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PIM Concepts

V2.2

Covers PIM DES V2.7.1



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1 Introduction

This guide is intended to help you understand concepts introduced by the Product Information Management (PIM) system.

An understanding of these concepts will help you to make best use of the PIM software applications relevant to your role. However, this guide does *not* contain procedures for using any of the applications. For references to sources of such information, see the "Related Information" section.

Most of the information in this guide applies to all PIM submissions, regardless of the version of the Data Exchange Standard (DES) used. The examples are all based on DES 2.7.

1.1 Who this Guide is For

This guide is primarily written for anyone who handles product information in any of the following organisations:

- Applicants and marketing authorisation holders (pharmaceutical companies) or contract research organisations (CROs) working on their behalf
- European Medicines Agency
- National Competent Authorities (NCAs)

This guide will also be useful for software vendors who develop PIM authoring tools.

Regarding the Centralised Procedure, it is assumed that you are already familiar with:

- The initial marketing authorisation procedure and post-authorisation procedures for human medicinal products
- Directives, guidelines, and standard operating procedures relevant to your role
- The parts of product information (Annex I Summary of Product Characteristics, Annex II, and Annex II Labelling and Package Leaflet) relevant to your role

Regarding the Product Information Management (PIM) system, it is recommended that you first obtain basic training and then use this guide for further information and reference. Many organisations that use PIM have their own PIM training materials, so check what training is available to you.

1.2 Where to Get further Help

PIM helpdesk: For technical questions and problems concerning PIM, contact the PIM helpdesk, as follows.

Email: pim@ema.europa.eu

Postal address: Eudra Service Desk
ICT User and Application Support
Information and Communications Technology
European Medicines Agency
7 Westferry Circus,
Canary Wharf
London
E14 4HB
United Kingdom

Tel: +44 (0)20 7523 7523

Opening hours: Monday – Friday, 09.00 – 17.30 (UK time)

Note: The helpdesk cannot answer questions about the *content* of the documents in a PIM submission or the regulatory procedure. For such questions, continue to contact the Agency's product team leader (PTL) for your product.

PIM website: For general news about PIM and the latest documentation, go to <http://pim.ema.europa.eu/index.htm>.

1.3 Note about the Examples

This is a work of software documentation. Any resemblance between the example medicinal products used in this documentation (PIM EX1 – PIM EX6 and other examples) and real products is not entirely coincidental. However, the examples of regulator comments, applicant responses, and activities at certain procedural steps do not relate to real evaluation procedures for these products.

1.4 How to Send your Comments

Your comments on this guide are important in helping to improve information. If you have any comments about this guide or any other PIM documentation, email your comments to pim@ema.europa.eu. In the subject line, include the text "Comments on PIM Guidance". In the body of the email, include the name of the guide and the version number.

In addition to your specific comments, the Agency is interested in your general opinion of the clarity and accuracy of this guide and on whether it was easy to find the information you were looking for.

1.5 How to Use this Guide

In this guide, the following icons are used to indicate which sections may be of particular interest to you.



Information of particular interest to applicants



Information of particular interest to staff in NCAs



Information of particular interest to European Medicines Agency staff

If you want only a high-level overview of PIM, just read Chapter”.

1.6 What’s New

Here is a list of what’s new in this guide, compared with v2.0.

- In accordance with the rebranding of the European Medicines Agency, the guidance has been re-formatted and references to the name of the Agency and the Agency’s website have been updated.
- The “Related Information” section has been updated.



2 Summary of PIM Characteristics

PIM is a system introduced by the European Medicines Agency with the aim of meeting the following objectives:

- Increasing the efficiency of the management and exchange of product information (PI) for all parties involved in the evaluation process by structuring the information and exchanging it electronically
- Improving the quality and consistency of the published product information



2.1 Indications for PIM

PIM is currently indicated only for the management of product information for human medicines in the Centralised Procedure in the EU and the EEA states.

2.1.1 Product Information in the Centralised Procedure – Anatomy

In the Centralised Procedure, there is a lot of information about each medicinal product. For each product, there are the following types of documents:

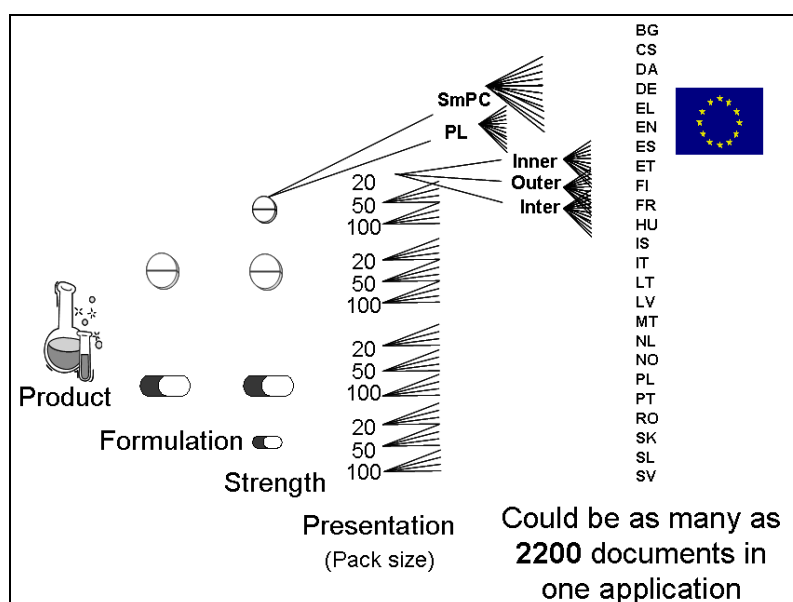
- Annex I: Summary of Product Characteristics (SmPC)
- Annex II: Manufacturer information, conditions of the marketing authorisation, and specific obligations
- Annex IIIA: Labelling
- Annex IIIB: Package leaflet (PL)

Although some documents can be combined, there may be separate documents for:

- Each pharmaceutical form (e.g. tablets or oral solution)
- Each strength (e.g. 150mg or 300mg)
- Each presentation (e.g. 20 tablets or 30 tablets)

And each of these documents has to be translated into all EU languages. Figure 1 shows how the number of product information documents can quickly multiply.

Figure 1. Quantity of product information



The number of documents depends on the complexity of the product. The average number of documents per invented name is 650–1000, and applications with over 2000 documents are possible. Furthermore, the quantity of documents increases every time the EU is enlarged, due to the addition of new languages.

Much information is repeated within and between documents:

- Some information should be the same in the same type of document for different presentations.
- Some information should be the same in the package leaflet as in the SmPC.
- All information should be consistently translated.

2.1.2 Product Information Management – Physiology

During the preparation and evaluation of an application for a marketing authorisation or a post-authorisation procedure, many activities are performed on the product information, including:

- Authoring
- Validating the structure and format
- Reviewing the content from scientific and linguistic perspectives
- Editing to implement regulators' comments
- Checking the implementation of comments
- Exchanging different versions
- Finalising the content and format
- Translating
- Production of EC Decision documents

Furthermore, much of this activity has to be done to a strict timetable, and many applications are in progress in parallel.

There are many challenges in managing these activities. The system used before PIM involves exchanging Microsoft Word and PDF files. The main challenges in the Word-based system are:

- **Maintaining consistency in repeated information.** Since there is a significant amount of repetition in the product information, consistency has to be maintained throughout the evaluation process. Whenever a change is made to certain information in one document, the same change has to be made in all places where that information appears.

In the Word-based system, maintaining the required consistency is time consuming and potentially error prone. One disadvantage of Word is that change tracking can be inadvertently switched off while editing. Another disadvantage is that changes made may be incorrectly accepted and thus lost from view. Consequently, regulators cannot be confident that the tracked changes show all the changes since the last version and that no additional changes have been inadvertently introduced.

- **Ensuring everyone is working on the same version.** The number of versions of Word or paper documents increases as an application progresses, making it difficult to ensure that the applicant, the Agency, and the NCAs are all working on the same version.
- **Consolidating many comments from multiple sources.** In the Centralised Procedure, comments come from reviewers in all NCAs but must be consolidated into a single coherent version for sending to the applicant.
- **Getting the formatting and other technicalities right.** A lot of effort is spent by all parties on checking that the formatting complies with the QRD templates and generating PDF files to check that the information looks right.



2.2 Mechanism of Action of PIM

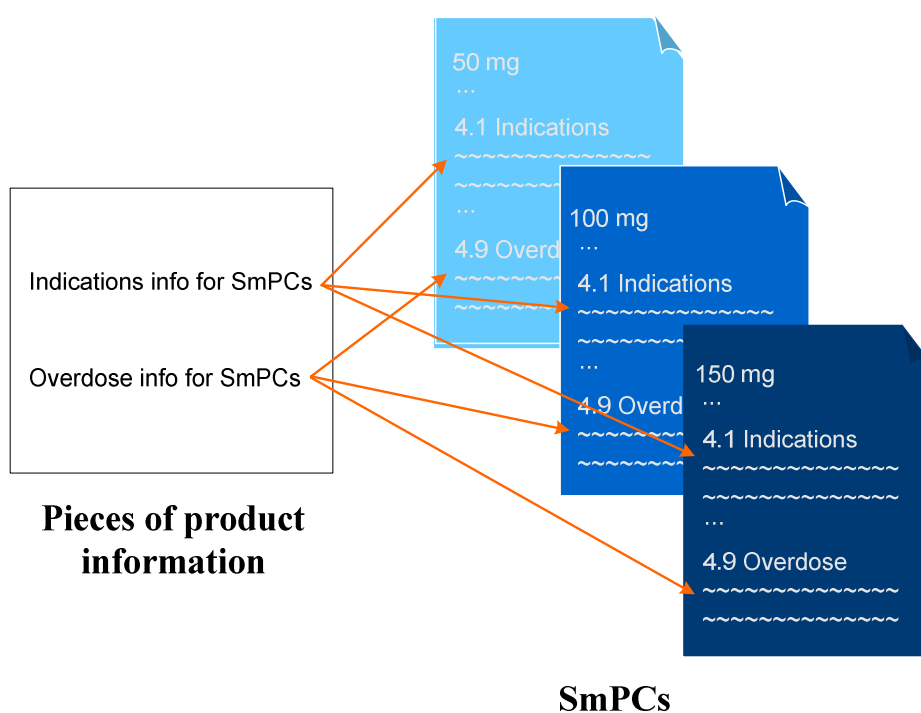
PIM works by reusing information. This section discusses reuse, the benefits of reuse, and the other benefits of PIM.

