Health authority
HL7	Health Level Seven International
HTML	Hypertext Markup Language
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	Identifier
IDMP	Identification of Medicinal Products
ISO	International Organization for Standardization
IT	Information technology
JAR	Joint assessment report
LAT	Light Authoring Tool
LOINC	Logical Observation Identifiers Names and Codes
LoOI	List of outstanding issues

LoQ	List of questions
MAA	Marketing authorisation application
MRP	Mutual recognition procedure
n/a	Not applicable
NCA	National competent authority
NLM	National Library of Medicine
OTC	Over-the-counter
PDF	Portable Document Format
PDVE	PIM Data Validation Engine
PI	European product information
PIM	Product Information Management
PIQ	Product Information Quality Review Group
PL	Package leaflet
PRS	PIM Review System
PSUR	Periodic safety update report
PTL	Product team leader
QRD	Working Group on the Quality Review of Documents
SaaS	Software as a service
SmPC	Summary of product characteristics
sPI	Structured product information
SPL	Structured Product Labeling
UID	Unique identifier
UK	United Kingdom
US	United States of America
W3C	World Wide Web Consortium
XHTML	Extensible Hypertext Markup Language
XML	Extensible Markup Language

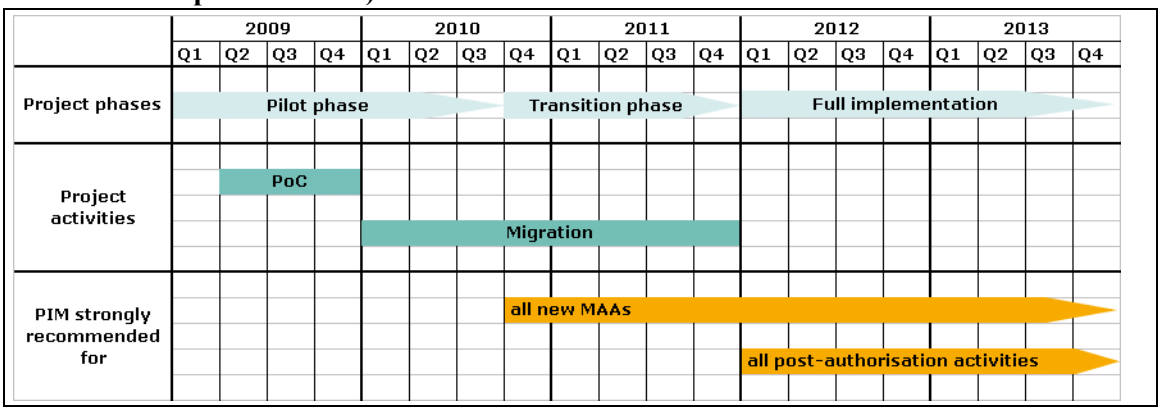
INTRODUCTION

The European Product Information Management (PIM) project was launched by the European Medicines Agency (EMA) in 1999. Its goal was to establish a new and simpler way of handling/exchanging product information in the European Union and to ultimately improve the quality and consistency of product information.

Even though PIM has never become productive except for a pilot program, considerable progress had been achieved since 1999: For the management of product information within the scope of the centralised procedure an Extensible Markup Language (XML)-based Data Exchange Standard (DES) had evolved which in the long-term was planned to be adapted to the specific requirements of both the European MRP/DCP and purely national procedures. In addition, software applications (LAT = Light Authoring Tool; PRS = PIM Review System; PDVE = PIM Data Validation Engine) had been developed that allowed for the bidirectional electronic communication between applicants and competent authorities.

New momentum was infused in the PIM project in September 2009 when EMA published a statement of intent with regard to the implementation of PIM in the centralised procedure [9]. In its statement, EMA described the current status and defined both a timeline of the project as well as the project's milestones until PIM was to become mandatory/strongly recommended (Figure 1).

Figure 1 EMA implementation plan for PIM for centrally approved products (Status: September 2009)



MAA = Marketing authorisation application; PIM = Product Information Management; PoC = Proof of concept

The statement of intent resulted in a burst of activities by the concerned stakeholders from the industry side, i.e. vendors of PIM tools and pharmaceutical companies, which became aware of the extremely short transition phase to full implementation as specified by EMA.

The timeline proposed in September 2009 has not been maintained and ultimately the PIM project was halted on March 28, 2011, as a consequence of EMA's review of its business strategy and IT system requirements in the context of new legislation and a budgetary review. In its announcement [11], EMA, however, confirms that it remains committed to the concept of structured content for product information and its efficient exchange, and that it will return to the issue once the review process will be completed.

Even though the PIM project, which in its complexity was certainly seen as a "sword of Damocles" by some pharmaceutical companies, has been halted, one must be aware that structured product information is already reality: The Structured Product Labeling (SPL) project of the US Food and Drug Administration (FDA) went live in October 2005 and was continuously expanded since then. In Europe, one will on the mid-term have to expect a follow-up project on structured product information with a similar short transition phase to full implementation once its pilot program has been exited.

One of the key features of structured product information certainly is the shift of paradigm associated with its implementation, the current document-based management of product information being replaced by a component-based authoring approach. Moving to structured product information will thus require considerable rethinking among the personnel/functions responsible for the generation of product information and major redesign of the related business processes in pharmaceutical companies.

The goal of this thesis is to provide an introduction into the area of structured product information from a global perspective. Both the health authority and the industry perspective will be discussed. The latter with a focus on biotech companies, i.e. small to medium-sized enterprises based at a single location with a limited product portfolio, which are directly concerned by any EMA initiative in this field since biotechnology products fall within the mandatory scope of the centralised procedure [47]. The ultimate target is to provide a basis for pharmaceutical companies for strategic decisions with regard to structured product information and the associated transition to a component-based mode of authoring product information.

Chapter 1 provides an introduction into the principles of component-based authoring. In the following, more technical, Chapter 2 the two health authority initiatives SPL and PIM are described using a comparative approach in order to highlight key differences of these systems. The impact of SPL and PIM on industry is discussed in Chapter 3. Chapter 4 investigates the question whether the transition to a component-based mode of authoring product information is associated with benefits in terms of process optimization independently of health authority requirements. It concludes with general cost-benefit considerations on different ways of implementing component-based authoring and defines basic criteria that may be helpful for decision analysis within pharmaceutical companies. Chapter 5, using the tools developed in Chapter 4, evaluates possible implementation designs in more depth from the specific perspective of biotech companies and analyses the impact of the PIM project being halted. Chapter 6, finally, provides an outlook and conclusions.

1 THE BASIS OF STRUCTURED CONTENT: COMPONENT-BASED AUTHORING

1.1 Principle of component-based authoring

Component-based authoring requires specific software tools with a more or less complex architecture. Since all tools will provide a graphic user interface which assists users in managing and writing component-based documents, most users will not have to deal with what happens behind the scenes in these systems.

In order to catch the benefits of this new way of writing documents it is, however, important to understand the basic principle of component-based document authoring, which is the separation of content, structure and layout management:

- Component-based authoring of a document implies that the actual content of a document is fragmented into its components or, in other words, its stand-alone information units.

  Fragmentation going down to the level of single paragraphs is often considered as being appropriate, but higher levels of fragmentation (e.g. single sentences) or lower levels (text blocks consisting of several paragraphs) may also be meaningful.

  The text fragments are managed individually in a component library (Figure 2, left) in which they have been assigned unique identifiers (UIDs) and other metadata such as information on use/content, version or status (draft/approved).
- Structure information, i.e. the sequence of the individual text fragments, is captured by means of component maps which only provide references to the components (Figure 2, center)[1].
- So-called style sheets[2] provide information about layout features that apply to particular output formats (Figure 2, right).

The actual document is generated by the software which integrates the structure/layout information and the data in the content repository.

Component-based authoring permits re-use of components in different documents by assigning the components to different maps (see Figure 2). One must, however, be aware that component re-use requires well-designed content units in terms of fragmentation degree as well as context and navigational independence: Large fragments consisting of several paragraphs are less likely to be suited for re-use. Similarly, referencing to external components (using wordings like “As mentioned previously ...”, or via hyperlink cross-references) may reduce the re-use potential of components.

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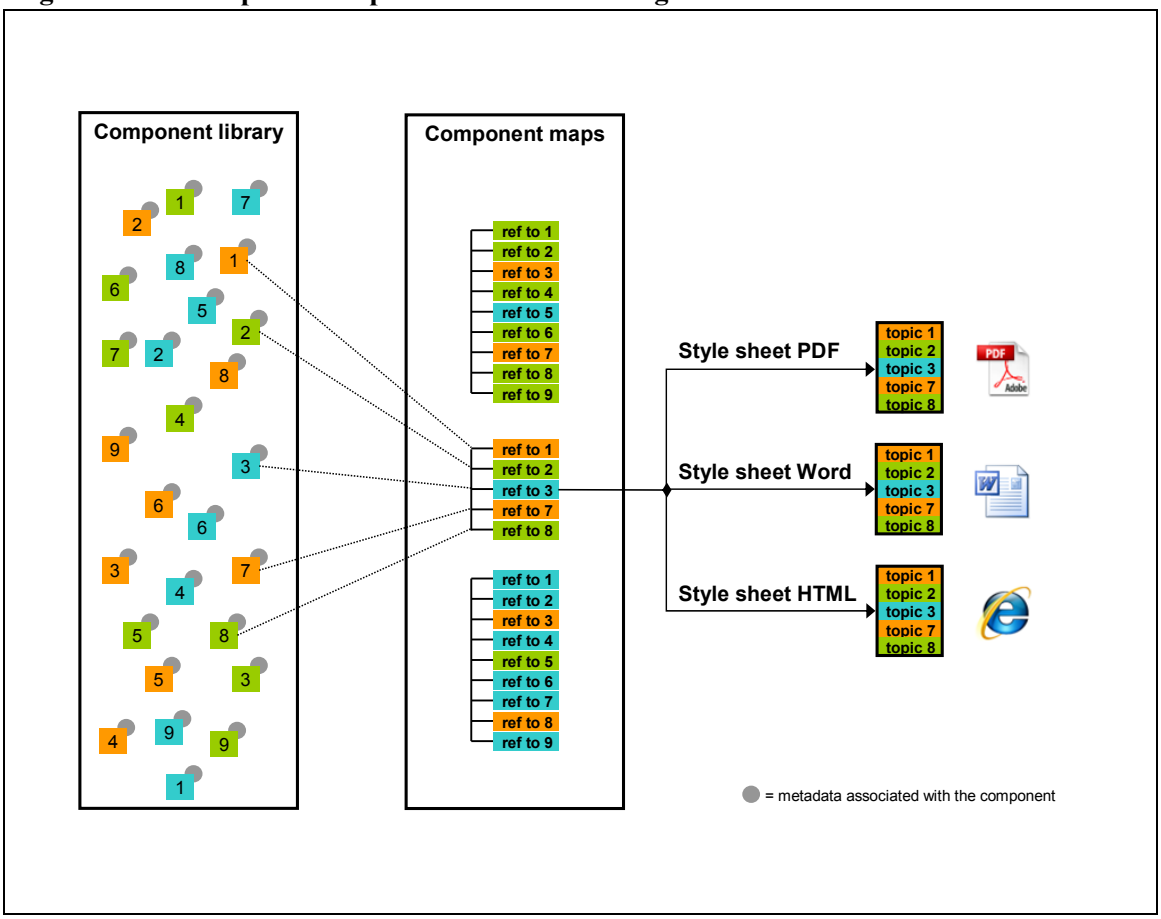
[1] The description of the behind-the-scenes processes associated with component-based authoring provided here follows steps that would be required in a component content management (CCM) system with a DITA (Darwin Information Typing Architecture) content model ([51], [52], [50]). Depending on the underlying content model these processes may thus vary in different CCM systems.

[2] In XML, style sheets are what templates are in the Word world. Style sheets allow for more flexibility in terms of output generation and support a multitude of output formats (e.g. Word, PDF, HTML).

Figure 2 Principle of component-based authoring



Component re-use has its major potential in cases where a common fragment needs to be updated: The fragment will have to be edited only once in the content base, because the change will be automatically applied to all output documents that use this particular fragment. Content re-use also provides the opportunity to streamline translation management processes by the 1:1 re-use of existing translations.

A further benefit of component-based authoring is the layout and format independence since different style sheets can be used to produce different outputs in terms of layout or file format (see Figure 2). Thanks to the automated output generation adherence to any layout requirements for a particular document can be built in by appropriately designed style sheets.

In this document rendition process it is the role of the style sheet to translate the actual formatting information embedded in the components by means of XML formatting markups defined in specific conventions (e.g. W3C's XHTML standard or HL7's NarrativeBlock schema). These conventions permit to define the appearance (e.g. bold, italics, underline, superscript, subscript) of text parts or whole fragments (e.g. background color) and to include symbols and special characters. Complex formatting to bulleted or numbered lists or tables is feasible and even figures may be embedded within the narrative part of the components.

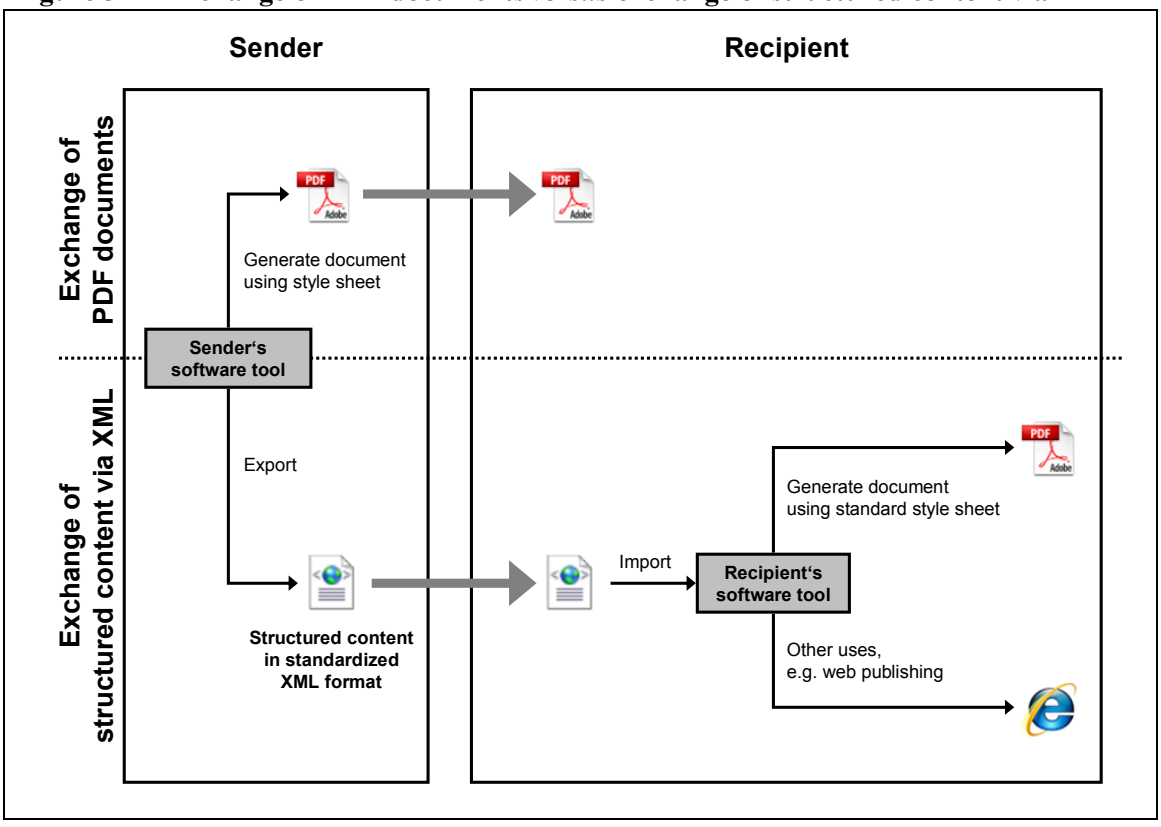
Authoring tools may expose the user to the XML formatting markup in different degrees. If the authoring tool relies on an XML editor for the entering of text, the user will be confronted with the plain XML markup, which in the case of e.g. tables will not at all correspond to the view in the final output. If, however, a WYSIWIG ("what you see is what you get") interface is used, the user will not at all have to deal with the XML and will have the familiar Word-like look and feel. Some authoring tools will use interfaces that permit to switch between both extremes.

1.2 Structured (= component-based authored) content exchange via XML

A further most interesting feature of documents authored in a component-based mode is that one can export the structured content, i.e. the plain text and the metadata as a whole or in parts as an XML file (Figure 3).

Provided the structure of the data transferred via XML files is standardized and a standard style sheet is used, the XML file can be used on the recipient's side not only to generate the actual document(s) of interest, but, more importantly, for various other purposes requiring direct access to structured information (see Chapter 2).

Figure 3 Exchange of PDF documents *versus* exchange of structured content via XML



2 POTENTIAL OF STRUCTURED CONTENT EXCHANGE: HEALTH AUTHORITY INITIATIVES

Health authorities have recognized the potential of structured content for the management of product information.

In the US, structured product information is fully implemented and by now mandatory for human prescription/over-the-counter as well as veterinary products. Its main purpose is to populate databases for product information.