2.2.1 Reuse: The Guiding Principle and Main Benefit of PIM

The guiding principle of PIM is: **hold any piece of information only once and allow its use as many times as necessary to create the required documents.**

This principle is achieved by splitting product information into pieces, labelling the pieces, and putting them into a database. Identical pieces are held once in the database and presented in multiple documents, as shown in Figure 2.

Figure 2. Reuse of product information



In the example in Figure 2, reuse means that if the indications change, the information only needs to be changed in one place, not in every SmPC.

Reuse can occur by design or by choice. The reuse of text for indications illustrated in Figure 2 is an example of reuse by choice. The text for indications is often the same for all strengths, so the applicant will usually choose to reuse it — but can use different text for some strengths, if necessary. By contrast, the ATC code in section 5.1 of the SmPC is always the same for all strengths. Therefore, PIM is designed to automatically reuse the ATC code in all SmPCs.

Reuse of information can even occur across languages. Certain information is the same in all languages, for example, the invented name, ATC code, manufacturers' addresses, and graphics. This language-neutral information is shared across documents in all EU languages.

When you use the PIM system to view or print a PI document, e.g. a package leaflet, the document looks the same as it would if it had been produced using Word. But there is one big difference from Word: **The document you see on screen does not actually exist permanently as a document. Rather, the system compiles the document from relevant pieces of information in the database on demand.**

If you are used to creating or reviewing documents in Word, the idea of storing product information in reusable pieces might initially seem odd. But reuse means that:

- **Consistency of information is ensured** because each piece of information is written once and then automatically included in multiple documents in the right sections.
- **Version control is ensured** because each piece of information (whether part of the applicant's text or a regulator's comment) is associated with a particular version of the PI.
- **A regulator can see which parts of a document they have already reviewed** as part of the review of another document and thus can focus on the text unique to the current document.
- **Authoring of new versions can focus on changes** because if a comment or a variation affects text that appears in many documents, the applicant only changes the text in one place.
- **Reviewing of new versions can focus on changes** because regulators can see applicant's changes and do not have to check that nothing else has been inadvertently changed.
- **Translation management is easier** because applicants can identify a block of text that is common to many documents, thus ensuring that it marked for translation only once.

2.2.2 Other Benefits of PIM

In addition to the benefits associated with reuse of information, PIM offers the following benefits:

- **Better compliance with the QRD templates.** PIM ensures that elements of the QRD templates are in the correct order and correct format within submissions. This saves time for the applicant when creating PI and for the Agency during the product information quality (PIQ) check.
- **Automatic validation.** PIM checks some rules automatically, e.g. that all mandatory elements are present (though the accuracy of information must still be checked by the reviewers).
- **Flexible way to comment and respond to comments.** In addition to proposing specific changes to content, regulators can include a reason and can also make open-ended comments. Likewise, applicants can justify not implementing a regulator's comment exactly as proposed and can give a reason for making a change that the regulators did not ask for.
- **Collaborative working.** At appropriate stages of an evaluation, NCAs can see each other's comments. Consequently, a scientific reviewer can avoid making a comment if a reviewer in another country has already made the same comment. Also, the system automatically identifies conflicting comments.
- **Easier consolidation of comments.** The comments from all NCAs are in one place rather than in many Word documents, which makes it easier for a Rapporteur or EMA Product Team Leader to consolidate comments.
- **Ability to view the history of an application.** The EMA and NCAs can get information from the system on the current status of an application and see comments on previous versions.
- **Everyone can focus on content rather than format.** PIM uses special files called style sheets to control the presentation of information (font sizes, margins, etc.). Thus, the database is a single source of information for display on screen, in PDF files, or as HTML in web browsers.
- **PI for the centralised procedure is truly centralised.** There is a central database for product information, so it is no longer necessary to distribute documents to all the NCAs and the information is more secure.
- **Saving paper.** There is no need to exchange paper documents for PI.

- **Integration with other software that uses structured data.** PIM uses XML (Extensible Markup Language) to structure PI, which makes it easier to share data with other applications that use structured data. For example, the Agency will be able to transfer data directly to the EudraPharm database, which lets the general public search for package leaflets online. And applicants might be able to integrate their PIM authoring tool with an XML-based translation management tool.

Ultimately, the improved quality of the published information benefits the people who read it — patients, pharmacists, and physicians.



2.3 Composition of PIM

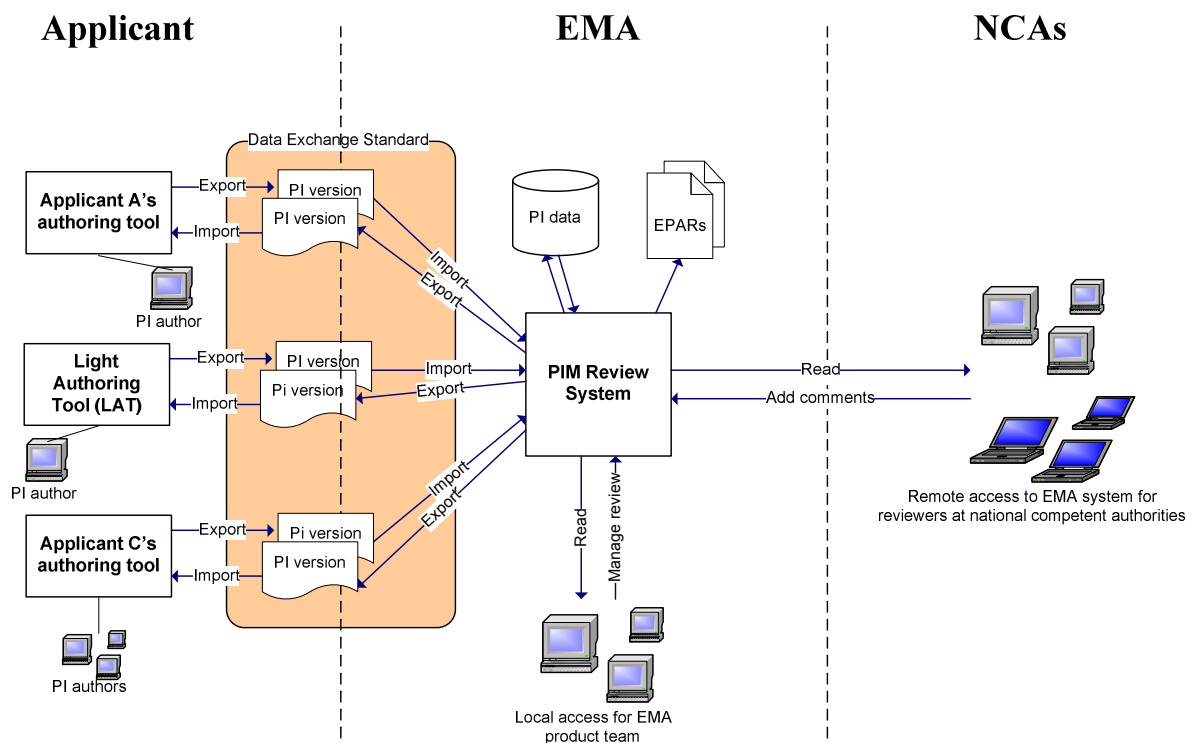
The term “PIM” encompasses both a standard for the electronic exchange of product information and some software applications that comply with that standard, as follows.

- The **Data Exchange Standard (DES)** describes how the required information should be created and validated so that it can be exchanged successfully between applicants and NCAs. The design of the standard aims to minimise the repeated adjustment of information that is included many times in different locations within the PI documents.
- The **software applications** support the tasks of authoring, validating, and reviewing product information. They are:
 - Authoring tools
 - PIM Review System (PRS)
 - PIM Data Validation Engine (PDVE)
 - PIM Viewer

As a PI author or regulator, you don’t need to know details of what is in the DES; you only need to know how to use the software. The DES specification is useful for technical staff at applicant companies or software vendors who intend to develop their own software for creating or validating PIM submissions.

The main software components of the PIM system are the applicants’ authoring tools and the PIM Review System, as illustrated in Figure 3.

Figure 3. The components of the PIM system



The DES is depicted as shading around the PI versions rather than as a separate component because it’s not a software application. Rather, it is a protocol that the authoring tools and the PIM Review System use to exchange data. The authoring tools and the PRS are like the active substances of a medicinal product, whereas the DES is like an excipient, binding it all together.

The rest of this section describes each component in more detail.



2.3.1 Authoring Tools

Every applicant company needs a DES-compliant tool that, as a minimum, supports the tasks of authoring product information, responding to regulator comments, entering or importing translations, and exchanging versions with the Agency. The options are:

- Use the Light Authoring Tool (LAT), which is a free tool from the Agency
The LAT is a single-user tool with basic functionality. It is primarily aimed at small- and medium-sized enterprises. However, it can also be used by larger organisations needing an interim solution or not intending to obtain a more comprehensive solution.
- Use another tool or service
Applicants can purchase a tool from a company that sells off-the-shelf PIM authoring tools, ask a software vendor to customise an off-the-shelf tool to their own requirements, or develop a tool in house. Alternatively, applicants can use PIM service providers.

The decision depends on several factors. For more information, see *PIM Guidance for Applicants (Centralised Procedure)*. For information on using the LAT, see *PIM LAT User Manual*.

Figure 4 shows an example of a window in the Light Authoring Tool.

Figure 4. Window for editing product information in the Light Authoring Tool

The screenshot displays the Light Authoring Tool interface. At the top, a status bar shows "The document position: Hard capsules->125 mg". The main content area is titled "ANNEX I" and "SUMMARY OF PRODUCT CHARACTERISTICS". Below this, there is a section "1. NAME OF THE MEDICINAL PRODUCT C+" with several lines of text containing placeholders like `{prs:qual_before_inv: 0/1}` and `{str:strength: 1/n}`. On the right side, there is a "Panel for editing" with a rich text editor toolbar and a "List of pieces of" panel. The "List of pieces of" panel shows a search for "Text" with "Nothing found to display." and "No results found". At the bottom, there is a navigation bar with buttons for "Back", "Attributes", "Manage Images", "Save", "Validate", and "Add Document Comment". The status bar at the very bottom shows "Product: PIM EX1 | Application: Application 1 | Version: 0000-w(Initial version) | DES: 2.3 | Document: spo | Language: en".