The transition from Word-based to XML-based product information was driven by the vision of the American healthcare community (e.g. federal healthcare agencies, healthcare providers, healthcare professionals, the healthcare industry and health information suppliers) to work toward the creation of a fully-automated health information system. In this system, the availability of structured, i.e. non-PDF, labelling information is a key to the development of e.g. electronic prescribing tools for use in clinics and hospitals with the aim to prevent prescribing errors ([2], [3]). The DailyMed website, a public service of the National Library of Medicine (NLM), is an integral part of this system and plays a key role as it supplies health information providers and the public with a standard, comprehensive, up-to-date, look-up and download resource of medication content and labelling as found in medication package inserts [6].

In Europe, EMA's halted structured product information project PIM had a different scope and the PIM-related documentation classified as only "other benefit" [16] the opportunity to enhance the quality of the European database for product information (EudraPharm). Its goal was primarily to support the process of negotiating the product information between applicants and health authority by establishing an XML-based way of handling/exchanging product information and to ultimately improve the quality and consistency of product information especially with regard to the required translations in all EU languages.

Future structured content exchange projects concerning product information might be triggered by ICH's project of a standard for the identification of medicinal products (IDMP; Guideline "ICH implementation guide for identification of medicinal products (IDMP) message specification" currently in development). The rationale for this ICH initiative is the lack of an internationally harmonized standard for the unequivocal identification of medicinal products, which impairs exchange and integration of for example pharmacovigilance data and thus hinders the accurate overall scientific evaluation of medicinal products (e.g. efficient detection of adverse reaction signals) ([12], [39]).

2.1 Structured Product Labeling (SPL) in the US

In the US, the format of XML-based product information is specified by the Structured Product Labeling (SPL) standard, which was developed by Health Level Seven International (HL7), a global, American National Standards Institute (ANSI)-accredited standard-developing organisation with focus on clinical and administrative data.

FDA's SPL project became productive end of October 2005 starting with CDER-regulated human drugs [34] and was subsequently expanded to CBER [33] and other products (e.g. veterinary medicines) [36].

SPL documents, i.e. the SPL XML files submitted to FDA, not only contain the human readable content of labelling for a product (all text, tables and figures) but also additional machine readable information (so-called drug listing data elements), which FDA uses to populate its drug registration and listing system (DRLS; also see the ICH IDMP project described above).

The structure of SPL files is rather straightforward (Figure 4). SPL documents consist of a header and a body, the latter is subdivided into two parts containing the actual content of labelling[3] and product data elements, respectively.

The header includes technical information, SPL identifying information (e.g. unique identifiers for the SPL document and its version, a LOINC[4] code for the SPL document type) and information on the labeller and the manufacturing.

The "content of labelling" part of the SPL document has a rather simple structure being made up of a single type of XML element called "section". Every section must be provided with a unique identifier and information on its effective time. Optionally a title and a section ID used to target hyperlink references may be added. So-called major sections correspond to the headings in the full prescribing information (defined by the appropriate labelling regulation, e.g. 21 CFR 201.56 for human prescriptions drugs) and are required to be tagged with the appropriate LOINC[4] code (e.g. 34067-9 for the major section describing the indications and the usage of the drug [53]).

Sections may contain text (i.e. the components described in Chapter 1.1) and/or nested sections (used to group related paragraphs). The formatting of the human readable text within the sections follows rules that are standardized within HL7 and defined in the so-called NarrativeBlock schema ([54]; also see Chapter 1.1) .

The sequence of the sections in the SPL XML file corresponds to the order in which the information appears in the actual product information rendered by the standard style sheet[5]. In this regard the SPL file thus pretty much resembles a Word/PDF file containing the same product information (Figure 4).

The "product data elements" part of the body, finally, includes information about the product (product and generic names, ingredients, ingredient strengths, dosage forms, routes of administration, appearance, DEA schedule) and the packaging (package

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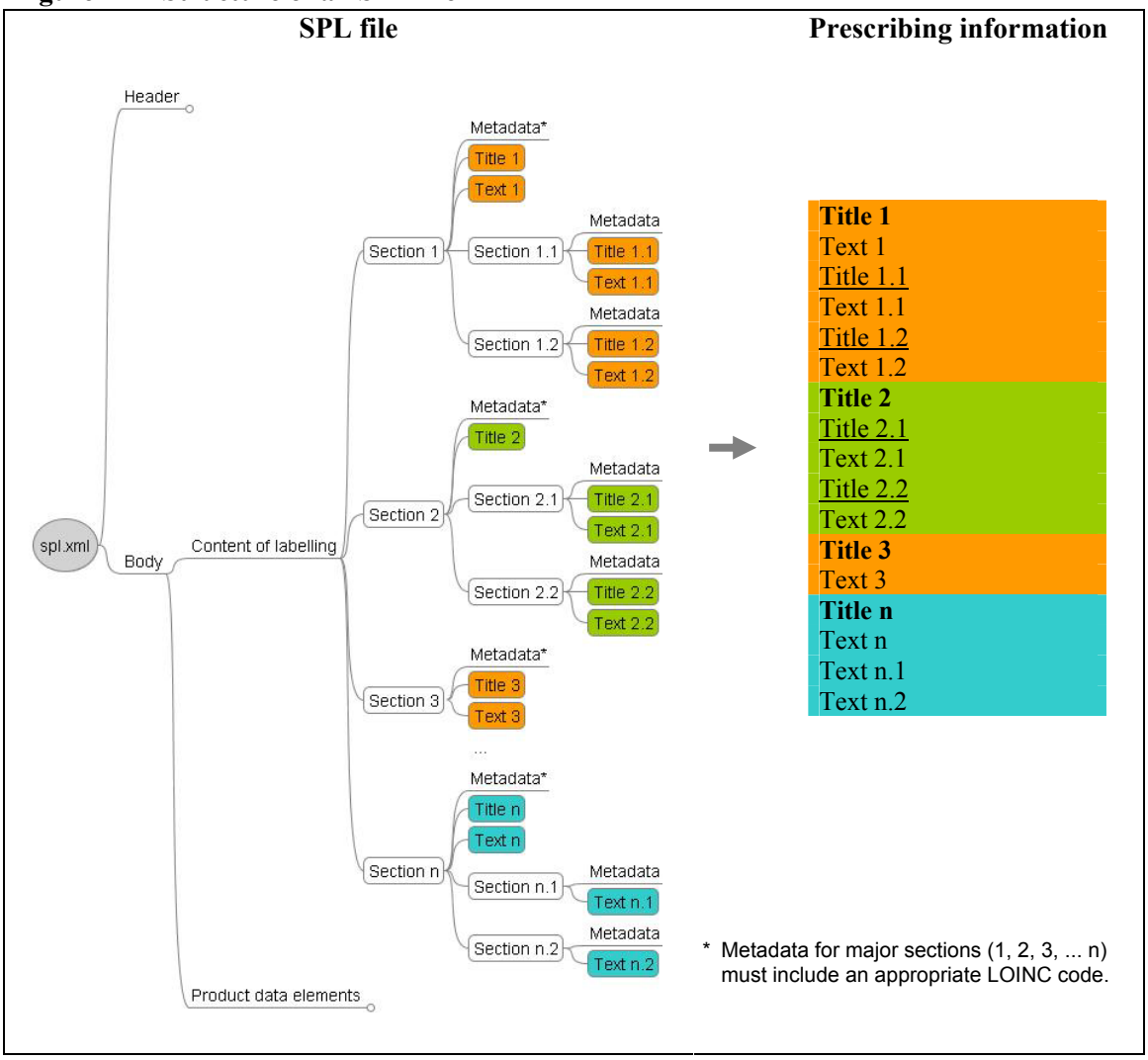
[3] Since June 1, 2009, SPL is also used for the submission of drug establishment registration and drug listing information. Content of labelling must only be provided for human prescription/over-the-counter and veterinary products [36].

[4] Logical Observation Identifiers Names and Codes (LOINC) is a database and universal standard (primarily for identifying medical laboratory observations) developed and maintained by the US non-profit Regenstrief Institute (www.regenstrief.org).

[5] This is not 100% true: The so-called highlights are defined within the major sections, but are processed by the SPL style sheet to appear at the beginning of the actual document.

quantity and type). Various terminologies and coding systems are in place to standardize the entries in the machine readable data elements.

Figure 4 Structure of an SPL file



2.2 Product Information Management (PIM) in Europe

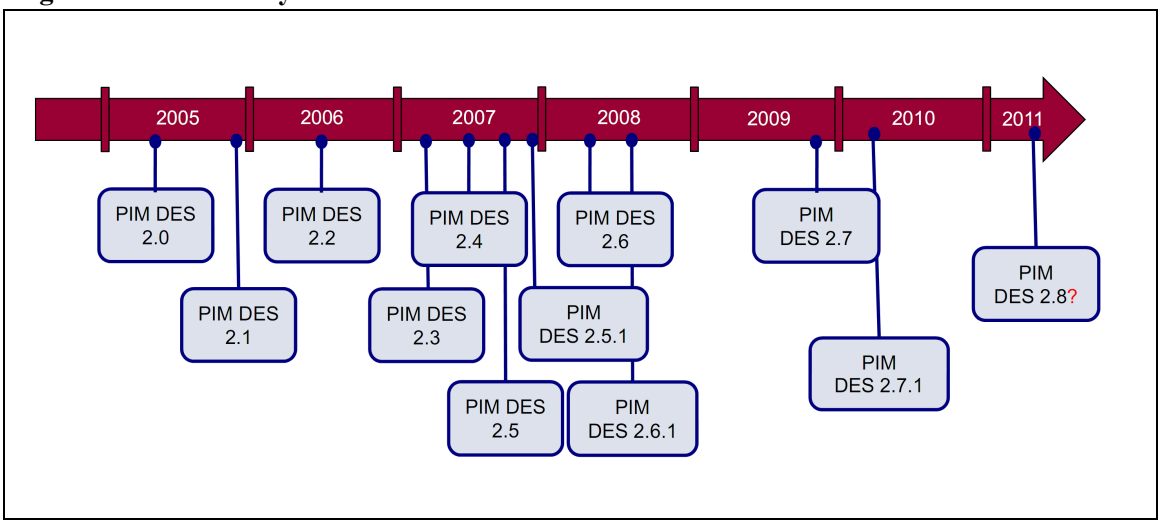
In contrast to SPL, the PIM specification (Data Exchange Standard; DES) is[6] a specific development that only partially relies on standards (e.g. W3C's XHTML standard for the formatting of text fragments).

PIM has only been implemented in a pilot program in which a couple of major pharmaceutical companies tested the processes associated with PIM.

Compared to the SPL standard, the PIM DES is much more complex and was less stable (Figure 5), which at least in parts might be due to the complexity of the European product information.

[6] For ease of readability the present tense is used in the following description of PIM.

Figure 5 Instability of the DES standard



Source: Healy T. Presentation: Challenges and best practice recommendations for implementing a PIM solution. Glemser Technologies 2010 [40].

The following description of PIM and the DES will start with a brief introduction into the European product information of centrally authorised products (PI of CAPs), then discuss how a productive PIM submission would have looked like, outline how PIM was designed to support the life cycle management processes associated with the PI negotiation processes and, finally, discuss the complexity of PIM by taking a closer look at the formatting of PI documents and customization of QRD templates.

2.2.1 Structure of product information for centrally authorised products

The PI of CAPs is highly complex and may consist of up to 2200 individual documents. The average number of documents per invented name is in the range of 650 to 1000 [15].

This high number of PI documents is due to the fact that the PI of CAPs per definition includes the required documents in all EU languages for all pharmaceutical forms of a product, for all strengths of a form and for all presentations of a strength approved for a given product.

Four document types exist and are required to be present at least once per language in the PI of CAPs:

- Summary of product characteristics (SmPC; Annex I[7])
- Annex II[7]
- Outer/Immediate labelling (Annex IIIA[7])

[7] Since the PI documents are annexed to the marketing authorisation issued by the European Commission, they are also designated by their annex number, i.e. Annex I (summary of product characteristics; SmPC), Annex IIA (information on the manufacturing authorisation holder) Annex IIB (conditions of the marketing authorisation), Annex IIIA (labelling) and Annex IIIB (package leaflet; PL).

- Package leaflet (PL; Annex IIIB[7])

Additional labelling document types with reduced information content (minimum particulars) have been defined for the labelling of blisters and small immediate packaging units. They are included in Annex IIIA, only if applicable.

The content of the SmPC, the labelling and the package leaflet are defined in Directive 2001/83/EC ([7]; Article 11, Articles 54 and 55, Article 59, respectively). Templates for these document types are prepared and maintained by the working group on the quality review of documents (QRD)[8].

Annex II with its information on the manufacturing authorisation holder (MAH) and, if applicable, conditions of the marketing authorisation is a product-specific document type. In contrast, the SmPC and PL are usually (see Chapter 2.2.2.2) specific for a defined strength of a pharmaceutical form of the product. The labelling documents are in general specific for a presentation.

As a result, the PI of CAPs will consist of one Annex II document, a variable number of SmPC and PL variants (each 1 document per strength) as well as a variable number of labelling document variants (1 or more per presentation). This is in contrast to the US product information which usually consists of a single document that includes the information for all pharmaceutical forms, strengths and presentation in a single document.

The variants of the European PI document types are very similar and contain long stretches of identical text. In the course of their life cycle they are thus predestined for an evolution leading to inconsistencies if managed in Word[9]. On the other hand, they are ideal candidates for component-based authoring with its content re-use opportunities.

2.2.2 Structure of a PIM file

Unlike the SPL XML document, the PIM XML file does not reflect the actual document structure. The structure of a PIM file is probably best understood if one considers the PIM XML file not as a document with XML markup, but as a self-contained database or component content management system (see Figure 7).

As specified in the DES, a PIM XML file consists of four different so-called zones:

- **Envelope zone:** The envelope zone contains technical and administrative information related to the PIM submission, such as the underlying DES version, the application type, the applicant, the product and the PIM sequence.

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[8] QRD templates are provided on the EMA website and not only applicable for the centralised procedure, but also for national, mutual recognition (MRP) and decentralised procedures (DCP).

[9] Inconsistencies may potentially arise during the authoring process, where it must be ensured that changes are implemented in all other variant documents where the information appears. Another source of inconsistencies could be the translation process, where it must be ensured that the English baseline documents are translated 1:1, but also that identical text in the English baseline documents is identified to make sure that the resulting translations are identical.

- **Tree zone:** The tree zone maps the components (for analogy, see the component maps in Figure 2, center). It provides only references to components (called templates or fragments in the PIM terminology), which are stored in the template zone and may be referenced multiple times from the tree zone, and thus allows content re-use.
- **Document zone:** The document zone is a PIM-specific feature and defines the document organisation (see Chapter 2.2.2.2 for the justification of this zone).
- **Template zone:** The template zone contains the actual fragments and corresponds to a component library (see Figure 2, left). It is divided into an area for neutral templates that do not require translation and 24 language-specific areas.

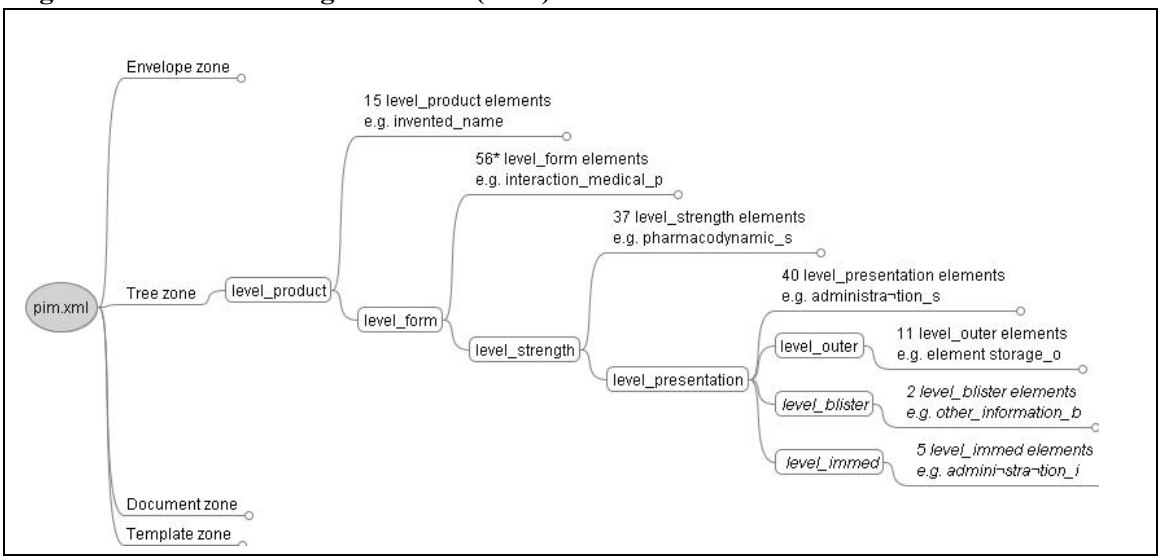
2.2.2.1 The tree zone: Flexible data model for the PI of CAPs

The tree zone mapping the components has a hierarchical structure and defines a rather large set of XML elements to which component references need to be assigned.

Version 2.7.1 of the DES defines 166 elements to which components can be assigned[10]. Of these only 46 are mandatory, the others are technically optional and to be used only if required in terms of contents. Additional specification via context attributes is required by 18 ([20], [43]).

Each element is assigned to a hierarchical level depending on its specificity for the product, the pharmaceutical form, the strength, the presentation and the outer/blister/ immediate labelling (Figure 6).

Figure 6 Data exchange standard (DES): Hierarchical data model



* Includes 44 technical elements for customizing headings in the package leaflet (see Chapter 2.2.4).
Italics: Levels that are used only if applicable.

[10] A couple of further elements with other functions exist to which no content can be assigned.

Elements do not map the sections of PI documents in a 1:1 fashion, i.e. there is not always a single element per QRD document section. SmPC section 4.2 (Posology and method of administration) for example is subdivided and may be made up of optional elements *posology_administration_s*, *posology_target_population_s*, *posology_paediatric_s*, *posology_special_population_s*, and the mandatory element *administration_s*.[11] Of these four elements only *posology_paediatric_s* and *administration_s* correspond to headings in the QRD template [45].

Another remarkable feature of the DES is that elements from different levels are used to generate a document (see Figure 7)[11]. This peculiarity can also be exemplified if one looks at the way the name of the medicinal product which appears in section 1 of the SmPC, the labelling documents and the package leaflet is generated. Instead of defining multiple document-specific elements with redundant information (e.g. the invented name), data pieces defined at appropriate hierarchical levels are combined and re-used. (Table 1, Figure 7).

The hierarchical DES data model is flexible. Individual branches of the basic structure shown in Figure 6 may be dupli-/multiplicated (with all associated sub-levels and level-specific elements) as needed to appropriately reflect the structure of a specific PI:

- For a simply structured PI (e.g. a medicinal product available in a single pharmaceutical form with only one strength and only one presentation) the simple data model shown in Figure 6 is sufficient.
- For a more complex PI (2 forms, each with 2 strengths and 2 presentations per strength) duplication is required on the form, strength and presentation levels (Figure 8).

In this so-called tree approach, unequivocal relationships between all elements, sub-levels and higher order levels are maintained by assigning unique identifiers to each component of the PI tree.

Two further features of the DES data model must be considered:

- Firstly, more than one text fragment may be assigned to a single element, and,
- secondly, many elements are allowed to be repeated within a level.[12,].

The order of multiple fragments and/or repeated elements is defined by the order in which they appear in their tree branch.

[11] For the mapping of elements to the QRD templates see DES specifications 2.7.1 [25].

[12] Repetition of elements on the same level is used to allow for some grouping of fragments (e.g. grouping of undesirable effects by system organ classes by repeating level_strength element *undesirable_s* system organ class-wise).

Figure 7 Structure of a PIM file

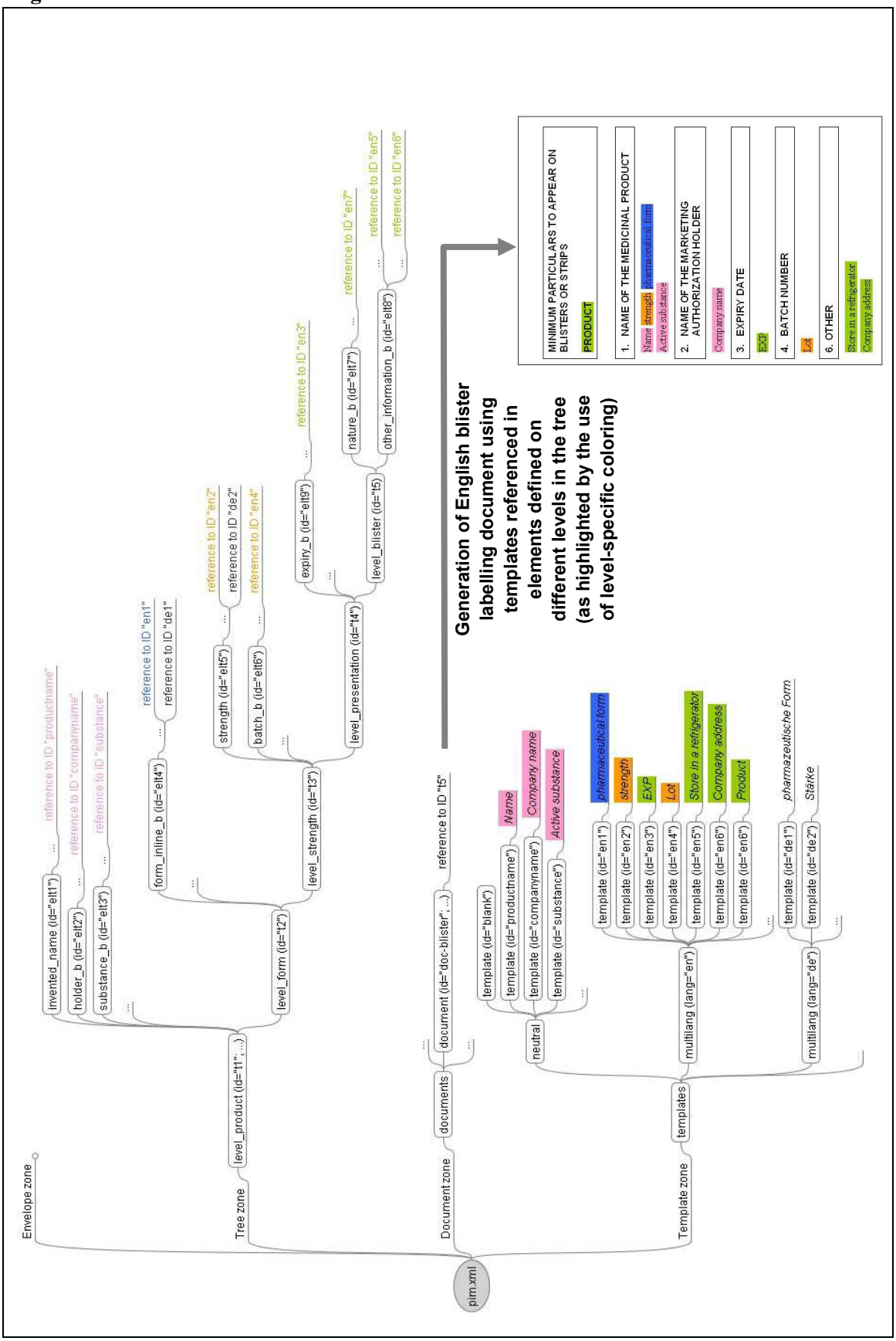
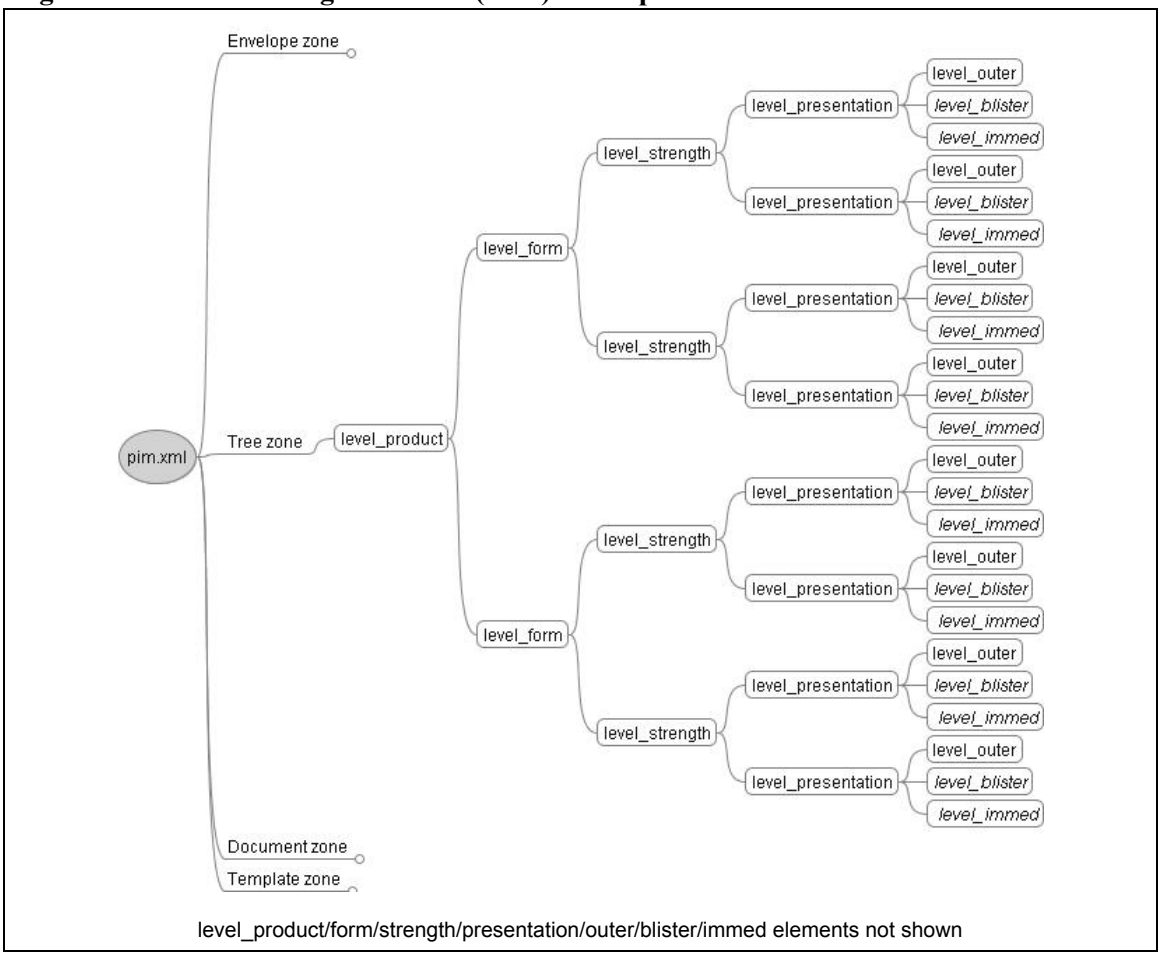


Table 1 Elements used for the generation of the name of the medicinal product in different PI documents

level_product	level_form	level_strength	level_presentation	
invented_name		strength	qual_before_inv qual_after_inv qual_strength	
	form_inline_s form_inline_p form_inline_o form_inline_i form_inline_b		qual_form_s qual_form_p qual_form_o qual_form_i qual_form_b	
qual_before_inv invented_name qual_after_inv strength qual_strength form_inline_s qual_form_s				SmPC
qual_before_inv invented_name qual_after_inv strength qual_strength form_inline_p qual_form_p				P.L.
qual_before_inv invented_name qual_after_inv strength qual_strength form_inline_o qual_form_o				OUT
qual_before_inv invented_name qual_after_inv strength qual_strength form_inline_i qual_form_i				IMM
qual_before_inv invented_name qual_after_inv strength qual_strength form_inline_b qual_form_b				BLI

Figure 8 Data exchange standard (DES): Multiplication of branches



2.2.2.2 The document zone: Flexible PI document generation

Defined style sheets are used to generate PI documents using the plain data transmitted via an XML file. The capacity of rendering PI data in document format is important because it is the legally required format (also see Footnote 7, Page 16).

As shown in Table 2, PI documents are typically associated with default hierarchical levels of information (also see Chapter 2.2.1).

Table 2 Levels where PI documents can be generated

	Product	Form	Strength	Presentation	Labelling
SmPC			**Default**		
Annex II	**Default**				
Outer			Allowed	**Default**	Allowed
Blister			Allowed	Allowed	**Default**
Immediate			Allowed	Allowed	**Default**
Leaflet		Allowed	**Default**		

Source: DES specifications 2.7.1 [20], Table 3-13

However, due to the diversity of CAPs, PIM has to allow for some flexibility to accommodate special situations (marked "Allowed" in Table 2) in which a combination of levels in so-called combined documents[13] is meaningful.

The definition of documents includes a document-specific unique identifier, specifies the document type, various document attributes and provides reference(s) to the level_id(s) of the branch(es) to be used to generate the content of the output document.

2.2.3 Life cycle management of the PI of CAPs with PIM

The scope of PIM, however, goes beyond the simple unidirectional provision of PI in a standard XML exchange format instead of the current document-based format, where it is the role of the applicant to submit both proposed and approved versions of the PI to the agency.

PIM is bidirectional and is intended to support the whole process of developing an approved version of the PI that is agreed by both CHMP/European Commission and applicant:

- A regulatory activity/application is started by the applicant who provides the initial PIM file,
- subsequently regulator and applicant versions are sent back and forth, and

[13] When generating the output of a combined document, the style sheet performs a comparison of equivalent fragments (i.e. fragments with same element tag but assigned to different branches in the combination). In case the fragments differ, both will sequentially appear in the PI document, whereas common fragments display only once. Balancing of fragments with regard to number and sequence on the different branches is required, if several fragments are assigned to an element (for details on balancing fragments see DES specifications 2.7.1 [24]).

- the final approved version, which will be used as baseline for further regulatory activities, is received from the agency.

In this complex and frequent interaction (Table 3), communication is based on comments that may be introduced by both regulators and applicants on the fragment, document section, document, or product level.

If for example a regulator suggests a change in a particular fragment, he will not edit the fragment itself (only the applicant is allowed to modify fragments), but introduce a comment with information on the original text and the proposed revised text, and, optionally, a reason for the change. The applicant can either respond with a counterproposal, i.e. a new comment with reference to the ID of the original comment and the PIM sequence in which the original comment was introduced, or accept the comment by providing a revised fragment (for details on commenting see DES specifications 2.7.1 [26]).

Traceability of changes between PIM sequences is achieved by assigning change control attributes (new, delete, replace, unchanged, merged) to the fragments. Provided fragment IDs are maintained across the PIM sequences (concept of permanent IDs [27]) track-change views can be generated (for details on life cycle management see DES specifications 2.7.1 [28]).

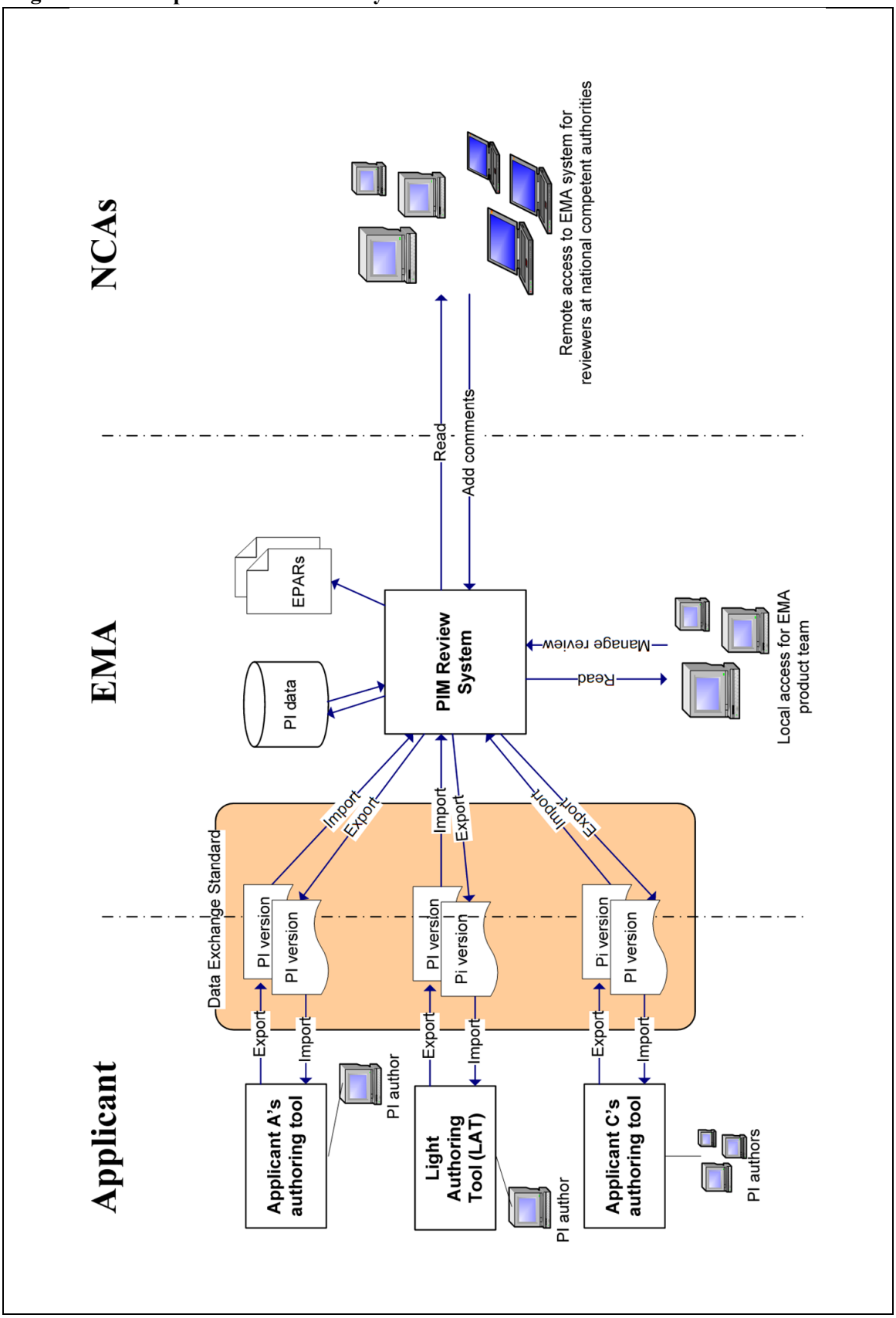
Following authorisation of the product parallel regulatory activities may be pursued which might eventually require merging of independent PIM sequences based on the same baseline PI but evolved in different aspects depending on the individual regulatory activities (for details on merging see DES specifications 2.7.1 [29]).