2.3.2 PIM Review System (PRS)

The PIM Review System is a web-based application hosted by the Agency. In other words, it is accessed through a web browser, such as Internet Explorer, so users do *not* need to have any software installed on their computers.

The main tasks supported by the PIM Review System are:

- Exchanging versions* with applicants
- Technical validation of applicants' submissions
- Scientific review of product information
- Linguistic (QRD) review of product information in English
- Linguistic (QRD) review of translations in all EU languages
- Consolidating comments from different reviewers
- Taking "snapshots" of comments at key stages of procedures
- Generating PDF files for reading offline and for the EC
- Setting approved versions as baselines for subsequent procedures
- Viewing the history of applications

For security reasons, only authorised personnel from the Agency and NCAs can obtain user accounts on the PIM Review System, and all users must access it over the secure EudraNet network.

The tasks that a user can perform in the PIM Review System depend on their role, ranging from only being able to view PI to being able to consolidate comments across the EU.

For information on using the PIM Review System, see *PIM Review System: Procedures for the EMEA (Centralised Procedure)* or *PIM Review System: Procedures for the National Competent Authorities (Centralised Procedure)*, as appropriate.

Figure 5 shows an example of a dialog box in the PIM Review System.

Figure 5. Dialog box for entering an open-ended comment in the PIM Review System

Review Type	Consolidation State	Visibility
Scientific	Draft	Personal

Comment

Paediatric aspects are missing.

Save Cancel

* The term *version* refers to any version of PI exchanged between the applicant and the Agency. However, a version sent from an applicant to the Agency for review or approval is also called a *submission*.



2.3.3 PIM Data Validation Engine (PDVE)

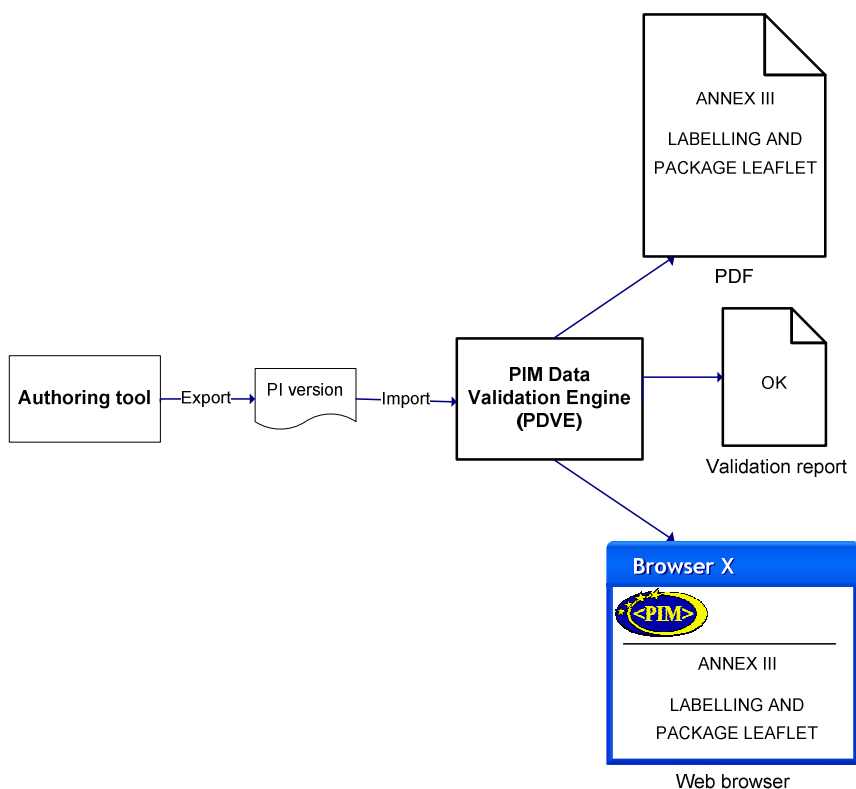
Every applicant company needs a tool that checks whether proposed submissions conform to the PIM rules. Such a tool should be used before submitting a version to the Agency. Otherwise, the applicant could waste time on sending an invalid submission and the Agency could waste time on checking and rejecting an invalid submission. The options are:

- Use the validation feature in the authoring tool, if the authoring tool has such a feature. (The LAT has a validation feature, and it is based on the validation feature used by the PRS.)
- Use the PIM Data Validation Engine (PDVE), which is a free tool from the Agency.

The PDVE performs all the functions shown in Figure 6, namely:

- **Validating a PIM submission** against the PIM data validation rules, largely based on the validation feature used in the PIM Review System
- **Generating a PDF file** containing the product information, so that the applicant can check what the Agency, NCAs, and EC will see
- **Displaying the product information in HTML format**, so that it can be viewed in a web browser

Figure 6. Features of the PIM Data Validation Engine



For submissions in a DES version before 2.7, the PDVE can work with delta submissions. (A delta submission contains only the changes since the last submission. From DES v2.7, all submissions are full submissions.)

For more information on the types of rules that the PDVE validates, see chapter 5.



2.3.4 PIM Viewer



The PIM Viewer displays a PI version in a web browser. It is *not* an authoring tool or review tool. However, it may be useful in the following situations:



- For applicants or their CROs or software vendors — if you suspect a problem with the way your own system is displaying PI, you can use the PIM Viewer for comparison with your system.
- For NCA reviewers or EMA product team staff — if the PIM Review System were unavailable, you could still look at PI in the PIM Viewer, though you would not be able to add or consolidate comments.
- For all users — if you are still learning about PIM and do not have access to an authoring tool or the PIM Review System (as appropriate) in a training environment, you can use the PIM Viewer to view the examples available on the PIM website.

Although the PIM Viewer behaves like a separate program, it's actually a collection of style sheets and related files. These files can be interpreted by recent versions of most popular web browsers as instructions for transforming a PIM file into HTML. The necessary files are automatically attached to every PI version. So you don't need to install any software on your computer. You just open a PIM file from your hard drive or a network drive, and your web browser transforms the file according to the instructions supplied by PIM, making the window look like it's specially for viewing PIM data.

Figure 7 shows an example of an applicant submission in the main page of the PIM Viewer, which shows the product structure. From this page, you can open individual documents or view the PI part of the European Public Assessment Report (EPAR).

Figure 7. Main page of an example applicant submission in the PIM Viewer

<PIM> PIM Submission (Ver. 2.7)

Application :	EMA/H/C/581	Invented Name :	PIM EX6	PIM Sequence :	0036-a
Procedure Type :	Centralised	Submission :	Initial Marketing Authorisation	Source Sequence :	0035-a (en fr de sv)
Step Day :	Day 210	Status :	-	Related Sequence :	0029-r (en fr de sv)
Applicant :	MAH-6	Agency :	EMA	eCTD Sequence :	-
ATC Code :	J05A F30	INN :	Abacavir Lamivudine	Product ID :	-
Description :	Reformat: conversion from Ms Word to PIM (EMA/H/C/581) PIM DES 2.7 Example 6 v0.1				
Additional Information to Labelling:			Alert Card		

Provided languages: **en** | fr | de | sv EPAR

Product	Form	Strength	Presentation
PIM EX6 	Film-coated tablets 	600mg/300mg 	Blister
			Bottle

PIM style sheet version 2.7.5 **Review format** | Pretty format (for copy/paste to Ms Word)

For instructions on how to use the PIM Viewer to view either real PI versions or the examples, along with a description of what is in the examples and a list of supported web browsers, see Appendix A.



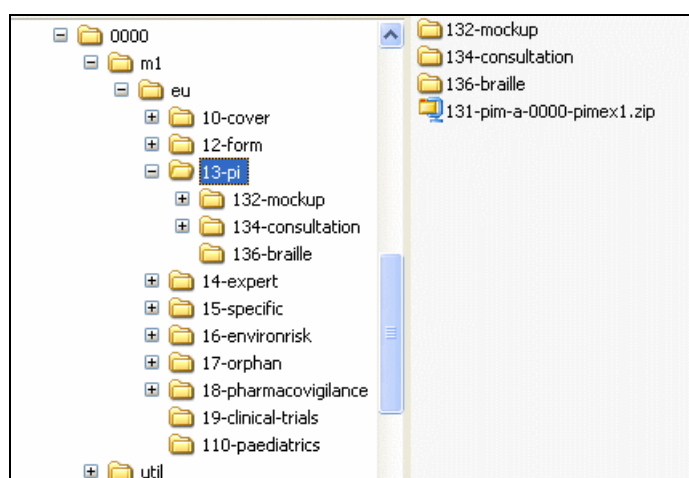
2.4 Interaction with other Products – eCTD

A PIM submission is provided as an archive file (compressed file), in either the ZIP format or the TGZ format. This file is created by the applicant's authoring tool when they "export" a version, and it may be provided either inside an eCTD¹ submission or outside the eCTD.

2.4.1 PIM Submission inside the eCTD

When product information is submitted as part of the eCTD, it forms part of the EU Module 1. The PIM archive file is placed in the 13-pi folder. This file replaces the whole of the 131-spclabelpl folder (which would contain many PDF files in a non-PIM submission). Folders 132-mockup to 136-braille are the same as in non-PIM submissions. See Figure 8 for illustration. In this figure, the archive file is called 131-pim-a-0000-pimex1.zip.

Figure 8. A PIM submission within the eCTD²



The "0000" in the PIM file name is a sequence number. eCTD also uses a 4-digit sequence number, in the root folder name. So the a-0000 PIM submission might be in the 0000 eCTD submission. However, eCTD and PIM sequence numbers do *not* remain synchronised. One reason is that PIM is based on a 2-way exchange of information, whereas eCTD works in one direction only, from applicant to regulator. So a regulator version sent by the Agency will always be outside the eCTD. Also, changes to PI are exchanged more frequently than eCTDs.