Figure 9 summarizes the complexity of the PIM process from an overall system design view. It shows that the system is made up of different software applications:

- Light Authoring Tool (LAT; also see Chapter 3.2)
- PIM Review System (PRS)
- PIM Data Validation Engine (PDVE; not shown in Figure 9, but used at step “Import into PRS”)

Figure 9 also illustrates that the PIM system not only involves EMA but in the linguistic review stage of the process virtually all national competent authorities (NCAs), too.

Figure 9 Components of the PIM system



Source: PIM guidance for applicants [17], Figure 1

Table 3 Key exchange steps for an initial MAA

Day	PIM sequence†	Direction of Exchange	Langua-ges	Procedure step
1	0000-a	Applicant → EMA	EN only	Start of the procedure
80	0001-r*	EMA → Applicant	EN only	AR (Rapporteur)
	0002-r*	EMA → Applicant	EN only	AR (Co-Rapporteur)
120	0003-r	EMA → Applicant	EN only	LoQ (CHMP and PIQ comments)
Clock-stop				
121	0004-a	Applicant → EMA	EN only	Response to LoQ
150	0005-r[1;]*	EMA → Applicant	EN only	JAR (CHMP comments)
157	0006-r[1;]*	EMA → Applicant	EN only	QRD comments
165	0007-r[2;]*	EMA → Applicant	EN only	EMA QRD subgroup comments
180	0008-r	EMA → applicant	EN only	LoOI (CHMP and QRD comments)
Clock-stop				
181	0009-a	Applicant → EMA	EN only	Response to LoOI
7 days before opinion	0010-r	EMA → Applicant	EN only	Pre-opinion with Annex II
By 210	0011-a	Applicant → EMA	EN only	CHMP opinion (final EN)
215	0012-a	Applicant → EMA	ALL	Translations (incl. agreed EN)
229	0013-r – 0035-r[3]	NCAs → Applicant	ALL	CC linguistic comments
235	0037-a[4]	Applicant → EMA	ALL	Response to linguistic comments
237	*n/a*	*EMA → EC*	*ALL*	*Annexes[5] to Commission*
277	0038-r	EMA → Applicant	ALL	Commission Decision (baseline)

Source: Modified from PIM guidance for applicants [17], Table 3

Abbreviations: AR = Assessment report; CC = Country code; CHMP = Committee for Medicinal Products for Human Use; EC = European Commission; EN = English; JAR = Joint assessment report; LoOI = List of outstanding issues; LoQ = List of questions; n/a = not applicable; PIQ = Product information quality review group; PTL = Product Team Leader; QRD = Working group on the quality review of documents

† Suffix "-a" = applicant version; suffix "-r" = regulator version

* For information only.

1 May be a single combined regulator PIM sequence if QRD comments are available by Day 150.

2 If there is a Day 165 QRD subgroup meeting or discussion with the QRD Secretariat by phone or email, agreed changes to the QRD comments are sent to the applicant in a new PIM version.

3 Applicant receives up to 23 separate PIM versions (one per language).

4 Exceptionally and in agreement with PTL, if Day 229 comments from some NCAs were late, multiple submissions can be made, each covering a subset of languages.

5 PDF files containing the PI for each language, generated by the PIM Review System, based on the final applicant submission.

2.2.4 Layout of PI documents and customization of QRD templates

Text fragments are formatted using formatting conventions defined in W3C standard XHTML (also see Chapter 1).[14] Layout control of PI documents is, however, not only restricted to fragments: Whether a fragment is followed by an empty line or not is specified within the tree zone (as an attribute of the purely technical DES element *pi-group*) [23].

Customization of PI documents is in parts an automated process. Depending on the presence of certain optional DES elements the style sheet will insert the appropriate subheadings accordingly. Section 4.2 of the SmPC (Posology and method of administration) for example displays without sub-headings, if all fragments are assigned to element *posology_administration_s*. If, however, fragments have been assigned to elements *posology_target_population_s*, *posology_paediatric_s*, and/or *posology_special_population_s*, a heading "Posology" will be inserted above the concerned fragments in the SmPC output document [22].

Similarly, some standard statements that appear in PI documents are dependent on values assigned to level attributes (e.g. the standard statement regarding biosimilars in SmPC section 5.1 depends on the value of level_product attribute *biosimilar*) [22].

In other instances, one has to actively assign values to document attributes in the document definition. An example is the standard statement "For instruction on reconstitution of the medicinal product before administration, see section 6.6." at the end of SmPC section 4.2, which will only appear, if the SmPC-specific document attribute *spc_sts_42* has been set to "reconstituted" [22].

In other cases, standard statements/headings are modified depending on the value assigned to attributes of special DES elements (see Footnote 10, Page 18), e.g. the *case* attribute of level_presentation element *legal_status* or the *verb* attribute of level_form element *mode_administration* [21].

Finally, for the package leaflet, the technical form_level elements mentioned in the footnote of Figure 6 (Page 18) are used to modify standard headings and to solve particular inflection in some languages [21].

[14] Not all XHTML features are supported or recommended in the context of PIM.

3 IMPACT OF HEALTH AUTHORITY INITIATIVES

3.1 Structured Product Labeling (SPL) in the US

Since Structured Product Labeling (SPL) is by now legally required for product information submitted to both the Center for Drug Evaluation and Research (CDER) [34] and the Center for Biologics Evaluation and Research (CBER) [33], most pharmaceutical companies seeking authorisation to market their product(s) in the US will need to submit structured product information.

SPL compliance can be achieved using a component-based authoring tool that must be able to generate Word files since the process of negotiating the product information with the FDA is still Word-based.

SPL compliance, however, does not necessarily require that US product information is managed by means of a component-based authoring tool. The preparation of required SPL documents[15] could as well rely on special web forms (XForms) developed by GlobalSubmit in collaboration with the FDA and made available free of charge ([36], [55]; see Appendix 1 for a screenshot). Companies opting for XForms could therefore stick to the familiar Word-based approach for the management of product information. The conversion of the Word file into an SPL file would only be an additional last step in the finalization process.

Preparation of SPL documents using XForms would require manual copy-pasting of the agreed wording of the product information from the Word source and most likely some re-formatting to an extent depending on the appropriateness of the formatting in the Word source. The main disadvantage of this manual, non-component-based authoring approach for the generation of SPL file is that the process is likely to be tedious and error-prone.

3.2 Product Information Management (PIM) in Europe

PIM, with its scope restricted to CAPs, would have concerned a much smaller number of pharmaceutical companies: In October 2009[16], the EMA website provided information on 643 CAPs involving a total of only 193[17] companies. If one considers that the European Federation of Pharmaceutical Industries and Associations (EFPIA)

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[15] FDA requires SPL for the proposed product information submitted with the initial application and the final agreed version.

[16] The cut-off date for the following analyses is 09 Oct 2010, when information available in HTML format on the EMA website (Find medicine > Human medicines > European Public Assessment Reports) was downloaded and further processed for incorporation into an MS Access database. An extract of the relevant data is provided in Appendix 3.

[17] The figure is not 100% accurate: The actual number is lower since some companies are counted twice or even more times due to non-standardized entries for company names and consequential parallel use of synonymous company names (e.g. “Schering-Plough Europe” and “SP Europe”). On the other hand the figure might be an underestimate since no information is published on EMA’s EPAR webpage on products of companies which were involved in a centralised procedure but withdrew their application.

alone represents approximately 2200 pharmaceutical companies [32], this is only a small proportion.

A further group of concerned companies would have been involved with PIM in conjunction with referral procedures [10].

Due to the complexity of PIM and, more importantly, the intended comment-based bidirectional communication between EMA and applicants/marketing authorisation holders, there is no way to bypass PIM as it can be done with manually prepared XForms-based SPL submissions. In consequence, all concerned companies would have had to implement an authoring tool capable to generate valid (i.e. PDVE-compliant) PIM files and with functions for authoring product information, responding to regulator comments, entering or importing translations as well as exchanging versions with EMA [18].

In its PIM guidance for applicants [18] EMA proposed to achieve implementation either by:

- the use of the free Light Authoring Tool (LAT),
- the purchase of a commercial PIM authoring tool (off-the-shelf/customized labelling systems)[18],
- the use of hosted PIM solutions,
- the use of tools developed in-house, or
- outsourcing (i.e. by subcontracting the whole PIM process to a service provider).

The statement of intent of 2009 [9] in combination with EMA's initiatives for the engagement of vendors such as the PIM vendor forum or the opportunity to perform PIM test simulations certainly resulted in increased activities from the vendor side. If one, however, looks at

- the limited market with only approximately 200 pharmaceutical companies as potential clients, and
- the challenges associated with bidirectional communication, processing of complex life cycle management activities, support of commenting features (see Chapter 2.2.3) as well as the complexity of customization and layout management (see Chapter 2.2.4)

it seems questionable whether PIM software tools that are able to generate valid PIM files would actually have been available at the time of full implementation of PIM with reasonable diversity to allow sound vendor selection processes.

In this context it is noteworthy that the already small market with regard to potential clients would have been at risk to be cannibalized by the LAT available free of charge which might have been an attractive tool for the more than two thirds of the companies involved in the centralised procedure with only a single or two products (Figure 10).

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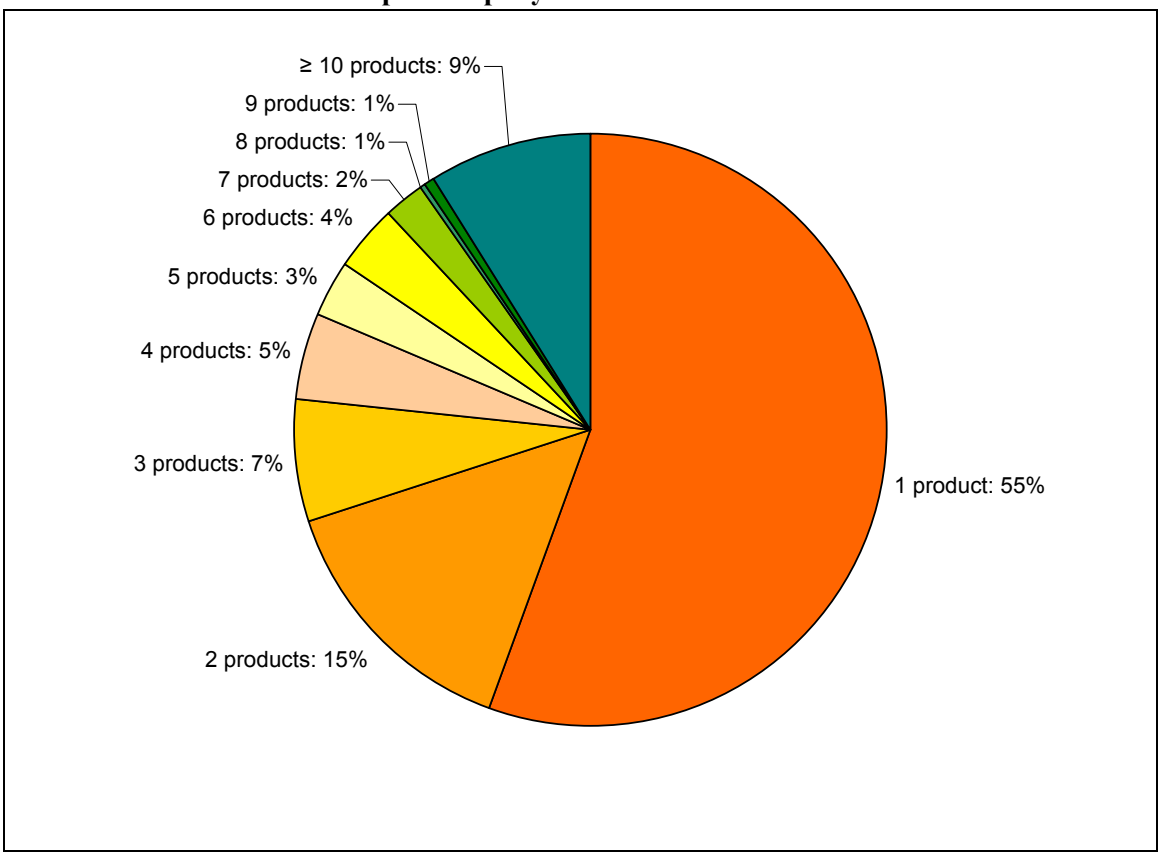
[18] Availability of at least 2 commercial tools that have been used successfully throughout a procedure was an exit criterion for the PIM pilot phase [30].

In the PIM pilot phase, the LAT had been tested and shown to fully support the PIM process (see Appendix 2 for a screenshot). However, it did have major limitations: It was a single user system, which possibly would have led to bottlenecks during the linguistic review phase (see Table 3), and it was not able to generate Word documents to support e.g. internal review processes (also see introduction to Chapter 4.4) [41]. Performance issues were reported as well, but it is likely that these would have been resolved in the future.

Figure 10 Statistics on companies involved in the centralised procedure according to the number of CAPs per company



Source: Appendix 3

4 THE PHARMACEUTICAL INDUSTRY PERSPECTIVE

The industry perspective on structured product information is of course strongly influenced by existing and future requirements of health authorities with regard to the exchange of structured product information via XML (SPL, and e.g. EMA's not yet defined PIM follow-up project respectively).

In view of these requirements, pharmaceutical companies will in any case have to develop appropriate strategies in order to be up to the mark. In the overall strategic decision process it is, however, important to also consider the potential of component-based authoring of product information from a perspective that is independent of regulatory requirements.

As discussed in Chapter 2.2.1, European product information is highly redundant as a consequence of the key documents – SmPC and PL – being defined on the strength level and not on the product level like it is practiced in other regions. This is particularly true for the PI of CAPs but also applies to the PI of nationally approved products (NAPs), which is also based on the QRD templates and in principle follows the same rules with regard to the structure.[19]

Industry should be aware that the generation of European product information of CAPs as well as NAPs can be streamlined and optimized by component-based authoring and re-use of identical content in different documents (see Chapter 4.1): The output of a component-based authoring process does not necessarily need to be an XML file that is exchanged with a health authority but can as well be a "conventional" Word and/or PDF file (see Figure 3).

Therefore, from the industry perspective, EMA's decree to halt the PIM project should not have a major influence on the decisions of pharmaceutical companies with regard to authoring tools, i.e. the transition from the document-based management of product information to a component-based one. On the contrary, the fact that systems will not have to comply with the complexities of PIM may even have a positive impact on the vendor market and costs since more basic functions will suffice to achieve consistent and high quality product information in Word or PDF format.

Industry, especially large pharmaceutical companies, may also think about a wider scope and may want to implement not only a simple "authoring tool" for component-based authoring and support of company-internal processes directly associated with the preparation of product information, but a comprehensive labelling system that also supports processes related to product information (e.g. artwork production or web publishing; see Chapter 4.3).

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[19] Some health authorities may be less restrictive with combination documents in which two or more strengths are combined in a single document (also see Chapter 2.2.2.2).

4.1 Potential benefits associated with the transition from Word-based to component-based authoring

4.1.1 Content re-use

As discussed in Chapter 2.2.1 and the introduction of Chapter 4, European product information is highly redundant and thus predestined for component re-use. For other formats of product information, e.g. the US prescribing information, which are defined on the product level, component re-use will, however, play only a minor role.

Another two, more comprehensive opportunities for component re-use are thinkable:

- Content re-use across regions, i.e. the use of harmonized components in different product information documents in the same language for the same product (e.g. English components in product information of English speaking countries such as the US, Canada, Australia and the UK) may be an option especially since the pharmaceutical industry is a global one.
- Content re-use across products, i.e. the use of harmonized components in different product information documents in the same language for different products may be interesting for companies that hold marketing authorisations for similar products (e.g. products of the same class with similar labelling), for information which is not product-specific (e.g. information on the manufacturer) or in the case of product clones (doublets).

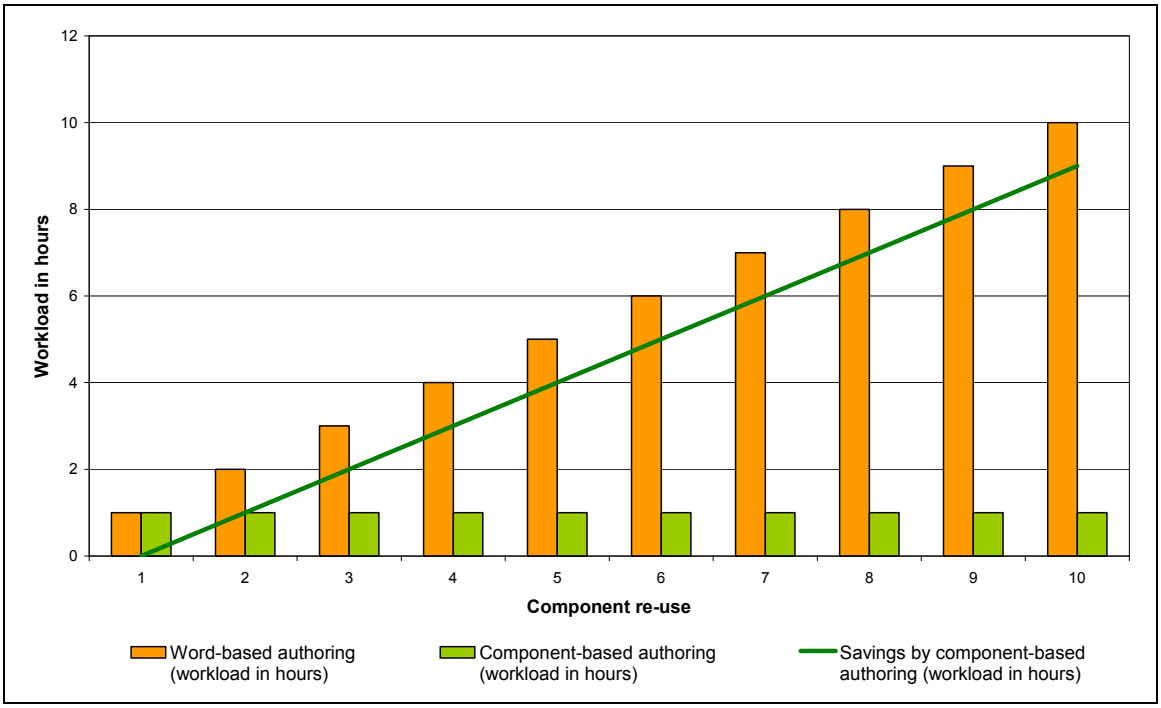
Both options, however, most likely are not practicable. Harmonization across regions will be difficult to implement due to regional differences in product information style with regard to wording and detail of information. Moreover, in both scenarios the life cycle of the product information and the associated components may not necessarily be synchronous which will add complexity to the processes an authoring system is required to manage and may negatively influence the cost benefit ratio. For these cases it would probably be simpler to work with a component “clone”, i.e. a copy of the component itself as well as all its available translations, which would then be subject to individual life-cycling.

Critical factors for the evaluation of potential content re-use benefits associated with the use of authoring tools supporting component-based authoring are therefore as follows:

- the number of European products (i.e. marketing authorisations) managed by a pharmaceutical company,
- the activity of the products, i.e. the frequency of required changes to the product information, and
- the complexity of the products in terms of pharmaceutical forms, strengths and presentations.

The workload savings potential in dependence of the complexity of the product information is shown in Figure 11. This analysis is based on a scenario in which a single component/Word document paragraph needs to be changed in connection with a variation and which arbitrarily assumes that the change takes 1 hour in both the

Figure 11 Workload savings potential in dependence of the complexity of the product information



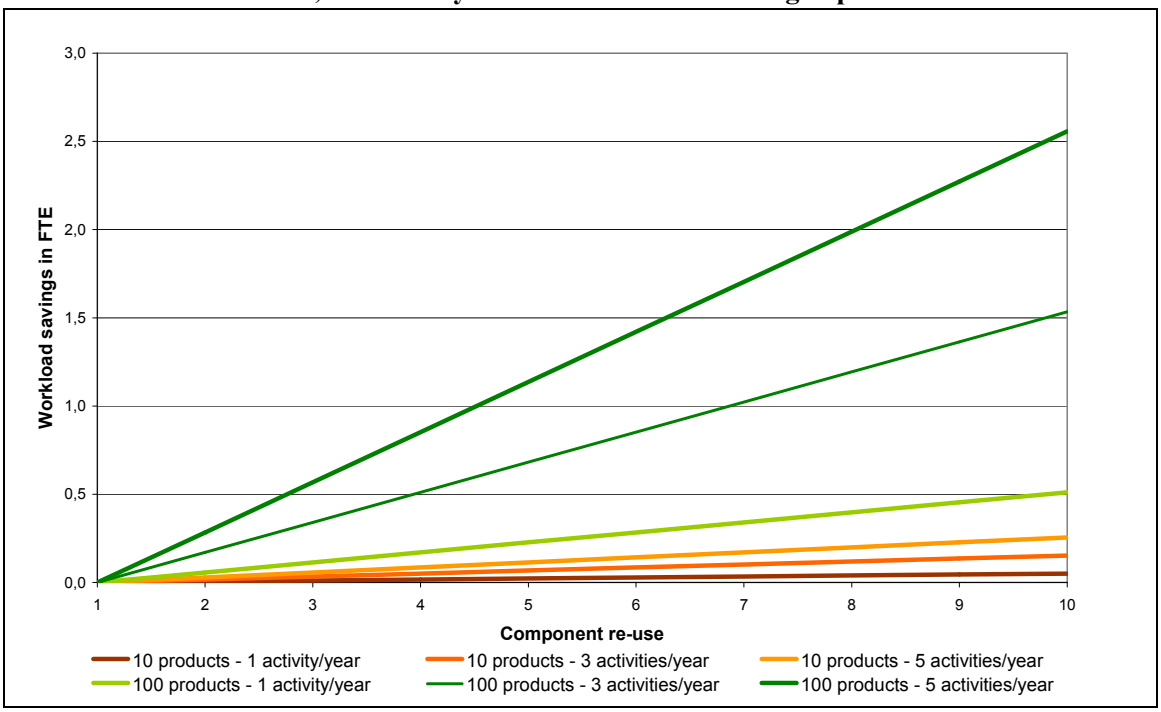
The values shown are based on the arbitrary assumption that implementation of the change of interest takes 1 hour. For an accurate estimate of the potential savings of workload associated with content re-use one would need to determine an average duration based on experience with variations of varying complexity.

component and the Word document. If the product information is simple and the component is not re-used, the component-based approach and the conventional Word approach will be equivalent. If, however, the component is re-used, the component-based authoring system will show a benefit, as no more editing is necessary. Conventional Word authoring, in contrast, will require additional edits of 1 hour duration to make sure all concerned documents are changed. The effect increases with the frequency in which a component is re-used.

Figure 12 analyzes the potential workload savings in full time equivalents (FTEs; 1 FTE defined here as 220 working days of 8 hours) for companies with different numbers of European marketing authorisations depending on varying average product activities and product complexities. Figure 12 demonstrates that the return of investment associated with the implementation of a component-based authoring system is faster for pharmaceutical companies with a high throughput, i.e. a large portfolio of highly active complex products.

In this context one has to keep in mind that migration of legacy product information in Word format into the structured format is a prerequisite for a full exploitation of the potential workload savings associated with content re-use. Migration, however, is time consuming and may not always be straightforward, since elimination of accumulated inconsistencies might require additional variations.

Figure 12 Workload savings potential in dependence of the complexity of the product information, the activity and the number of managed products



1 FTE defined here as 220 working days of 8 hours

4.1.2 Preparation of product information documents

Component-based authoring by separating content, structure and layout management also offers potential to streamline and optimize the processes associated with the generation of product information through automated generation of formally valid product information documents based on appropriate style sheets.

Automated generation of output documents will reduce the workload for formal quality control activities (see the checklist applying to the PI of CAPs [13]) and thus allow authors to focus on the actual contents. Quality control of how the content is displayed in the final output is still necessary, to identify errors in the XML markup.

The potential for workload savings in this regard will depend on the number of products/marketing authorisations managed by a company and the activity of the products.

4.2 Basic functional requirements for authoring tools

Table 4 summarizes the basic requirements with regard to functions that need to be available in an authoring tool to support the company-internal processes directly associated with the preparation of product information, such as review and approval workflows but also translation management.

The availability of adequate collaboration functions will certainly be most crucial in the evaluation of different authoring tools: Product information documents are key

documents for pharmaceutical companies and accordingly require complex review and approval processes involving virtually all functional departments of a pharmaceutical company. In this context one must also consider that change management efforts would be considerable if reviewers were exposed to plain XML formatting markup rather than a Word-like look and feel (also see Chapter 1.1).

Functions supporting the efficient management of translations seem to be critical as well, especially in view of the tight time frames that apply to the centralised procedure (Table 3, page 25).

Table 4 Basic functions required for authoring tools

Content format	Agency-neutral format to ensure independence from life cycles of health authority standards, to maximize re-use across submission standards and to ensure scalability for new structured product information projects of other health authorities.
Flexible output formats	Transformation of content prior use as needed according to country-specific submission standards (SPL, Word, PDF).
Management of components and documents	Fully automated management of versions and version status (Draft/Final; Proposed/Approved/Outdated) of components and documents.
	Integrity of versions of components and documents secured via locking mechanisms.
	Possibility to clone components including all associated translations to support independent life cycles of components (see Chapter 4.1.1).
	Easy storage and retrieval of documents via automated file management.
	Support of complex versioning operations, such as parallel editing (branch versioning) and merging required in the context of parallel post-approval regulatory procedures.
Security	Control of access to content and of available functions (e.g. viewing, editing, publishing, archiving) based on content types, user roles, life cycle status, countries and products.
Revision tracking	Automated document comparison features to identify differences between versions.
Collaboration	Review and approval processes supported by adequate output format which permits tracking of changes and commenting.
	Customized automated workflows.
Translation management	Management of translations (e.g. workflows, automated status reporting).
	Streamlining of translation process (e.g. re-use of available translations, selective translation of changed components).

4.3 Extended scope: Comprehensive labelling systems

As mentioned in the introduction to Chapter 4, industry may also think about a wider scope and may want to implement not only an authoring tool but a comprehensive labelling system that in addition supports company-internal processes related to product information.

4.3.1 Support of legal compliance

In the area "support of legal compliance", one interesting option would be to manage additional documents closely related to product information such as promotional material or mandatory information texts on promotional materials. The labelling system could ensure that only current documents or texts in line with approved product information are used. Such a scope extension would, however, be associated with the inclusion of new sets of users from for example the marketing department which would normally not be addressees of an authoring tool.

Similarly, it could be meaningful to use a labelling system for the maintenance of the company core data sheet (CCDS; includes the company core safety information [CCSI]).[20] As the CCDS/CCSI is the basis of global product information variants (e.g. the European PI or the US prescribing information) the content of the CCDS should cover global labelling requirements and reflect a company's position on topics such as indications/usage, contraindications, warnings/precautions, interactions (with other medicinal products or other forms of interaction), undesirable effects, posology/method of administration, use in specific populations (e.g. use during pregnancy/nursing, paediatric use, geriatric use, use in different ethnic groups, use in patients with underlying diseases), drug abuse/dependence, overdosage, clinical pharmacology (mechanism of action, pharmacodynamic/-kinetic properties) and nonclinical toxicology (genotoxicity, carcinogenicity, reproductive toxicology).

Each time a new product information variant needs to be developed, the CCDS components with statements on the above mentioned topics could be cloned (see Chapter 4.1.1) and used as baseline which is then further adapted to the specific local requirements in terms of wording and style.

Provided the labelling system is designed in a way that permits to track the relationship between CCDS statements and corresponding components in the product information, one could easily identify which product information needs to be changed if an adaptation of the original CCDS is required due to new data generated post-authorisation (e.g. identification of new adverse reactions or changes in the frequency of known adverse reactions following re-evaluation of available data within a periodic

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[20] The concept of the CCDS/CCSI (for definition see [38]) was originally developed in 1995 by the Council for International Organizations of Medical Sciences (CIOMS) [4] and revised in 1999 [5]. The purpose of the CCDS/CCSI is:

- to define minimum drug safety information that should be communicated by manufacturers to physicians and other prescribers, i.e. the information most needed to help prescribers balance a product's risks against its benefits, and thus make good therapeutic decisions, and
- to form the basis for the preparation of all official national data sheets, package inserts, product labels, and other official statements issued by the manufacturer of the drug and thus to ensure harmonization of product information.

The guidelines published by the involved CIOMS working groups (CIOMS working group III: Marketed products; CIOMS working group V: Products in development) furthermore contribute to the standardization of drug safety information across products by defining criteria for the decision on the information that should be included, standard terms and definitions, and a standard format for the placing of information in different sections of the manufacturer's data sheets [57].

safety update report [PSUR]). Initiation of the regulatory activities required to adapt the product information could then be triggered by the system.

Such a "push approach", which relies on tracked relationships of text components in different documents, could also be valuable to trigger updates of the above mentioned promotional texts, once the underlying revised product information has reached the status "approved".

Tracking of relationships between components in a labelling system could also help to improve consistency of product information across regions in order to mitigate business risks associated with legal prosecution due to divergences in product information statements in different countries/regions.

4.3.2 Support of GMP compliance

Comprehensive labelling systems could also provide functions for the management of artwork, i.e. the printing templates of the labelling. Labelling texts available as components of the product information could for example be exported in XML format and thus directly feed the layout/publishing software for the preparation of artwork without a detour via a Word file that is handed over to artwork producers. This XML-based transmission of labelling texts is likely to minimize the extensive workload for quality checks on printing templates[21], since in contrast to a Word file the XML file used as basis is stringently formatted and includes a reference to a defined character encoding system.

In this context, labelling systems could also contribute to GMP compliance by restricting this function to versions of the labelling that are current and approved. Further support of GMP could result from the use of defined, audit-trailed release workflows for artwork within the system. The need to circulate hardcopies of artwork within a company, a time-consuming process, would then become obsolete.

4.3.3 Translation support

A third area in which labelling systems could improve the general performance of company-internal processes related to product information concerns the translation process. Sophisticated translation management tools may be integrated and, provided they permit to build up translation memories, speed up and streamline translation preparation by re-using previous translations: Based on fuzzy-logic technologies translation memories will propose possible translations even in cases where there is no 100% match to an already translated original text.

4.3.4 Support of associated processes

Last but not least, one could conceive that companies may take advantage of the possibility to publish structured content in different formats. An example would be automated HTML publishing of approved current versions of product information on company web sites e.g. for marketing purposes or for support of sales forces.

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[21] Specific text verification tools have been developed for this purpose.

4.4 Implementation options: General cost-benefit considerations and basic criteria for decision analysis

Currently, two basically different approaches with regard to the implementation of structured product information seem possible.

In the first approach, companies would mainly react to health authority initiatives and would rely on free tools made available by health authorities (XForms, LAT follow-up tool?) to generate the required XML files. Currently, and this is not likely to change in the future, these tools only provide those basic functions that are needed to create the valid XML files health authorities require to support their own processes. Company-internal processes associated with the authoring of product information (e.g. reviewing or approval processes) are not supported by such tools. As a consequence, companies would most probably need to stick to the conventional Word-based mode for the management of associated company-internal processes. This would require work-around procedures and/or additional process steps (see Chapter 3).

A variant of this approach, where companies stick to the existing Word-based mode of managing product information, would be the outsourcing of the "technical" part. In this case a service provider would be responsible for the conversion of the product information into the format requested by the health authorities.

The alternative strategy would consist of the implementation of more sophisticated authoring or labelling systems (off-the-shelf/customized/own developments; in-house/hosted), that are able to generate both the requested XML files by means of a component-based authoring approach and at the same time support company-internal processes.

The decision on which road to go has to be carefully evaluated in order to achieve the optimum balance between costs and benefits. This requires a thorough review of the overall business process including an analysis of the potential benefits of component-based authoring (e.g. content re-use) and the identification of optimization opportunities either directly associated with the preparation of product information or in related processes (see Chapter 4.3).

Table 5 and Table 6 define a basic set of general decision criteria which can be used to evaluate the different options with regard to performance/benefits and costs, respectively. The tables compare different implementation scenarios:

- **Word + XForms (Implementation scenario C):** This Word-based implementation scenario relies on XForms to generate SPL submissions. In this scenario described in Chapter 3.1, product information would be managed in Word within the company. The generation of SPL files would be an additional last step, in which the final version of the product information is converted into the SPL format via the XForms. Since XForms are intuitively and easy to use, i.e. comparable to PDF forms, no major IT support is required for implementation and maintenance of this scenario.

- **Hosted authoring tool (SaaS) (Implementation scenario D):** In this scenario, i.e. the use of a hosted component-based authoring system (SaaS = Software as a service), only the basic functions necessary for preparation, management and review/approval of product information (see Chapter 4.2) are implemented.
- **In-house authoring tool (Implementation scenario E):** This scenario is equivalent to implementation scenario D, except that it is not hosted but a tool that is installed in-house.
- **In-house labelling system (Implementation scenario F):** This implementation design is the most sophisticated in terms of functional deployment and implements all opportunities described in Chapter 4.3.

The development of an own authoring tool or labelling system is not included in this analysis, since it does not appear to be a realistic and competitive alternative. For interest, however, two further Word-based implementation options are included which would have been relevant only, if PIM had gone productive:

- **Word + XForms + PIM CRO (Implementation scenario A):** This scenario is identical to implementation scenario C, except for the PIM part. In this design the generation of PIM files is outsourced to a service provider (CRO), which receives product information in Word format for conversion. In the course of the interactions with EMA (see Chapter 2.2.3) the CRO is responsible for extracting comments received from EMA in a format suited for further processing by the CRO's client (e.g. a list of comments or comments incorporated in a Word file). The ordering customer will thus not have to deal with PIM directly.
- **Word + XForms + PIM LAT (Implementation scenario B):** This scenario is again identical to implementation scenario C, except for the PIM part, which in this design is managed by means of the Light Authoring Tool (LAT). This approach requires workarounds (e.g. export of product information for review and approval workflows in Word) and imposes additional tasks (e.g. extraction of comments received from EMA for further processing within the company). Moreover, since the LAT is more complex than the XForms, substantial IT support is assumed to be required for the implementation and maintenance of this scenario.

The evaluation of the performance criteria in Table 5 is based on scores ranging from:

-2 (strong negative impact)
-1 (negative impact)
0 (neutral)
1 (positive impact)
2 (strong positive impact).