2.4.2 PIM Submission outside the eCTD

When product information is submitted outside the eCTD, the PIM archive file (ZIP or TGZ) is submitted as an independent PIM submission but is still loaded into the PRS. The reviewers access the rest of the dossier via the eCTD review system as normal (or from a network drive if an eCTD review system is not yet operational).

¹ eCTD is the electronic version of the Common Technical Document (CTD) standard from the ICH. For details, visit <http://estri.ich.org/eCTD/index.htm>.

² Folder 135-approved is always present in an eCTD submission but isn't used in the Centralised Procedure so will be empty.



2.5 Interaction with other Products – QRD Templates

The DES is modelled on the QRD templates, i.e. the DES corresponds to the QRD templates in terms of the format, presence, and location of elements. Consequently, PI is presented to reviewers in a familiar format.

2.5.1 Compliance with the QRD Templates

Although the DES enforces compliance with the overall structure and layout of product information specified in the QRD templates, it does not enforce compliance with the detailed guidance in the templates. Applicants are still responsible for ensuring that submissions comply with the detailed guidance in the annotated QRD templates and other relevant guidelines, such as the guidelines on readability and SmPCs.

For example, any DES-based authoring tool will ensure that all package leaflets contain section 4 and that the heading for the section is *POSSIBLE SIDE EFFECTS*. Furthermore, it will automatically include the standard statements at the beginning and end of this section, even substituting the invented name for the “X” in the QRD template. But it cannot enforce the detailed QRD guidance on section 4 (shown in Figure 9); the PIM software cannot know how urgent the necessary actions are.

Figure 9. Extract from QRD annotated template (EN), version 7.2

4. POSSIBLE SIDE EFFECTS

[Description of side effects.]

[Begin this section with:]

Like all medicines, X can cause side effects, although not everybody gets them.

[Describe, if necessary, the actions to be taken. If the patient needs to seek help urgently, the use of the term <immediately> is recommended; for less urgent conditions, <as soon as possible> can be used.]

[Close this section with:]

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your <doctor> <or> <pharmacist>.

2.5.2 Upgrades to the QRD Templates

The DES is upgraded whenever the QRD templates change. This makes it easier for applicants to apply new QRD template standards to existing PI. The effort required by applicants depends on the type of changes in the new templates, as follows.

- If sections are simply reordered within a QRD template, there will be a new style sheet with the revised ordering, so there is no need for the applicant to provide any updated documents.
- If a new section is introduced, the applicant only has to provide one block of text for that new section, rather than adding the same section to several different Word documents.

Note: New releases of the DES require an upgrade to authoring tools and the PIM Review System. Submissions based on older versions will be accepted for some time after a new release of the DES, just as Word submissions based on older versions of the QRD templates are accepted for a while. Authoring tools should support multiple versions of the DES simultaneously, so that the PI for some products can be based on one version of the QRD templates while the PI for other products is based on a different version. Thus, applicants can decide when to convert the PI for a particular product, if conversion is necessary. For further guidance on this, see *PIM Guidance for Applicants (Centralised Procedure)*.

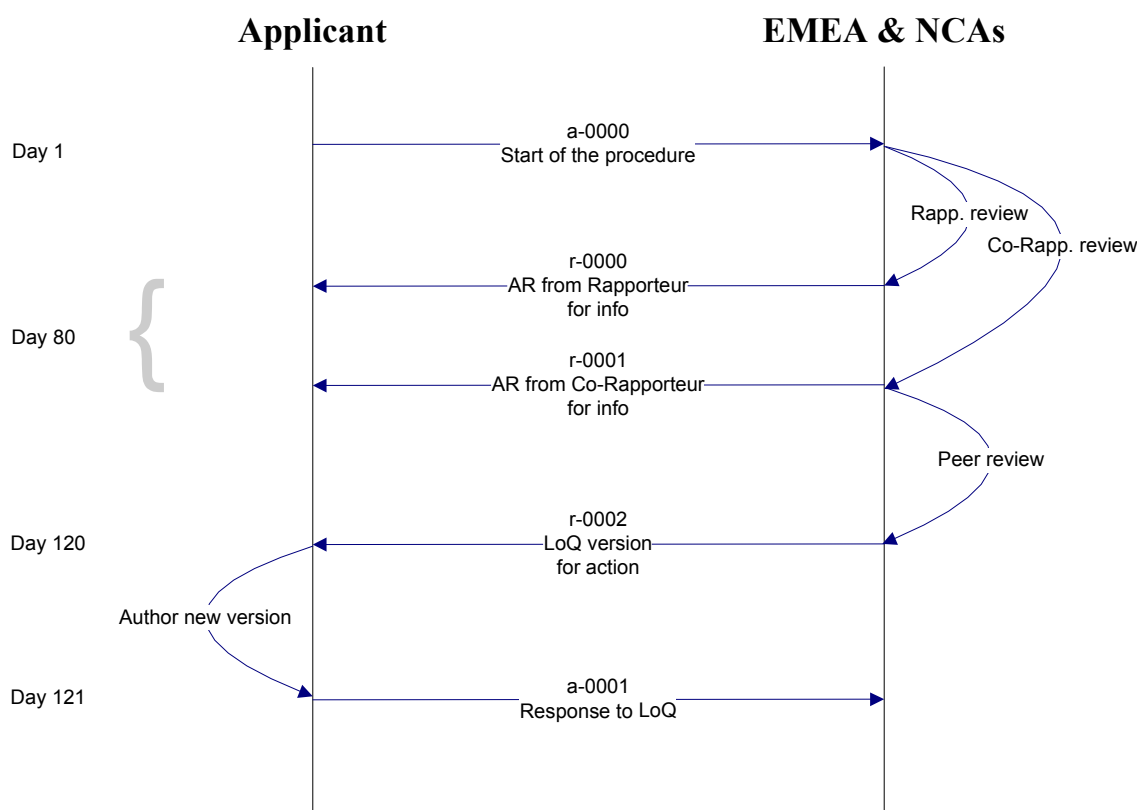


2.6 Dynamic Properties – Lifecycle Management

PIM not only structures and stores the information for a product at a given point in time, it also supports regulatory activities during the evaluation of an initial marketing authorisation application (MAA) and any subsequent changes during the life of the product (variations, notifications, annual reassessments, renewals, and so on).

PIM is based on a 2-way exchange of PI versions. Each version is labelled with a sequence ID. Figure 10 shows a typical scenario for exchanges from Day 1 to Day 121 of an initial MAA. This shows that there are two sets of sequence numbers, one for each side (starting in “-a” for applicant versions and “-r” for regulator versions³). It also shows that there can be multiple versions from one side before the next version from the other side.

Figure 10. Sequences of PIM exchanges



Note that Figure 10 is just one possible scenario. The sequence number on a given day will not be the same in every application, for various reasons. For example, the Day 1 submission for the first post-authorisation procedure for a product continues the sequence numbering used in the initial MAA for the same product.

The sequence IDs are more than just labels; **the sequence IDs relate one version to another**. In the example in Figure 10, there is an indication inside r-0000 that it is a response to a-0000.

A version also contains information on the changes to PI since the last version. Changes in a regulator version are in the form of comments on the PI. Changes in an applicant version usually consist of the implementation of comments made in the previous regulator version. PIM keeps track of the changes and can match applicant responses to regulator comments during the exchange of versions.

³ For submissions in a DES version before v2.7, the “a” or “r” comes after the sequence number, e.g. 0000-a.



2.7 Differences from Other Products – Microsoft Word

If you are used to using Microsoft Word for exchanging product information, be aware of the following differences when you start using PIM.

Table 1. Differences between the Word-based process and the PIM process

Characteristic	Word	PIM
Structure of PI	PI consists of a set of documents.	PI consists of pieces of text, which are automatically compiled into documents.
Number of files for translations	Each language is in a separate file.	All languages are in the same PI version (though a QRD member can just review their own language).
Track changes	The applicant controls what text is highlighted as changed.	The PIM Review System controls what text is highlighted as changed.
Conflicting comments from NCAs	Conflicting comments could be left in a regulator version for CHMP review and could be sent to the applicant.	Conflicting comments must be resolved before a regulator version is created.



2.8 Contraindications

PIM cannot be used for mock-ups or specimens. Mock-ups are still required in the main submission as paper and possibly additionally as a PDF. Specimens are still to be supplied as physical examples of the packaging items.

PIM cannot be used for Annex A (the table of all authorised presentations) or, if applicable, Annex IV (conditions and restrictions with regard to safe and effective use). These are still handled as Word files outside PIM.

3 Product Information

This chapter describes the organisation of product information within a PI version.



3.1 The Organisation of a PI Version

The information within a PI version is organised into the following parts:

- The envelope — information about the application
- A hierarchical structure — a way of organising (1) the forms, strengths, presentations, and labelling of a product, and (2) the elements of product information
- Fragments — pieces of product information
- List of documents — a list of documents to be created and what forms / strengths / presentations they apply to

PIM combines this information with its own information, such as section headings, to create documents.

The rest of this chapter describes each part of the user-supplied information and the PIM-supplied information in more detail.



3.2 The Envelope

The envelope contains information about the application, which enables an authoring tool and the PIM Review System to exchange files and manage versions correctly. Examples of envelope elements are:

- PIM sequence ID
- Applicant name
- Agency name (always “European Medicines Agency” while PIM supports only the Centralised Procedure)
- Invented name of the product
- International Non-proprietary Name (INN)
- ATC (Anatomical Therapeutic Chemical) code
- Application type (e.g. initial MAA)
- Procedure step day (e.g. 121)
- Status (Under Review, Positive Opinion, Negative Opinion, Approved, etc.)

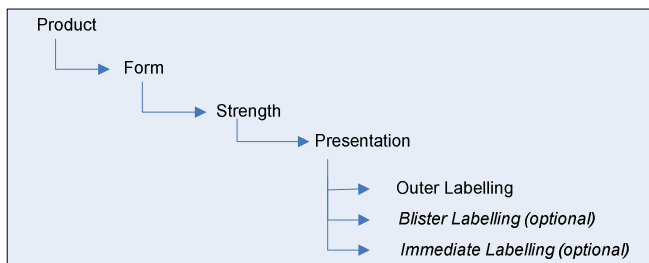
Most elements of the envelope are entered initially by the applicant using the authoring tool, e.g. invented name, ATC code. Some elements are entered by the Agency using the PIM Review System, e.g. the status. Some elements are generated automatically, e.g. the sequence numbers.



3.3 Product Structure, Elements, and Fragments

Products can be viewed as having a hierarchical structure, as shown in Figure 11. This represents the fact that a product has one or more pharmaceutical forms, a form has one or more strengths, and so on.

Figure 11. The hierarchical structure of product information

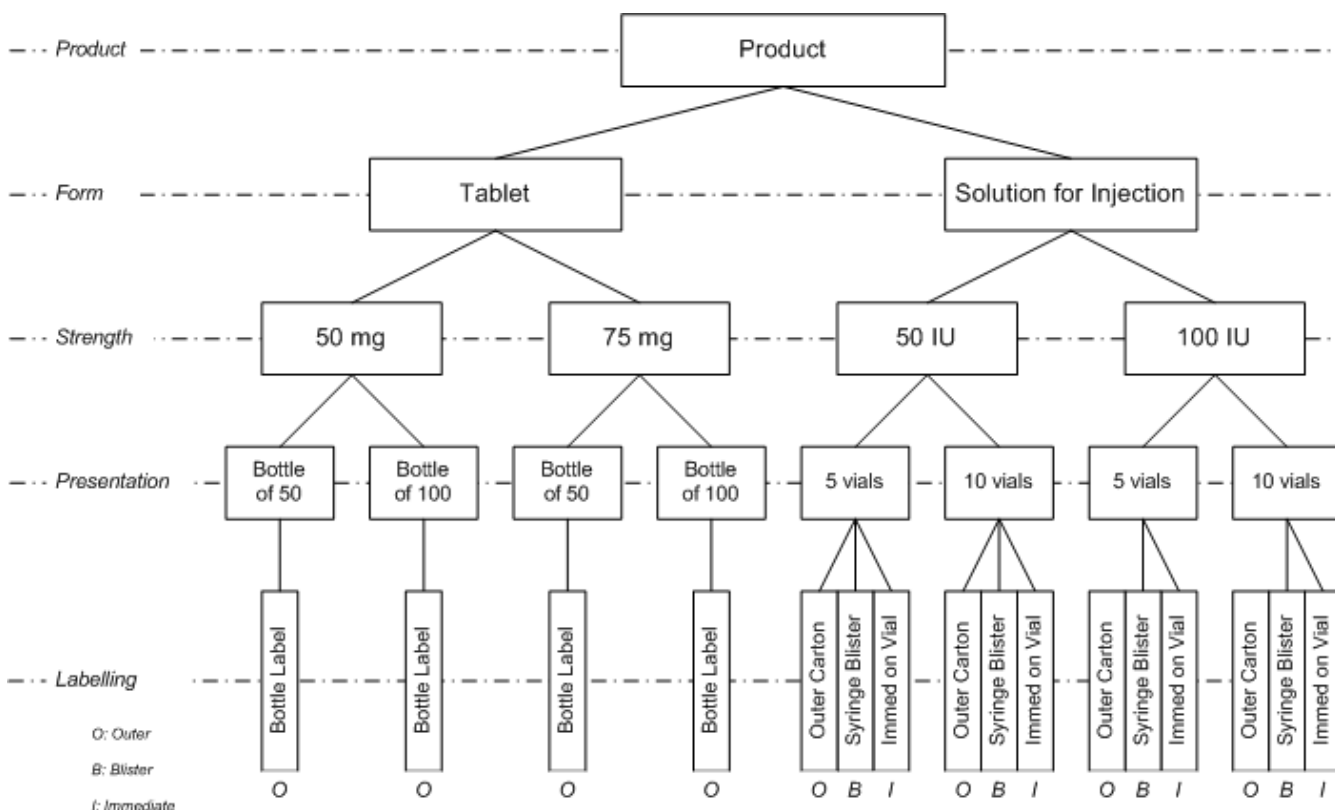


3.3.1 Product Structure

Because products have a hierarchical structure, PIM also represents products in a hierarchical structure, which conforms to the following rules:

- A PI version relates to one product.
- A product has one or more forms.
- A form has one or more strengths.
- A strength has one or more presentations.
- A presentation has one or more outer labelling documents.
- A presentation has zero, one or more blister labelling documents.
- A presentation has zero, one or more immediate labelling documents.

Figure 12. The hierarchical structure used in PIM



An example of the hierarchical structure that PIM uses is shown in Figure 12. In this example, the product has two forms. Each form has two strengths. Each strength has two presentations. Each presentation has outer labelling, and some presentations have blister and immediate labelling.



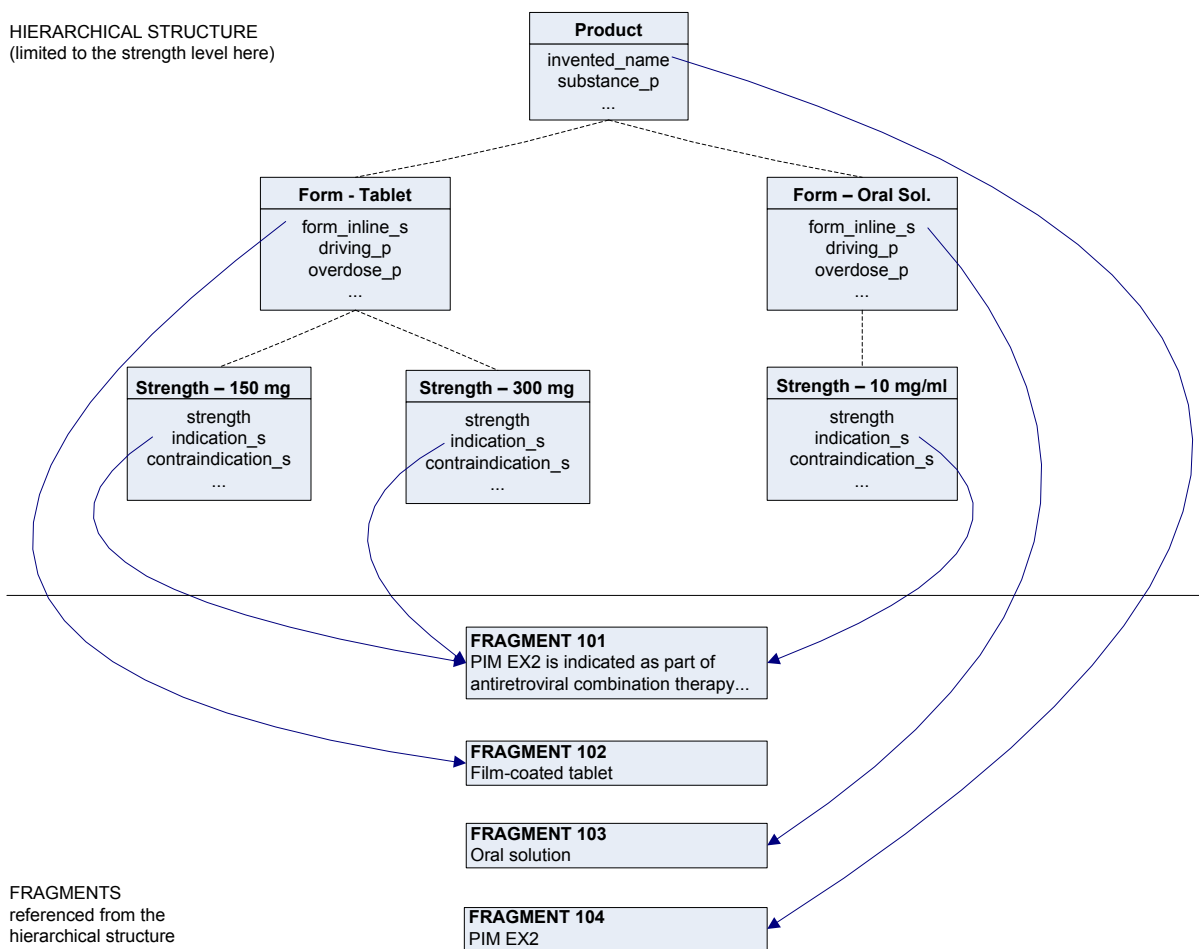
3.3.2 Elements and Fragments

The guiding principle of PIM is to hold any piece of information only once and allow its use as many times as necessary to create the required documents. What enables the reuse of information is a combination of:

- The use of predefined elements of PI, *held in* the hierarchical structure
- The use of fragments to contain the information for the elements, *referenced from* the hierarchical structure

Figure 13 represents an extract of the information held in PIM for a product with two forms, in which one form has two strengths and the other form has one strength. The indications are the same for all three strengths. The element for therapeutic indications in the SmPC is called `indication_s` and is held at strength level. The text for this element has been entered in Fragment 101. This text will automatically be included in section 4.1 of the SmPC for all three strengths. And if the applicant needs to change this text, they change it only in Fragment 101 and it is automatically updated in all the SmPCs. Likewise, if a reviewer needs to comment on this text, they only have to make the comment in one place.

Figure 13. Product structure, elements, and fragments



3.3.2.1 Element Names

You don't have to remember the names of the elements. Authoring tools show applicants what elements need to be supplied and display them in the context of the documents that will ultimately be created. Also, some authoring tools use instructional text to indicate what needs to be entered into a particular area. And the PIM Review System *doesn't* require regulators to know element names.

Nonetheless, if you see an element name (perhaps in an error message), it's often easy to guess the purpose from the name. For example, you can guess what information goes in the element called `invented_name`. If similar information is normally phrased differently in different types of documents, there are different elements for it, and the suffix indicates the type of document. For example:

This element...	Is for indications as expressed in...	as in this example text...
<code>indication_s</code>	SmPCs	Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy...
<code>indication_p</code>	Package leaflets	PIM EX3 is used ALONG WITH OTHER MEDICINES to prevent nausea and vomiting caused by chemotherapy treatment...