The evaluation of the cost criteria in Table 6 is based on scores ranging from:

0 (neutral)
1 (medium costs)
2 (high costs).

Brief justifications for the scoring are provided in both tables below the scores.

Table 5 Evaluation of alternative implementation designs: Performance criteria

Decision criteria	Word-based			Component-based		
	Word + XForms + PIM CRO	**Word +XForms + PIM LAT**	**Word + XForms**	**Hosted authoring tool (SaaS)**	**In-house authoring tool**	**In-house labelling system**
	A	**B**	**C**	**D**	**E**	**F**
Efficiency of authoring	**-1**	**-2**	**-1**	**2**	**2**	**2**
	A+B+C: Authors responsible for administrative tasks (file management/ versioning), document rendering, workflow management; **A:** Additional tasks assumed to be minor; **B:** Additional tasks major (e.g. extraction of comments for in-house distribution); **C:** Additional tasks minor; **D+E+F:** Authors can focus on content, i.e. administrative tasks/rendering workflows supported by system, convenience functions (merging, document comparison) available					
Scalability for new sPI projects of other HAs	**0**	**0**	**0**	**2**	**2**	**2**
	A: Scope in this analysis defined as support of PIM only, new contract/ CRO would be required; **B+C:** New HA tool/process required; **D+E+F:** Agency-neutral format, implementation by vendor					
Content re-use for non-CP EU products (national, MRP, DCP;)	**0**	**0**	**0**	**2**	**2**	**2**
	A: Scope in this analysis defined as support of PIM only; **B:** System designed for PIM only (no Word output); **C:** No content re-use; **D+E+F:** Systems designed for content re-use for all EU products					
Translation support (e.g. translation memories; see Chapter 4.3.3)	**0**	**0**	**0**	**0**	**0**	**2**
	A: Not applicable (provision of translations assumed as part of service agreement); **B+C:** No integration of translation management systems possible; **D+E:** Translation support not part of basic implementation **F:** Integration of translation management systems possible					
Support of associated processes (e.g. web publishing; see Chapter 4.3.4)	**0**	**0**	**0**	**0**	**0**	**2**
	A: Scope in this analysis defined as support of PIM only; **B+C:** No support of associated processes possible; **D+E:** Support of associated processes not part of basic implementation; **F:** Support of associated processes possible					
Support of GMP compliance (see Chapter 4.3.2)	**0**	**0**	**0**	**1**	**1**	**2**
	A: Scope in this analysis defined as support of PIM only; **B+C:** No support of GMP compliance possible; **D+E:** Support of GMP compliance not part of basic implementation; **F:** Support of GMP compliance (e.g. artwork management) possible					
Support of legal compliance (see Chapter 4.3.1)	**0**	**0**	**0**	**0**	**0**	**2**
	A: Scope in this analysis defined as support of PIM only; **B+C:** No support of legal compliance possible; **D+E:** Support of legal compliance not part of basic implementation; **F:** Support of legal compliance (e.g. tracking of component relationships, notification of CCDS changes) possible					
Sum of scores	**-1**	**-2**	**-1**	**7**	**7**	**14**

sPI = structured product information; HA = health authority

Table 6 Evaluation of alternative implementation designs: Cost criteria

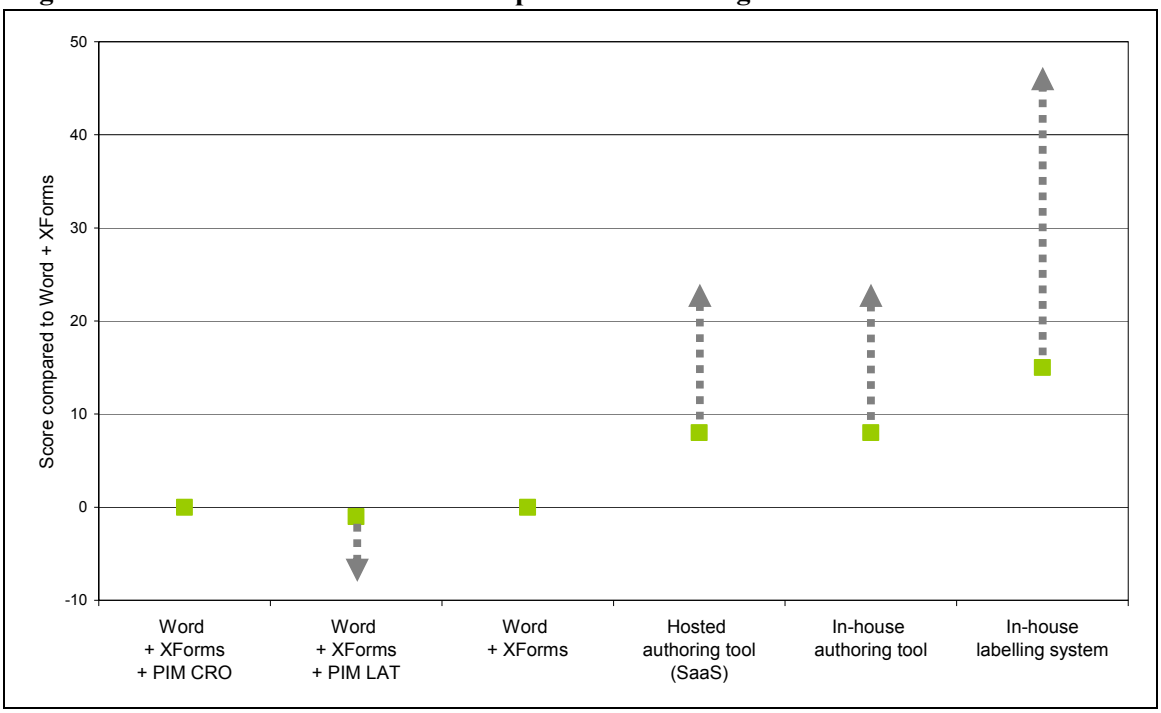
Decision criteria	Word-based			Component-based		
	Word + XForms + PIM CRO	**Word +XForms + PIM LAT**	**Word + XForms**	**Hosted authoring tool (SaaS)**	**In-house authoring tool**	**In-house labelling system**
	A	**B**	**C**	**D**	**E**	**F**
Direct implementation costs (software, additional hardware etc.)	**0**	**0**	**0**	**0**	**1**	**2**
	A: No costs; **B+C:** XForms/LAT free of charge; **D:** No costs for installation assumed; **E:** Software and hardware required; **F:** More extensive software and hardware requirements compared to E					
Indirect implementation costs (IT support)	**0**	**1**	**0**	**1**	**2**	**2**
	A: No IT support required; **B:** Medium amount of IT support required (installation not straightforward); **C:** Limited IT support required (browser configuration, add-ons etc.); **D:** Medium amount of IT support required (integration of in-house and host IT infrastructure); **E:** Major IT project (system set-up, qualification/validation, etc.); **F:** more extensive IT project compared to E					
Indirect maintenance costs (IT support)	**0**	**1**	**0**	**0**	**2**	**2**
	A: No IT support required; **B:** Medium amount of IT support required (work-arounds necessary to bypass performance issues); **C:** Limited IT support required (browser upgrades, new add-ons etc.); **D:** Limited IT support required (mainly vendor responsibility); **E+F:** Major support from IT required (administration, upgrades, etc.)					
Effect of throughput on maintenance costs	**2**	**0**	**0**	**1**	**0**	**0**
	A: Billing is on project basis, costs per project assumed to be high (full service is provided); **B+C:** No throughput effect on costs; **D:** Hosting fees dependent on transaction volume, assumed to be lower than A; **E+F:** No throughput effect on costs					
Sum of scores	**2**	**2**	**0**	**2**	**5**	**6**

Note: Migration costs (see Chapter 4.1.1) and costs due to change management activities are not considered in this analysis as they are more relevant for large companies with a high number of legacy marketing authorisations and a high degree of deployment of a labelling system within a company.

Figure 13 and Figure 14 show the overall results of the above evaluations, i.e. the sum of scores from Table 5 and Table 6 compared to implementation scenario C (Word + Xforms = the baseline), with regard to performance and costs, respectively.

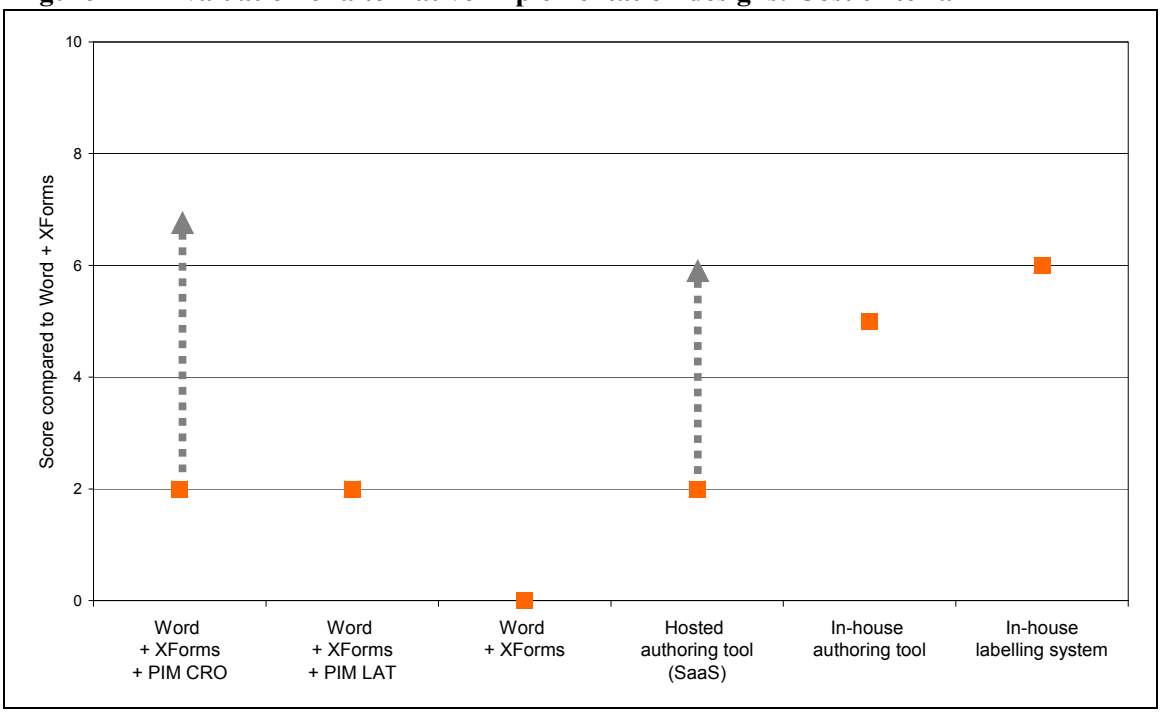
As expected, with regard to performance criteria (Figure 13) one can clearly see that component-based systems perform better. The highest improvements of performance are achieved with the labelling system. Effects of high throughput are indicated by grey dashed arrows: In the component-based scenarios, high throughput increases the benefit a company can achieve with such systems as a consequence of the direct cumulative

Figure 13 Evaluation of alternative implementation designs: Performance criteria



Grey dashed arrows: Effect of high throughput on score.

Figure 14 Evaluation of alternative implementation designs: Cost criteria



Grey dashed arrows: Effect of high throughput on score.

effects associated with component-based authoring (see Chapter 4.1). The effect of throughput is higher with labelling systems due to the additional, indirect cumulative performance increase associated with implementation of features described in Chapter 4.3. In the case of the LAT, the effect of high throughput is opposite, due to the negative scoring in this implementation scenario for efficiency of authoring.

With regard to costs (Figure 14), one can see that the in-house labelling system is the most expensive implementation design. One can also observe that the in-house authoring tool is more expensive than the hosted authoring system. This, however, applies only for low throughput. High activity in a hosted system will have an impact on hosting fees and may result in higher overall costs compared to in-house systems as indicated by the grey dashed arrows. The same is true and, most likely, even more pronounced for implementation scenario A (Word + XForms + PIM CRO) since outsourcing agreements will most probably be on a product basis and may also contain activity-dependent billing, i.e. new contracts are needed for each product and possibly each regulatory activity.

A further conclusion that one can draw from Figure 14 is that in implementation scenario B (Word + XForms + PIM LAT) PIM compliance was not to be achieved for free even though the LAT is free of charge. IT support required for maintenance must be considered and negatively contributes to the overall cost score. As a result, hosted authoring tools might have been serious alternatives to the LAT in achieving PIM compliance.

5 THE BIOTECH VIEW ON STRUCTURED PRODUCT INFORMATION MANAGEMENT

5.1 Evaluation of implementation options from the biotech perspective

When companies perform a decision analysis in order to determine which implementation variant suits best to their specific requirements, it will be necessary to weight the general criteria developed in Chapter 4.4 according to their importance for the company. In the course of such a decision analysis, companies might also think about including additional decision criteria (e.g. security of the IT infrastructure), which more accurately reflect internal business processes or requirements.

Figure 15 (Page 44) shows the results of such a weighting based on the needs of a biotech company: From the list of criteria in Table 5, only the efficiency of authoring and the scalability for new structured product information projects of other health authorities were identified as being relevant.

Content re-use for non-CP EU products (national, MRP, DCP) in this biotech-specific assessment was not considered to be a relevant criterion, since biotech products fall within the mandatory scope of the centralised procedure [47].

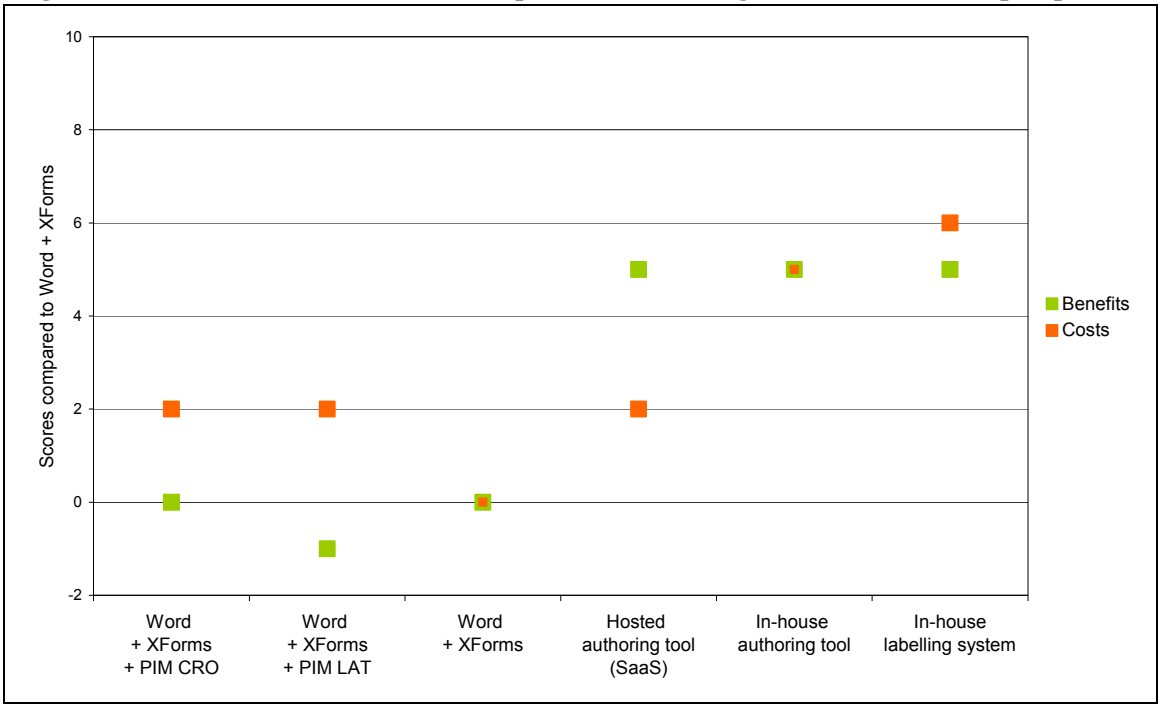
Similarly, the criteria specific for comprehensive labelling systems such as translation support (e.g. translation memories), support of associated processes (e.g. web publishing) and/or support of legal/GMP compliance were not considered to be relevant for biotechs. These features are more interesting for large companies with many affiliates managing an extensive product portfolio. Smaller companies and especially biotechs face fewer issues regarding the conventional manual management of processes related to product information, because the critical volume that requires software support to maintain efficiency in these areas is not reached. The basic functions of an authoring tool should therefore be sufficient.

As shown in Figure 15, component-based systems perform better compared to the Word + Xforms baseline. Labelling systems are, in this biotech-specific analysis, not associated with a further gain of benefits. The use of the LAT to achieve PIM compliance would have had a slightly negative impact on performance. This is due to the efficiency loss of authors associated with the LAT tool which does not blend in seamlessly with internal processes.

Interestingly for biotechs, if one looks at the cost side[22], the benefit-cost relation seems to be best for hosted authoring solutions. This would have been especially true if PIM had gone productive, since the corresponding implementation designs would have been associated with unchanged (Word + XForms + PIM CRO) and decreased performance (Word + XForms + PIM LAT), while costs might have been comparable to a hosted authoring tool.

[22] The scores for costs are taken from Table 6: Weighting of cost criteria did not have an impact on scores (Rationale: Low system costs are desirable for any type of company).