Here is the complete list of suffixes for elements that depend on the document type:

<code>_s</code>	S mPC
<code>_o</code>	O uter labelling
<code>_b</code>	B lister labelling
<code>_i</code>	I mmEDIATE labelling
<code>_p</code>	P ackage leaflet

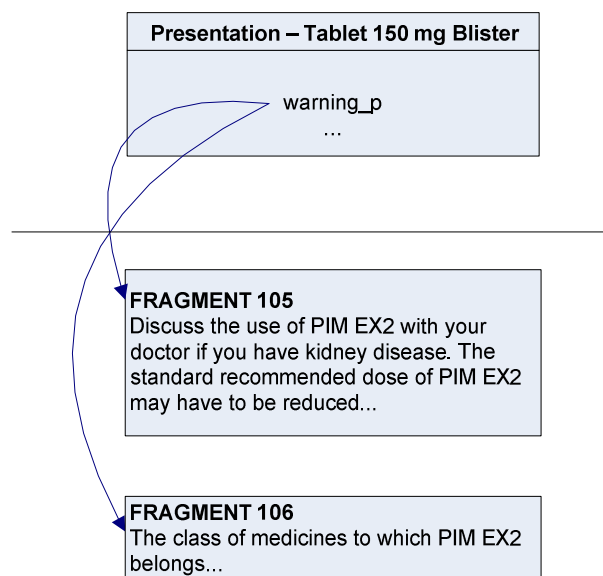
If the phrasing of a piece of product information *doesn't* vary depending on the types of documents it appears in, there is no suffix in the element name, e.g. `invented_name`, `manufacturer`.



3.3.3 Fragments and Paragraphs



In the example given in Figure 13, there is only one fragment per element; the fragment for the element `indication_s` is Fragment 101. For short pieces of information, this is appropriate. But some elements typically contain several paragraphs or even several pages of information e.g. the "Before you Take" section of the package leaflet or the "Pharmacodynamic Properties" section of the SmPC. For such elements, the applicant can split the text into several fragments, as shown in Figure 14.

Figure 14. Multiple fragments for one element

Splitting the text for an element into multiple fragments offers the following benefits:

- It increases the opportunities for reuse. If it is appropriate to reuse just one paragraph of an element elsewhere, this can be done if the paragraph is in a separate fragment.
- It makes it easier for the applicant to manage the information during the life of the product. For example, if just one paragraph in a section changes in a future version, only that paragraph is marked for re-translation.
- It makes it easier for the regulators to avoid making apparently conflicting comments.

So applicants typically use one fragment per paragraph (or list or table or other piece of information).

Note: For applicants, the policy on splitting text across fragments is very important. The policy should be decided before starting to create the PI for a new product or migrating existing PI from Word into PIM. For further guidance, see *PIM Guidance for Applicants (Centralised Procedure)*.



3.3.4 Reuse by Design and Reuse by Choice

Every element is associated with a certain level of the hierarchical product structure. These associations are based on an analysis of PI for many existing products and are designed to enable reuse of information. There are also opportunities to reuse information by choice.

3.3.4.1 Reuse by Design

An element located at a high level in the hierarchical structure applies to all the lower levels. For example, the ATC code is always exactly the same for all strengths. Therefore, the `atc_code` element is located at the highest level, the product level. This means that the applicant enters it once and PIM applies it to section 5.1 of all SPCs. This is an example of reuse by design. PIM knows that the preclinical safety data applies to the whole product, so it automatically reuses the information across the product.

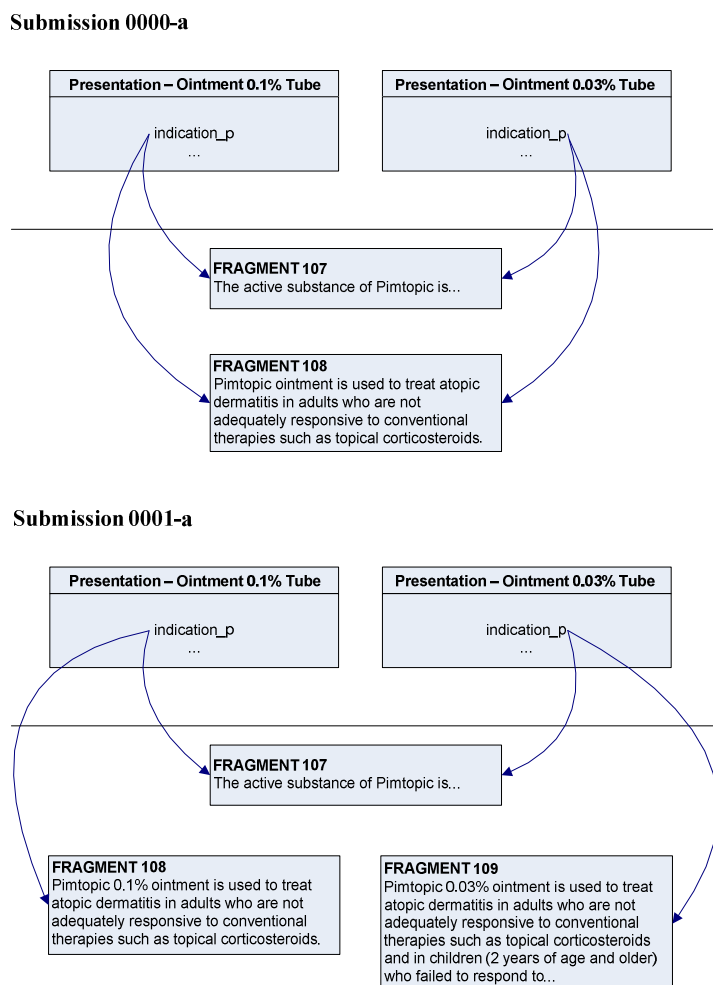
3.3.4.2 Reuse by Choice

The reuse of text for indications illustrated in Figure 13 is an example of reuse by choice. The text for indications is often the same for all strengths, so the applicant will usually choose to reuse the same fragment.

Reuse by choice provides more flexibility for applicants in situations where reuse by design does not apply. Some elements are located at a lower level than you might expect. For example, storage warnings normally depend on the form and thus are usually the same for all presentations of a given form. Therefore, you might expect the element `storage_s` to be located at the form level. In fact, it is located at the presentation level because the storage warnings for some products depend on the pack size. However, if the storage warnings are in fact the same for all presentations of a product, the applicant can reuse the text.

Reuse does not limit the freedom to change text. Figure 15 shows a change made as a result of a regulator comment on the first version. In the first version, the same fragments are used for the indications for both the 0.03% ointment and the 0.1% ointment (Fragments 107 and 108). In the second version, the regulator has asked for different text for the second fragment. This means that Fragment 108 needs to diverge across presentations. So the applicant has retained Fragment 108 for one presentation and has created a new fragment (109) for the other one.

Figure 15. Change of fragment usage across submissions





3.4 Documents

How does PIM know how many documents of each type are to be created from the fragments and what strengths / forms / presentations / labelling they apply to? Applicants' authoring tools let them define the documents as part of a 3-step process, namely:

1. Define the structure of the PI version, i.e. the forms, strengths, presentations, and labelling.
2. Define the documents. For each document, the applicant indicates:
 - The type of document (SmPC, Annex II, outer labelling, blister labelling, immediate labelling, package leaflet)
 - The places in the product structure to which the document applies (combined documents being created by selecting more than one place in the structure).
 - The order of documents in the EPAR
3. Define the order of documents in the EPAR, if the applicant wants to override the default order.

Once the documents have been defined, the following things can happen:

- **Placeholders for the elements** in each document can be created by the authoring tool. (For more information, see section 3.4.3).
- **Fragments** can be created by the PI authors and assigned to elements in documents, with fragments being reused across documents as appropriate (as described in section 3.3.2).
- **Section headings** can be created by the authoring tool in each document. (For more information, see section 3.4.4.)
- **Standard statements** can be put in the relevant sections of the document by the authoring tool. (For more information, see section 3.4.5.)
- **Page layout and text formatting** can be set. (For more information, see section 3.4.6.)
- After the version is submitted to the Agency, the **documents for review** can be compiled by the PIM Review System.
- After the opinion, **preparation for translation** can be done. (For more information, see section 3.5.)

3.4.1 Document Levels

Documents can be created at different levels, as shown in Table 2. The decision on exactly where to have documents created depends on the applicant's knowledge of the product and the rules for combining documents. For more details on combined documents, see section 3.4.2.

Table 2. Default and allowed levels for PI documents

	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		
Additional Information (e.g. Alert Card)	Default				

The placement of documents at different levels is best understood by looking at an example. Figure 16 shows an example of a product structure in the Light Authoring Tool, and Figure 17 shows where documents have been placed. This product has one form, hard capsules. There are two strengths. Both strengths have a 1-capsule presentation and a 5-capsule presentation. The 80 mg strength additionally has a trifold pack. Each of the capsule presentations needs an outer label and a blister label. The trifold pack needs an outer label and an immediate label.

Figure 16. Definition of product structure (in the Light Authoring Tool)

Form	Strength	Presentation	labelling	
Hard Capsules	125mg	1 Capsule	level_outer: Outer for 1 Capsule level_blister: Blister	
		5 Capsules	level_outer: Outer for 5 Capsules level_blister: Blister	
		80mg	1 Capsule	level_outer: Outer for 1 Capsule level_blister: Blister
		5 Capsules		level_outer: Outer for 5 Capsules level_blister: Blister
		Trifold Pack		level_outer: Outer for Trifold Pack level_immed: Immed for Trifold Pack content: product

Figure 17. Placement of documents in the product structure (in the Light Authoring Tool)

Form	Strength	Presentation	labelling
Hard capsules	125 mg	1 Capsule	level_outer: Outer for 1 capsule level_blister: Blister
		5 Capsules	level_outer: Outer for 5 capsules level_blister: Blister
	80 mg	1 Capsule	level_outer: Outer for 1 Capsule level_blister: Blister
		5 Capsules	level_outer: Outer for 5 capsules level_blister: Blister
		Trifold pack	level_outer: Outer for trifold pack level_immed: Immed for trifold pack

In this example, there is one package leaflet for all strengths and presentations, so it is at the form level. There is a separate SmPC for each strength, so the SmPCs are at strength level. For the 125 mg strength, all the labelling is common to all presentations, so it is at strength level — and likewise for the outer labelling for the 80 mg strength. In contrast, the blister label for the 1-capsule pack and the 5-capsule pack and the immediate label for the trifold pack are at labelling levels. (They could alternatively be at the presentation level but would be placed at labelling levels if a need is foreseen to add more labelling with different content later; see the following notes.)