Figure 15 Evaluation of alternative implementation designs from the biotech perspective



In the decision process for or against possible designs of systems for the management of product information and for achieving compliance with health authority requirements, it seems that a biotech company should therefore always consider hosted authoring tools. In-house authoring tools are probably not so relevant due to the less favourable benefit-cost relation.

5.2 Impact of the PIM project being halted

For the decision of biotech companies with regard to authoring tools, i.e. the transition from the document-based management of product information to a component-based one, costs will be most critical.

If PIM had gone productive, the “hidden” LAT costs due to IT support required for system maintenance, would have influenced the decision towards a hosted authoring solution or, alternatively, the PIM outsourcing variant.

Since PIM has been halted, one can argue that there is no longer a need for biotech companies to think about structured product information management. However, this is only partially true, since the benefits are still there: Component-based authoring of the PI of CAPs with Word and PDF outputs instead of a PIM file might be associated with substantial benefits so that a hosted authoring tool might be a serious option.

Compared to costs, the potential benefits due to performance effects are likely to be more difficult to quantify in terms of savings. One possibility would be to perform an analysis of potential workload savings through content re-use like the one described in Chapter 4.1.1. The outcome of this analysis will depend on the actual number of

products that are managed by the company, the complexity of the product, i.e. the potential for content re-use, and its activity.

But other factors need to be considered as well: The overall global regulatory strategy, for example, is likely to influence the decision for or against the implementation of an authoring tool within a biotech company. Biotechs in contrast to companies focusing on single regions have a major interest to optimize their return on investment in product development by marketing their single or few products globally. Depending on the specific constellation (e.g. licensing strategy) a more or less substantial amount of non-EU product information documents needs to be managed. Authoring tools could be used for this purpose, provided they are flexible and customizable with regard to the specific output formats and layouts required by different health authorities.

In this context, it might also be meaningful for biotech companies to extend their functional requirements on a hosted authoring tool beyond those listed in Table 4 (see Chapter 4.2, Page 34) by including requirements for the support of legal compliance, i.e. by managing the CCDS/CCSI within the authoring tool and tracking the relationships between CCDS statements and corresponding components in the product information variants .

It might even be worthwhile, to think about the other features typical for labelling systems described in Chapter 4.3 (e.g. artwork production based on XML files) and to evaluate whether they could contribute to increased performance and process optimization within a biotech company.

In summary, even though EMA has halted the PIM project, one must come to the conclusion that component-based authoring tools and structured product information have potential not only for larger companies but also for biotechs. It is, however, questionable whether biotech companies will engage into these considerations and kick-off the corresponding activities without being forced to do so. Insofar it seems that the halting of the PIM project is a major drawback for structured product information in Europe.

6 OUTLOOK AND CONCLUSIONS

As discussed in Chapter 2, health authorities have recognised the high potential of structured product information. Interestingly, FDA and EMA had a different focus with regard to the target of their initiatives: While FDA's goal was to make structured product information publicly available, EMA's primary focus was to support the complex processes associated with the negotiation of the product information between applicant and health authority by means of XML technology.

FDA's SPL project with its vision to, in the long-term, work towards the creation of a fully-automated health information system must be considered a success. This is demonstrated by the availability of the comprehensive DailyMed drug databases on the web and, maybe even more significant, by the possibility to download up-to-date labels for human prescription, OTC and homeopathic medicinal products as well as veterinary drugs from the DailyMed website.

The fact that unrestricted access to these data is granted is certainly key for further commercial or non-commercial initiatives like the development of software applications such as electronic prescribing tools for use in clinics and hospitals that may have great potential in the prevention of prescribing errors. Interestingly one of these follow-up projects is undertaken by FDA itself: FDA further enhances the SPL files submitted by indexing them, i.e. adding index information to the file. This indexing project follows a staged approach and started with information on the pharmacologic class (since 2008) followed by the indication (since 2010). When the indexing of these categories is complete, FDA plans to index additional labelling information categories such as warnings and precautions, other adverse reactions, drug interactions, paediatric, or pregnancy information [37].

In the context that structured product information is used to feed databases, it is remarkable that the opportunity to enhance the quality of the European database for product information (EudraPharm) only had a secondary focus within the PIM project [16], even though an improvement would have been highly desirable:

- The EudraPharm database is still incomplete with regard to nationally approved products and does not yet fulfil all criteria of Regulation (EC) No 726/2004 of the European Parliament and of the Council [46], which commits EMA to create a database that (a) provides appropriate and comprehensible information on medicinal products to the general public and includes the summaries of product characteristics (SmPCs), the patient or user package leaflets (PLs) and the labelling ([48], [49]), and (b) is to be developed in a staged approach starting with centrally approved products and subsequently expanded to all medicinal products marketed in the European Community ([49]).
- The current publishing format has strong limitations in terms of web-based searchability (most of the relevant product information is hidden in partially very large PDF documents with only limited navigational enhancement such as table of contents, hyperlinks or bookmarks). EudraPharm's aptitude for healthcare

professional or patient audiences is limited: The current format does not allow selective searches for real-life questions such as "Are there medicinal products approved in a particular indication that have been investigated with regard to paediatric use?"

- The labelling is presented in the QRD format. Inclusion of mock-ups of the labelling which could easily be embedded in structured product information might, however, be more desirable (e.g. to identify counterfeit medicines).

Even though the database aspects were communicated without strong emphasis within the PIM project, one must, however, assume that an improvement of EudraPharm had always been in the scope, as demonstrated by the fact that EMA in its envisaged long-term perspective clearly anticipated the use of PIM in national procedures once well-established in the centralised procedure [10]. This strategy is inline with the above mentioned staged approach for the development of the EudraPharm database.

PIM is interesting for another reason: Its process-oriented focus with true exchange of information and bidirectional communication represented a totally different application of the potential of structured product information. In view of the complexity of the process PIM intended to support (see Figure 9, Page 24), one must admit that considerable progress had been achieved since 1999: All required system components – Data Exchange Standard (DES), Light Authoring Tool (LAT), PIM Review System (PRS) and PIM Data Validation Engine (PDVE) – were available and, in the PIM pilot phase, also shown to interoperate successfully. It is therefore regrettable that PIM was halted as a consequence of a budgetary review process.

If one compares the standards SPL and PIM are based on (see Chapters 2.1 and 2.2), one must clearly say that the SPL standard is simple whereas the DES is complex. Some of the complexity of the DES is certainly a consequence of the intricate process PIM was intended to support. It is, nevertheless, highly desirable that the standard underlying a PIM follow-up project, whether it is process-oriented or not, will be simpler. This would certainly contribute to the stability of standard in terms of life cycle, but also to a broader acceptance by the vendor community, which needs to develop the corresponding software tools, and by the pharmaceutical industry, which has to translate the health authority requirements.

A key aspect in the development of a future standard must, however, be the cooperation with relevant standard-developing organisations, possibly with the goal to develop a global standard for structured product information. In this regard, the history of the ICH's project of a standard for the identification of medicinal products (IDMP; see introduction to Chapter 2) is particularly interesting: ICH's corresponding guideline (ICH M5) had already reached step 2 of the ICH process, when ICH decided to no longer develop in-house specifications. Subsequently, the project was submitted to ISO and other relevant standards development organisations (e.g. HL7 for the US, CEN for the EU) were taken on board (the resulting ISO standard is expected to be published in 2012 [39]).

If one looks at structured product information and the concurrent transition to a component-based authoring mode from the industry side, there seems to be great potential for performance increase and process optimization (Chapters 4.1 and 4.3). Various implementation designs with varying degrees of deployment ranging from free tools made available by health authorities to simple authoring tools or comprehensive labelling systems may be thought of and are worthwhile to be evaluated by all types of companies depending on their specific needs and business processes (Chapters 4.4 and 5).

In Europe with the PIM project being halted, the trigger to undertake the required decision analysis has faded and it is questionable whether the momentum infused into the area of structured product information management by EMA's statement of intent in September 2009 will be maintained in Europe. PIM becoming mandatory/highly recommended was certainly a "sword of Damocles" for some pharmaceutical companies, but this was certainly also true for companies involved in the US which had to cope with SPL when it started to go live at the end of October 2005. Insofar, especially in view of the success of SPL, it would be interesting to investigate which experience US companies have made with SPL and whether they have changed their attitude towards SPL since the initial implementation phase. The insights gained by such research may be useful for setting-up future structured product information projects like a PIM follow-up project.

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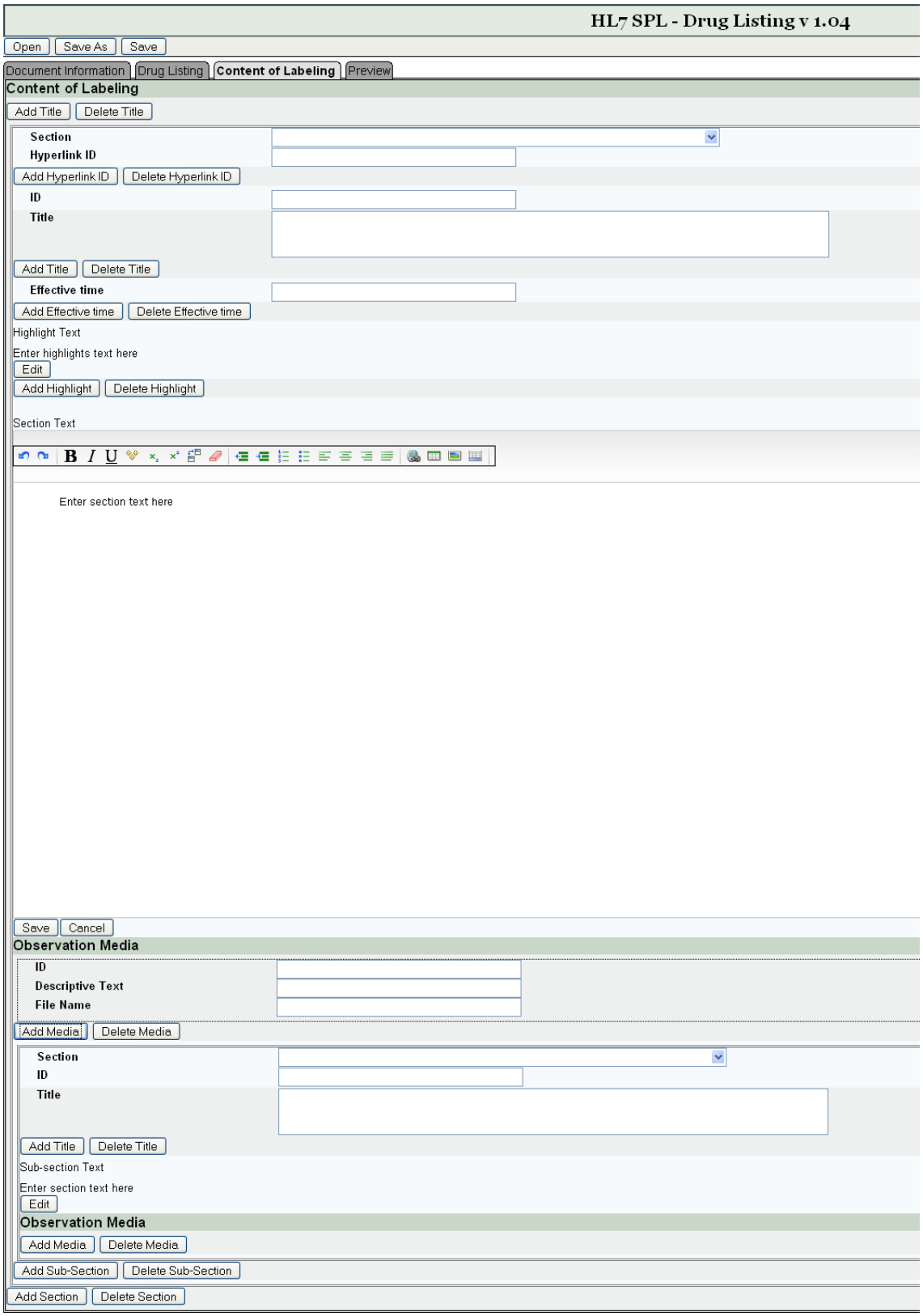
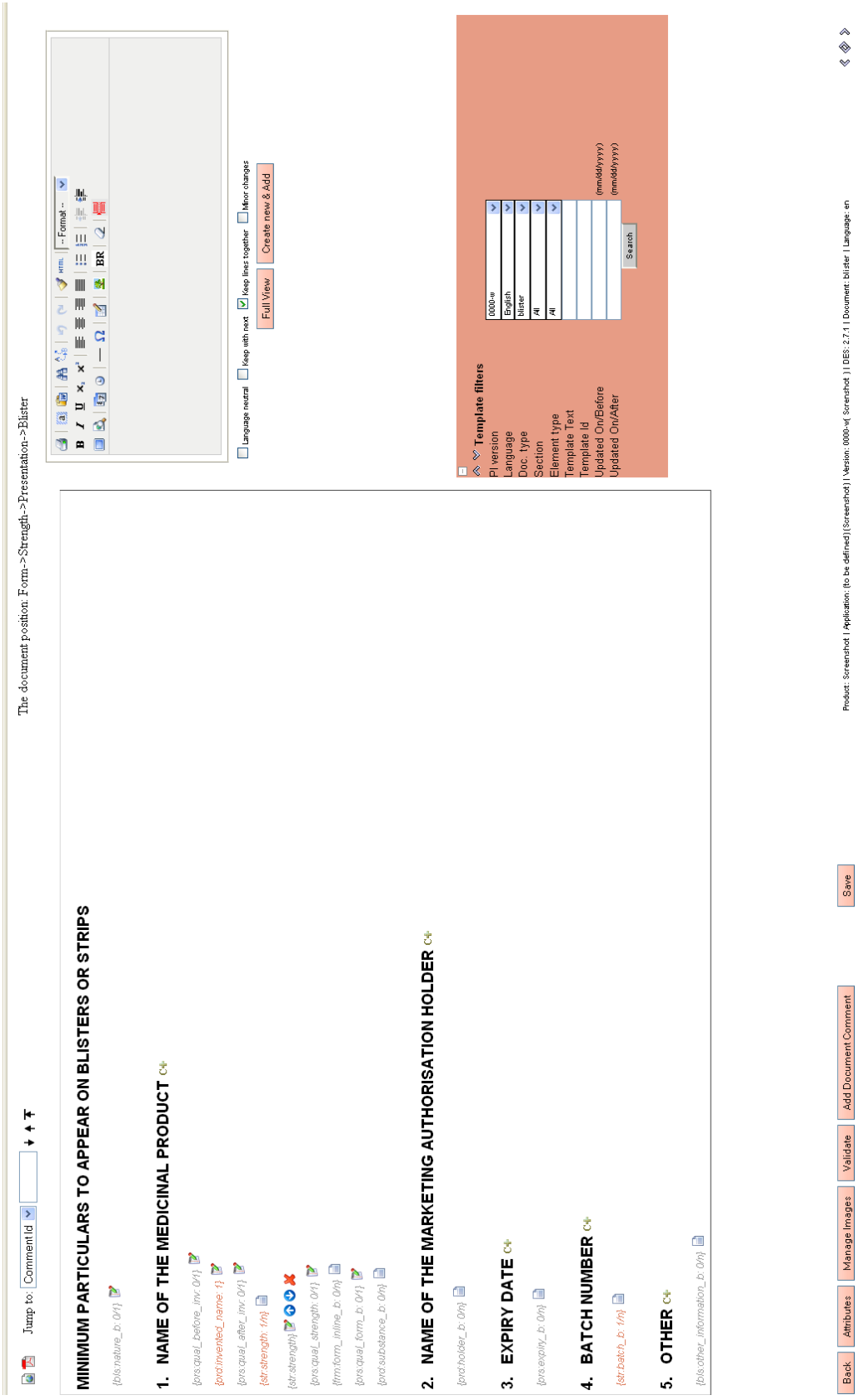
APPENDIX 1:
SCREENSHOT SPLFORM_DRUGLISTING.XHTML



APPENDIX 2: SCREENSHOT LAT V 4.2



APPENDIX 3:
COMPANIES WITH CENTRALLY APPROVED PRODUCTS

The cut-off date for the list below is 09 Oct 2010, when information available in HTML format on the EMA website (Find medicine > Human medicines > European Public Assessment Reports) was downloaded and further processed for incorporation into an MS Access database. The list below is an extract of this MS Access database (Symbols: [W] = Withdrawn; [R] = Refused)