Notes:

1. There is a difference between a *labelling document* and a *labelling level*. Labelling documents are simply the outer, blister, and immediate labels. Labelling documents do not have to be at labelling level. Indeed, they are often at the presentation level.

The labelling levels are needed for situations where there are more levels of labelling than usual. For example, if the immediate packaging is large and therefore has room for all the information normally only put on the outer labelling, the applicant might be advised by the Agency to put an *outer labelling document* on the *immediate packaging*. As another example, a product needs more than one outer label if it is presented within a series of containers; if there is a box containing several foil pouches, each containing several syringes, the product needs outer labels for the box and the pouch and an inner label for the syringe.














2. The PIM Viewer doesn't show the labelling levels; any documents created at the labelling level are displayed at the presentation level. Figure 18 shows PIM EX2 in the PIM Viewer, with no labelling level in sight (though the labelling really is at the presentation level in this product).

Figure 18. Placement of documents in PIM Example 2 (in the PIM Viewer)


PIM Submission (Ver. 2.7)

Application :	EMEA/H/C/107	Invented Name :	PIM EX2	PIM Sequence :	0032-a
Procedure Type :	Centralised	Submission :	Initial Marketing Authorisation	Source Sequence :	0031-a (en)
Step Day :	Day 210	Status :	-	Related Sequence :	0029-r (en)
Applicant :	MAH-2	Agency :	EMA	eCTD Sequence :	-
ATC Code :	J05A F05	INN :	Lamivudine	Product ID :	-
Description :	Reformat: conversion from Ms Word to PIM (EMA/H/C/107) PIM DES 2.7 Example 2 v0.1				
Comments :	qrd : Define term HIV qrd(fr) : VIH in French				

Provided languages: **en**
EPAR

Product	Form	Strength	Presentation
PIM Example 2 	Tablet 	150 mg 	Blister 
		300 mg 	Bottle 
		300 mg 	Blister 
		10 mg/ml 	Bottle 
	Oral Solution 	10 mg/ml 	Bottle 

PIM style sheet version 2.7.5
Review format | Pretty format (for copy/paste to Ms Word)

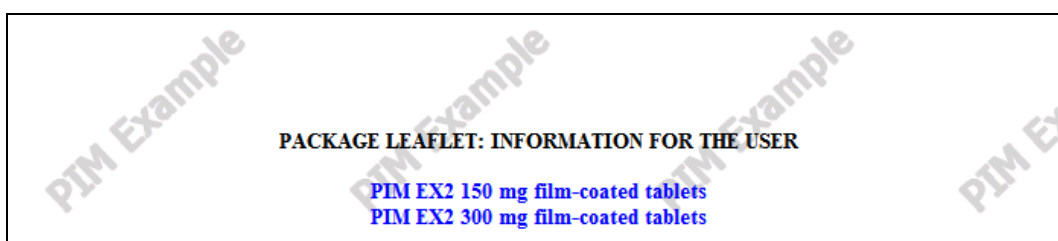
3.4.2 Combined Documents

Like non-PIM submissions, PIM submissions can include combined documents. This section describes different types of combined documents and limitations on combining.

3.4.2.1 Simple Combination

If a document simply combines items from a lower level in the product structure, the PIM system will find any elements that need to be repeated and display them one after the other. For example, Figure 19 shows an extract of the leaflet in PIM EX2 at form level for both strengths of the tablet; here, the elements for the invented name, strength, and form are repeated.

Figure 19. Simple combined package leaflet



3.4.2.2 Special Combination

PIM lets applicants combine documents without following the product structure. For example, it might make sense to have a package leaflet for two out of three strengths at form level and another package leaflet for the third strength at strength level.

3.4.2.3 Limitations to Combined Documents

The following list shows the types of combined documents supported by PIM. For completeness, non-combined documents are also shown.

- SmPC
 - At strength level, referring to one strength
 - At strength level, referring to many presentations of the same strength
- Annex II
 - At product level, referring to the whole product
- Outer labelling (there are corresponding rules for blister and immediate labelling)
 - At strength level, referring to one strength
 - At strength level, referring to many presentations of the same strength
 - At strength level, referring to many outer labelling levels for the same strength
 - At presentation level, referring to one presentation
 - At presentation level, referring to many outer labelling levels
 - At labelling level, referring to one outer labelling level
- Package leaflet
 - At form level, referring to one form
 - At form level, referring to many strengths
 - At strength level, referring to one strength
 - At strength level, referring to many presentations

Notes:

1. The fact that a combination is supported by PIM doesn't necessarily mean that it is allowed by the Agency. If an applicant is unsure whether a proposed combination would be allowed for a particular product, the applicant should ask the Agency at the pre-submission stage.
2. Successful creation of combined documents relies on applicants "balancing" the fragments. For example, if a package leaflet is at form level and a given element for one strength of the form has three fragments, the same element for the other strengths must also have three fragments. For further information, see *PIM Guidance for Applicants (Centralised Procedure)*.

3.4.3 Placeholders for Elements

Once a document has been defined, the authoring tool will provide a view of the document with placeholders for the elements relevant to the document type. The PI author can then write fragments and associate the fragments with the elements of the document. If appropriate, the author can reuse fragments written for other documents (usually the same elements of other documents).

Some elements are mandatory, whereas others are optional. For example, the `contraindication_s` element is mandatory but the `dosimetry_s` element is optional.

Some elements can be used only once, whereas others can be repeated. For example, the element for the manufacturer of the active substance, `manufacturer_active`, can be repeated in Annex II because there can be more than one manufacturer.

Note: Do not confuse the concept of repeating elements with the concept of associating multiple fragments with a single element. For most elements of PI, you will have a single element comprising several fragments (where a fragment usually contains a paragraph).

You don't have to remember which elements are mandatory and which ones are repeatable. Authoring tools should prompt applicants to supply fragments for mandatory elements and prevent attempts to repeat non-repeatable elements. The PDVE and the PIM Review System will catch anything that has slipped through the net.

3.4.4 Section Headings

PIM applications (authoring tools and the PIM Review System) automatically include section headings at the correct location in relevant documents. These headings are the same as in the QRD templates.

Wherever a heading in the QRD template contains an "X", PIM automatically substitutes the invented name. So, in the package leaflet for PIM Example 6, the heading *What X is and what it is used for* automatically becomes *What PIM EX6 is and what it is used for*.

PIM also automatically chooses among variant forms of section headings as appropriate. For example, if there is only one manufacturer, PIM uses the singular form of the relevant heading in Annex II (*Manufacturer of the Biological Active Substance...*). If there is more than one manufacturer, PIM uses the plural form (*Manufacturers of ...*). As another example, PIM chooses between the verbs "take" and "use" in the subheading *Read all of this leaflet carefully before you start <taking> <using> this medicine*. The choice of "take" or "use" in this and other headings in the package leaflet is based on the mode of administration.

Applicants can customise the text (but not the format) of headings used in the package leaflet. For example, the verbs "take" or "use" can be replaced by "inject" if appropriate to the mode of administration. Or a heading can be customised in response to the results of user testing on the readability of the leaflet.

Note: Applicants still have to justify the use of alternative headings, in accordance with the guidance in the annotated QRD templates.

3.4.5 Standard Statements

Some standard statements from the QRD templates are automatically included at the correct location in relevant documents, when applicable.

Some standard statements are included in all versions. For example, section 2 of an SmPC always ends with the following statement:

For a full list of excipients, see section 6.1.

Some standard statements are needed only in certain conditions. For example, if the applicant indicates that a product is an orphan, the following statement is automatically included at the end of the leaflet.

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu/>. There are also links to other websites about rare diseases and treatments.

Some standard statements only become necessary at later steps of a procedure. For example, if a product gets approved under exceptional circumstances due to the rarity of the disease, the following statement is automatically included in section 5.1 of the SmPC and in the package leaflet.

This medicinal product has been authorised under "Exceptional Circumstances". This means that due to the rarity of the disease...

Applicants can customise the text and the format of standard statements used in the package leaflet.

Note: Applicants still have to justify the use of alternative statements, in accordance with the guidance in the annotated QRD templates.

3.4.6 Page Layout and Text Formatting

The page layout and text formatting of documents is controlled by style sheets. This means that margins and fonts and other aspects of the overall appearance of documents are automatically set whenever a PIM application creates a document.

Obviously, applicants sometimes need to format content within a fragment in a specific way, such as underlining a word, superscripting a number, tabulating text, inserting an image, or inserting a special symbol. Also, an applicant might want to specify that one fragment should be kept on the same page as the next one to prevent an inappropriate page break. Occasionally, reviewers may also want to format the replacement text in a comment.

Consequently, authoring tools and the PIM Review System have features that let applicants and reviewers apply specific formatting to selected text. Use these features in preference to entering HTML tags.

Note: Inside a PI version, PIM uses HTML (XHTML, to be precise) to apply the formatting attributes selected in an authoring or review tool. Some PIM applications have a feature that lets you edit the HTML tags directly. Use this feature only if advised to do so by your software supplier's technical support staff or by the PIM support staff. Uncontrolled use of HTML can cause a version to fail the validation process.

3.5 Multilingualism



PIM supports all the EU languages as well as Icelandic and Norwegian. The names of languages are abbreviated on screen using the ISO codes, as follows.

bg	Bulgarian
cs	Czech
da	Danish
de	German
el	Greek
en	English
es	Spanish
et	Estonian
fi	Finnish
fr	French
hu	Hungarian
is	Icelandic
it	Italian
lt	Lithuanian
lv	Latvian
mt	Maltese
nl	Dutch
no	Norwegian
pl	Polish
pt	Portuguese
ro	Romanian
sk	Slovak
sl	Slovenian
sv	Swedish



3.5.1 Reuse of Fragments in Translated PI

After a positive opinion for an initial MAA, the applicant translates the text in the opinion version. This text is either written in the authoring tool or imported into the authoring tool, depending on the authoring tool and translation tool in use. The new version will contain fragments in each language corresponding to the English fragments.