Company	Product(s)
1 A Pharma GmbH	Rivastigmine 1A Pharma
Abbott Laboratories Ltd.	Humira; Kaletra; Norvir; Synagis; Trudexa[W]; Uprima[W]
Abbott S.r.l.	Taluvian[W]
Abraxis BioSciences Ltd.	Abraxane
Acino Pharma GmbH	Clopidogrel 1A Pharma; Clopidogrel Acino; Clopidogrel Acino Pharma; Clopidogrel Acino Pharma GmbH; Clopidogrel Hexal; Clopidogrel ratiopharm; Clopidogrel ratiopharm GmbH; Clopidogrel Sandoz
Actavis Group PTC ehf	Rapilysin; Sildenafil Actavis; Topotecan Actavis
Actelion Registration Ltd.	Tracleer; Zavesca
Addmedica	Siklos
Adienne S.r.l.	Tepadina
Alcon Laboratories (UK) Ltd.	Azarga; Azopt; DuoTrav; Emadine; Nevanac; Opatanol; Travatan
Alexion Europe SAS	Soliris
Alimenterics B.V.	Pylori-Chek[W]
Allergan Pharmaceuticals Ireland	Ganfort; Lumigan; Ozurdex
Almirall, S.A.	Vaniqa
Amersham Sorin.S.r.l.	Tecnemab K1[W]
Amgen Europe B.V.	Aranesp; Mimpara; Neulasta; Nplate; Prolia; Vectibix
Apotex Europe B.V.	Clopidogrel Apotex; Ferriprox; Olanzapine Apotex
Archimedes Development Ltd.	PecFent
Astellas Pharma Europe B.V.	Advagraf; Infergen[W]; Modigraf; Mycamine; Protopic; Qutenza
Astellas Pharma GmbH	Protopy[W]
AstraZeneca AB	Iressa
AstraZeneca UK Ltd.	Faslodex
Aventis Pharma S.A.	Ketek; Levviax[W]; Rilutek; Taxotere
Axcan Pharma International B.V.	PhotoBarr
Baxter AG	Advate; Celvapan; Ceprotin; Kiovig; Pandemic Influenza Vaccine H5N1 Baxter
Bayer HealthCare AG	Levitra; Vivanza
Bayer Schering Pharma AG	Betaferon; Helixate NexGen; Kinzalkomb; Kinzalmono; Kogenate Bayer; Nexavar; Pritor; PritorPlus; Ventavis; Xarelto; Zevalin
Beecham Group plc	Evotopin[W]
BIAL - Portela & Ca, S.A.	Exalief; Zebinix
Biocodex	Diacomit
Biogen Idec Ltd.	Avonex
biolitec pharma ltd.	Foscan
BioMarin Europe Ltd.	Firdapse; Naglazyme

Company	Product(s)
BioMimetic Therapeutics Ltd.	Gemesis[R]
BioPartners GmbH	Alpheon[R]; Ribavirin BioPartners; Valtropin
Biotest Pharma GmbH	Zutectra
Biovitrum AB (publ)	Kepivance; Kineret
Boehringer Ingelheim International GmbH	Aptivus; Beromun; Duloxetine Boehringer Ingelheim[W]; Metalyse; Micardis; MicardisPlus; Mirapexin; Pradaxa; Sifrol; Tenecteplase Boehringer Ingelheim Pharma GmbH & Co. KG[W]; Viramune
Bracco International B.V.	SonoVue
Bristol-Myers Squibb and Gilead Sciences Ltd.	Atripla
Bristol-Myers Squibb Pharma Belgium Sprl	Luminity
Bristol-Myers Squibb Pharma EEIG	Baraclude; Clopidogrel BMS[W]; DuoCover; Irbesartan BMS[W]; Irbesartan Hydrochlorothiazide BMS[W]; Iscover; Karvea; Karvezide; Orencia; Reyataz; Sprycel; Sustiva; Zerit
Bristol-Myers Squibb/AstraZeneca EEIG	Onglyza
Cangene Europe Ltd.	ImmunoGam
Canyon Pharmaceuticals Ltd.	Revasc
Celgene Europe Ltd.	Refludan; Revlimid; Thalidomide Celgene; Vidaza
Centocor B.V.	Remicade; Simponi; Sovrima[R]
Cephalon Europe	Effentora; Myocet; Trisenox
Chiesi Farmaceutici SpA	Nymusa
Chiron S.p.A.	Triacelluvax[W]
CIS bio international	Indimacis 125[W]; NeoSpect; Quadramet; Scintimun; Ytracis
Covidien Deutschland GmbH	OptiMARK
Crucell Sweden AB	Dukoral
CSL Behring GmbH	Privigen
CT Arzneimittel GmbH	Biograstim; Biopoin
Daiichi Sankyo Europe GmbH	Evista
Dompé Biotec S.p.A.	Nespo[W]; Neupopeg[W]; Parareg[W]
Dr. Gerhard Mann, Chem.-Pharm. Fabrik GmbH	Vitrasert Implant[W]
Dr. Karl Thomae GmbH	Daquiran[W]
Eckert & Ziegler Nuclitec GmbH	Yttriga
Eisai Ltd.	Inovelon; NeuroBloc; Panretin; Prialt; Targretin; Zonegran
Elan Pharma International Ltd.	Natalizumab Elan Pharma[R]; Tysabri
Eli Lilly & Co. Ltd.	Olansek[W]
Eli Lilly Nederland B.V.	Adcirca; Alimta; Ariclaim; Byetta; Cialis; Cymbalta; Efient; Forsteo; Humalog; Liprolog; Optruma; Xeristar; Xigris; Yentreve; Zypadhera; Zyprexa; Zyprexa Velotab
Epicept GmbH	Ceplene
Evans Vaccines Ltd.	Hepacare[W]
Ferring Pharmaceuticals A/S	Firmagon; Tractocile
Fresenius Biotech GmbH	Removab
GE Healthcare AS	Optison; Teslascan
GE Healthcare Ltd.	DaTSCAN
Generics [UK] Ltd.	Olanzapine Mylan
Genta Development Ltd.	Genasense[R]
Genzyme Europe B.V.	Aldurazyme; Cerezyme; Cholestagel; Evoltra; Fabrazyme; MabCampath; Mozobil; Myozyme; Renagel; Renvela; Thyrogen
Gilead Sciences International Ltd.	Cayston; Emtriva; Hepsera; Rapiscan; Truvada; Viread; Vistide

Company	Product(s)
Glaxo Group Ltd.	Agenerase; Alisade; Alli; Altargo; Arixtra; Arzerra; Atriance; Avamys; Integrilin; Quixidar[W]; Tyverb; Volibris; Votrient; Zeffix
GlaxoSmithKline Biologicals S.A.	Ambirix; Arepanrix; Cervarix; Daronrix; Fendrix; Infanrix HepB[W]; Infanrix hexa; Infanrix penta; Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals; Pandemrix; Prepandemic influenza vaccine GlaxoSmithKline Biologicals; Prepandrix; Quintanrix[W]; Rotarix; Synflorix; Tritanrix HepB; Twinrix Adult; Twinrix Paediatric
GlaxoSmithKline Trading Services Ltd.	Revolade
Glenmark Generics (Europe) Ltd.	Olanzapine Glenmark; Olanzapine Glenmark Europe
Glenmark Pharmaceuticals s.r.o.	Olazax; Olazax Disperzi
H. Lundbeck A/S	Ebixa
Helsinn Birex Pharmaceuticals Ltd.	Aloxi
Hexal AG	Epoetin alfa Hexal; Filgrastim Hexal; Rivastigmine Hexal; Temozolomide Hexal
Hospira UK Ltd.	Nivestim; Retacrit; Temozolomide Hospira; Topotecan Hospira
Howmedica International S. de R. L.	Opgenra; Osigraft
IDM PHARMA SAS	Mepact
Immunomedics GmbH	Cea-SCAN[W]; LeukoScan
INFAI GmbH	Helicobacter Test INFAI
INO Therapeutics AB	INOmax
Instituto Grifols S.A.	Flebogammadif
Intercell AG	Ixiaro
IPSEN Ltd.	NutropinAq
Ipsen Pharma	Increlex
Janssen-Cilag International NV	Doribax; EVRA; Intelence; Invega; Ionsys[R]; Prezista; Regranex; Stelara; Velcade; Zeftera[R]
Jerini AG	Firazyr
Krka, d.d., Novo mesto	Clopidogrel Krka; Enyglid; Ifirmasta; Nimvastid; Oprymea; Repaglinide Krka; Tolura; Vizarsin; Zalasta; Zylagren; Zyllt
KS Biomedix Ltd.	HumaSPECT[W]
Laboratoire HRA Pharma	ellaOne; Lysodren
Laboratoires 3M Sante	Zartra[W]
LEO Pharma A/S	ATryn
Les Laboratoires Servier	Corlentor; Osseor; Procoralan; Protelos; Valdoxan
Lipomed GmbH	Litak
MDS Nordion S.A.	Theryttrex[W]
Meda AB	Aldara; Sonata; Tasmar; Zerene
medac Gesellschaft für klinische Spezialpräparate mbH	Leflunomide medac; Temomedac
medac GmbH	Gliolan
Medice Arzneimittel Pütter GmbH & Co. KG	Abseamed
Menarini International Operations Luxembourg S.A. (MIOL)	Adenuric; Ranexa
Merck KGaA	Erbitux; Kuvan
Merck Santé S.A.S.	Cyanokit
Merck Serono Europe Ltd.	Cetrotide; Ovitrelle

Company	Product(s)
Merck Sharp & Dohme Ltd.	Adrovance; Brinavess; Cancidas; Crixivan; Efficib; Emend; Fosavance; Invanz; Isentress; Ivemend; Janumet; Januvia; Pelzont; Ristaben; Ristfor; Silgard; Stocrin; Tesavel; Tredaptive; Trevaclyn; Vantavo; Velmetia; Xelevia
Merz Pharma GmbH + Co. KGaA	Axura
Movetis NV	Resolor
Mylan dura GmbH	Clopidogrel DURA
Mylan S.A.S.	Clopidogrel Mylan
N.V. Organon	Bridion; Elonva; Orgalutran; Puregon; Sycrest
Neopharma Ltd.	Olanzapine Neopharma
NeuTec Pharma plc	Mycograb[R]
Nicobrand Ltd.	Kentera
Norpharm Regulatory Services Ltd.	Zopya
Norton Healthcare Ltd.	Paxene[W]
Novartis Europharm Ltd.	Aclasta; Afinitor; Comtan; Copalia; Copalia HCT; Cubicin; Dafiro; Dafiro HCT; Emselex; Enviage; Eucreas; Exelon; Exforge; Exforge HCT; Exjade; Extavia; Galvus; Glivec; Hirobriz Breezhaler; Icandra; Ilaris; Imprida; Imprida HCT; Jalra; Lucentis; Onbrez Breezhaler; Oslif Breezhaler; Prometax; Rasilez; Rasilez HCT; Riprazo; Sebivo; Simulect; Sprimeo; Starlix; Tasigna; Tekturna[W]; Trazec[W]; Visudyne; Xiliarx; Xolair; Zelnorm[R]; Zomarist; Zometa
Novartis Ophthalmics Europe Ltd.	Vitravene[W]
Novartis Vaccines and Diagnostics GmbH & Co. KG	Optaflu
Novartis Vaccines and Diagnostics S.r.l.	Focetria; Foclivia; Menveo
Novo Nordisk A/S	Actraphane; Actrapid; Insulatard; Levemir; Mixtard; Monotard[W]; NovoMix; NovoNorm; NovoRapid; NovoSeven; Prandin; Protaphane; Ultratard[W]; Velosulin[W]; Victoza
Nycomed Austria GmbH	TachoSil
Nycomed Danmark ApS	Instanyl; Preotact
Nycomed GmbH	Controloc Control; Daxas; PANTECTA Control; PANTOLOC Control; PANTOZOL Control; SOMAC Control
OMRIX biopharmaceuticals S.A.	Evicel
Orion Corporation	Comtess; Fareston; Stalevo
Orphan Europe S.A.R.L.	Carbaglu; Cystadane; Cystagon; Pedea; Vedrop; Wilzin
Otsuka Pharmaceutical Europe Ltd.	Abilify; Samsca
Pacira Ltd.	DepoCyte
PASTEUR MERIEUX - MSD	Primavax[W]
Pfizer Ltd.	Celsentri; Champix; Dynastat; Ecalta; Exubera[W]; Fablyn; Lyrica; Macugen; Onsenal; Patrex[W]; Revatio; Somavert; Sutent; Thelin; Tikosyn[W]; Toviaz; Trovan[W]; Trovan IV[W]; Turvel[W]; Turvel IV[W]; Valdyn[W]; Vfend; Viagra
Pharma Mar S.A.	Yondelis
Pharmacia - Pfizer EEIG	Bextra[W]
Pharmacia Europe EEIG	Rayzon[W]; Xapit[W]
Pharmathen S.A.	Grepid
Pharming Group N.V.	Rhucin[R]
Pierre Fabre Medicament	Busilvex; Impulsor[R]; Javlor; Milnacipran Pierre Fabre Medicament[R]
Procter & Gamble Pharmaceuticals Germany GmbH	Livensa
Qualimed	Clopidogrel Qualimed

Company	Product(s)
RAD Neurim Pharmaceuticals EEC Ltd.	Circadin
ratiopharm GmbH	Eporatio; Filgrastim ratiopharm; Ratiograstim; Sildenafil Ratiopharm
RB Pharmaceuticals Ltd.	Suboxone
Recordati Ireland Ltd.	Silodyx; Urorec
Regeneron UK Ltd.	Rilonacept Regeneron
Roche Registration Ltd.	Avastin; Bondenza; Bondronat; Bonviva; CellCept; Destara[W]; Ecokinase[W]; Fortovase[W]; Fuzeon; Herceptin; Invirase; MabThera; Mircera; NeoRecormon; Pegasys; RoActemra; Tamiflu; Tarceva; Viracept; Xeloda; Xenical; Zenapax[W]
Sandoz GmbH	Binocrit; Omnitrope; Zarzio
Sandoz Pharmaceuticals GmbH	Rivastigmine Sandoz; Temozolomide Sandoz
Sanofi Pasteur MSD, SNC	Gardasil; HBVAXPRO; Hexavac[R]; Intanza; M-M-RVAXPRO; Procomvax[W]; Proquad; RotaTeq; Zostavax
Sanofi Pasteur S.A.	Humenza; IDflu
Sanofi Pharma Bristol-Myers Squibb SNC	Aprovel; Clopidogrel Winthrop; CoAprovel; DuoPlavin; Irbesartan Hydrochlorothiazide Winthrop; Irbesartan Winthrop; Plavix
sanofi-aventis	Acomplia[W]; Fasturtec; Multaq; Zimulti[W]
sanofi-aventis Deutschland GmbH	Apidra; Arava; Insulin Human Winthrop; Insuman; Lantus; Leflunomide Winthrop; Optisulin
Sanofi-Aventis Pharma S.A.	Docetaxel Winthrop
Sanquin	Nonafact
Schering-Plough Europe	Aerinaze; Aerius; Allex[W]; Azomyr; Caelyx; Cotronak[W]; Fertavid; Neoclarityn; Noxafil; Opulis[W]; Posaconazole SP[W]; Rebetol; Temodal; Viraferon[W]
Schwarz Pharma Ltd.	Neupro
Serono Europe Ltd.	GONAL-f; Luveris; Pergoveris; Raptiva[W]; Rebif
Servier (Ireland) Industries Ltd.	Thymanax
Shire Human Genetic Therapies AB	Elaprase; Replagal
Shire Pharmaceutical Contracts Ltd.	Dynepo[W]; Xagrid
Shire Pharmaceuticals Ireland Ltd.	Vpriv
Sipaco Internacional Lda.	Orlaam[W]
SmithKline Beecham Ltd.	Avaglim; Hycamtin
SmithKline Beecham Plc	Avandamet; Avandia; Nyracta[W]; Venvia[W]
Sonus Pharmaceuticals Ltd.	EchoGen[W]
SP Europe	IntronA; PegIntron; ViraferonPeg
SpePharm Holding B.V.	Savene
STADA Arzneimittel AG	Silapo
Sun Pharmaceutical Industries Europe B.V.	Docefrez
Swedish Orphan International AB	Ammonaps; Orfadin
Tad Pharma GmbH	Clopidogrel TAD
Takeda Europe R&D Centre Ltd.	Ixense[W]
Takeda Global Research and Development Centre (Europe) Ltd.	Actos; Competact; Glubrava; Glustin; Tandemact
Teva Generics GmbH	Tevagrastim
Teva Pharma B.V.	Clopidogrel Teva (hydrogen sulphate); Clopidogrel Teva Pharma; Docetaxel Teva; Irbesartan / Hydrochlorothiazide Teva; Irbesartan Teva; Lamivudine Teva; Lamivudine Teva Pharma B.V.; Mycophenolate mofetil Teva; Myfenax; Nevirapine Teva; Olanzapine Teva; Pramipexole Teva; Raloxifene Teva; Repaglinide Teva; Ribavirin Teva; Ribavirin Teva Pharma B.V.; Rivastigmine Teva; Sildenafil Teva; Telmisartan Teva; Temozolomide Teva; Topotecan

Company	Product(s)
	Teva
Teva Pharma GmbH	Azilect
The Medicines Company UK Ltd.	Angiox
Three Rivers Global Pharma Ltd.	Ribavirin Three Rivers
TiGenix NV	ChondroCelect
TMC Pharma Services Ltd.	Vasovist
Torbet Laboratories Ltd.	Pylobactell
UCB Pharma Ltd.	Xyrem
UCB Pharma SA	Cimzia; Keppra; Vimpat
Unigene UK Ltd.	Forcaltonin[W]
ViiV Healthcare UK Ltd.	Combivir; Epivir; Kivexa; Telzir; Trizivir; Ziagen
Warner Chilcott UK Ltd.	Intrinsa
Wyeth Europa Ltd.	BeneFIX; Conbriza; Enbrel; InductOs; Mylotarg[R]; Rapamune; ReFacto AF; Relistor; Torisel; Tygacil
Wyeth Lederle Vaccines S.A.	Prevenar; Prevenar 13; RotaShield[W]

Eidesstattliche Erklärung

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

München, den 4. Juli 2011

Dr. André Dorochevsky