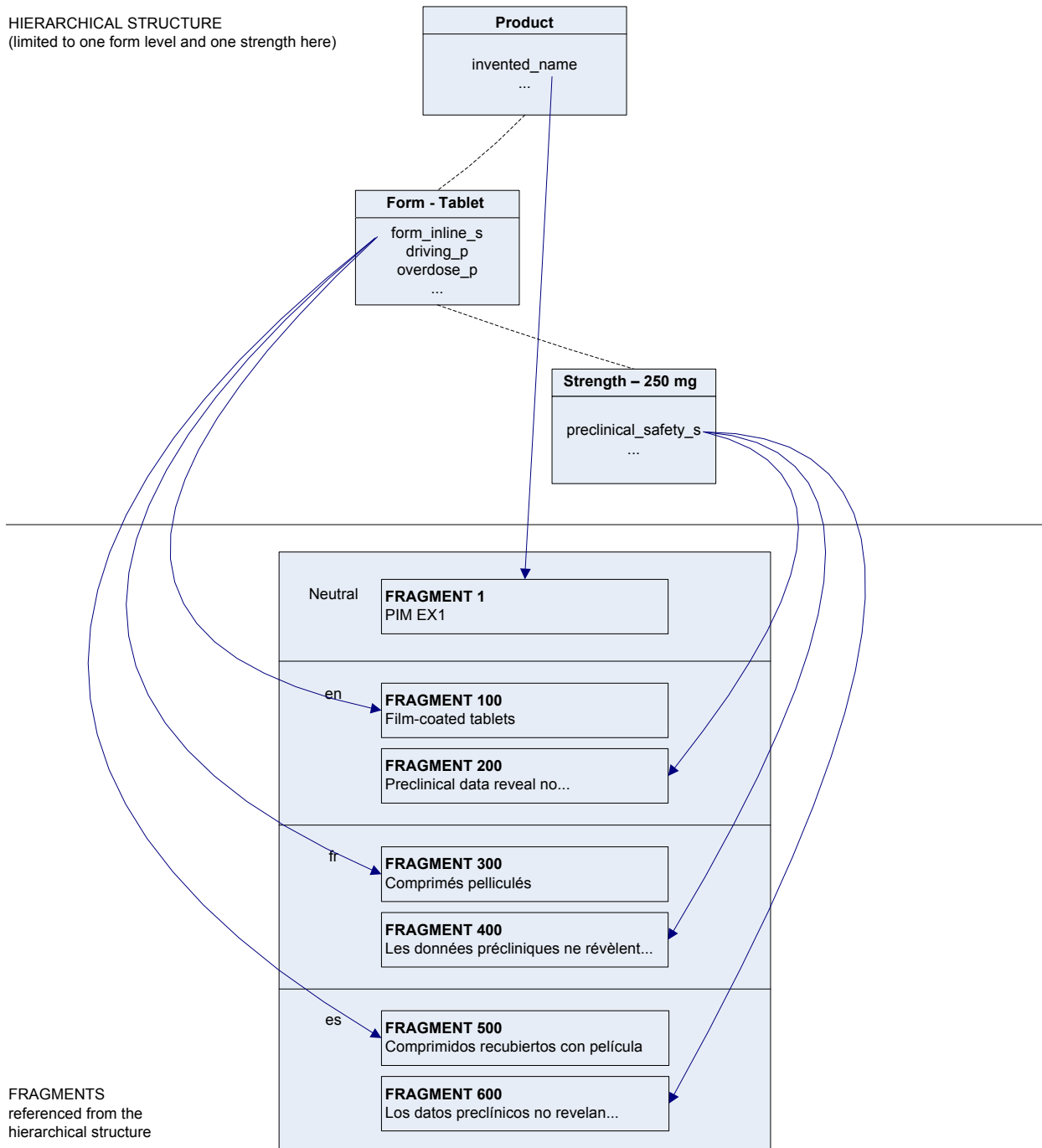
Therefore, fragment reuse in translated PI occurs in the same way as in the English PI, as shown in Figure 20. For example, if a correction is needed to the French translation of the preclinical safety information, the applicant changes it only in fragment 400 and it is automatically updated in all the French SmPCs. Similarly, if the English text for the preclinical safety information (in Fragment 200) is changed in a subsequent variation procedure, the French translator can be notified that Fragment 400 has to be re-translated.

Another thing illustrated by Figure 20 is that one PI version normally holds all the translations.

Note that, in some post-authorisation procedures, the translations are not updated until after the opinion. Therefore, if the translations are present in a pre-opinion submission for such a procedure, they may not match the revised English text.

Figure 20. Extract from a version after the creation of multilingual fragments

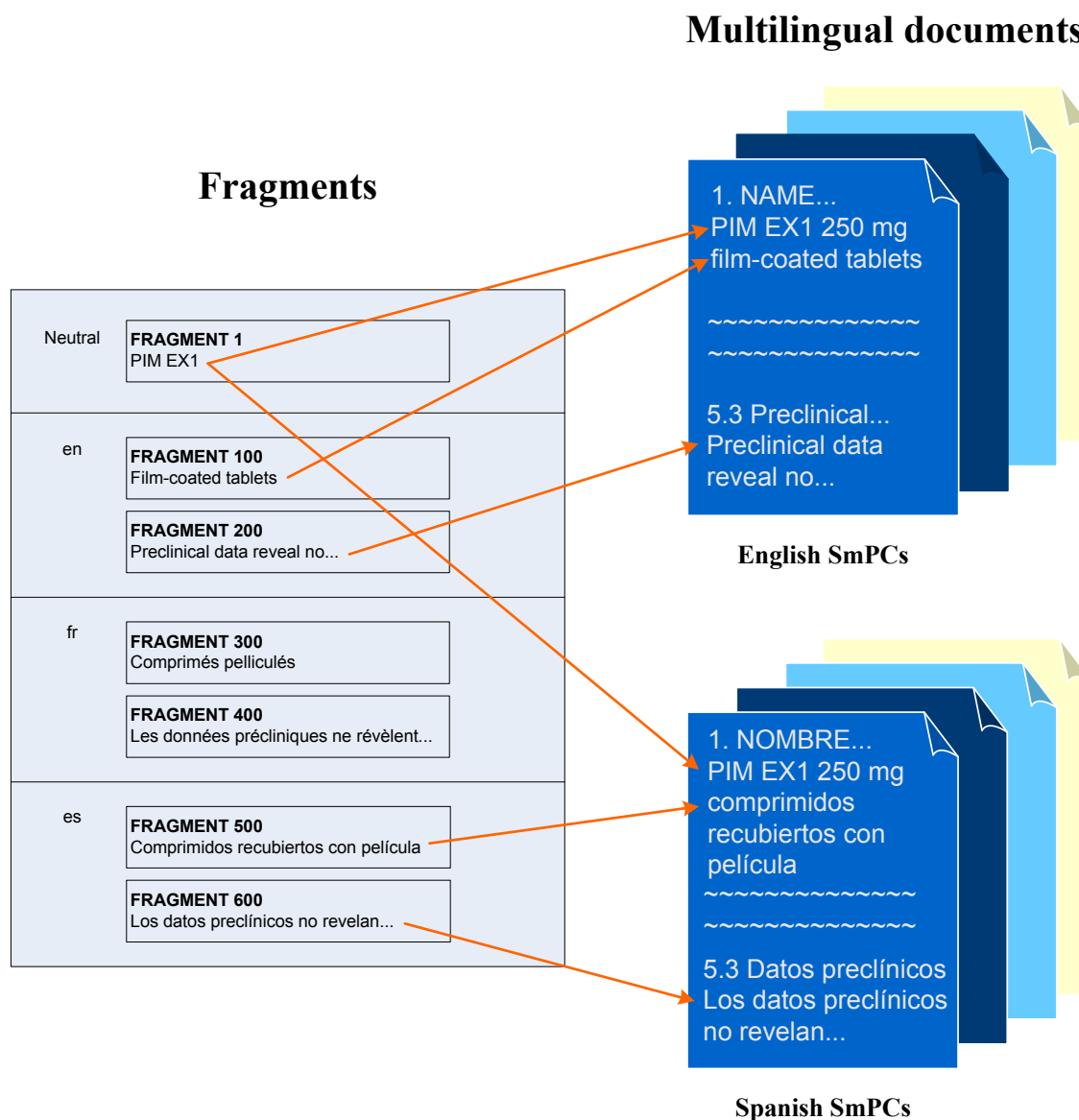
HIERARCHICAL STRUCTURE
(limited to one form level and one strength here)



3.5.2 Reuse of Fragments across Languages

Some elements contain fragments which are the same in all languages. For example, the following elements are usually the same in all languages: the invented name, code, and the list of contact details for local representatives. Language-neutral information is held in a neutral zone and shared across documents in all languages, as shown in Figure 21.

So, if there is a variation which includes the appointment of a new local representative, the MAH only changes a single list of representatives. This updated list is then automatically included in all package leaflets in all languages.

Figure 21. Sharing neutral text across languages

3.5.3 Translation of Section Headings and Standard Statements

When PIM applications create documents, they automatically include the translations of the section headings and standard statements.

As with the English headings, PIM also automatically substitutes the invented name into the translated headings. So, in the German package leaflet for PIM Example 6, the heading *Was ist X und wofür wird es angewendet?* automatically becomes *Was ist PIM EX6 und wofür wird es angewendet?* Similarly, PIM also automatically chooses among variant forms of the standard headings (such as singular/plural and the translations of the verbs “take” and “use”).

Obviously, if a custom heading is used in the English PI, the heading must also be customised in all the translations.

But custom headings are a potential exception to the general rule that there is a one-to-one correspondence between items in the English PI and items in the translated PI. For grammatical reasons, it may be necessary to customise a heading in some languages even if the standard section heading is used in English.

For example, the heading for section 2 of the package leaflet in English is:

BEFORE YOU <TAKE> <USE> X

The Finnish translation is:

ENNEN KUIN <OTAT> <KÄYTÄT> XA

The "X" will be replaced by the invented name. If the medicinal product is "ASPIRIN", this heading needs to end with "ASPIRINA". But a different inflection is needed for names with a different grammatical gender. The "A" ending is the default in PIM because it is the most common one in this context.



3.6 PI, Additional Documents, and External Information

This chapter has focused on the text of the product information, which is created in authoring tools. A PI version can also contain additional documents and references to external information. This section explains how PIM handles the text of the PI, the additional documents, and the external information.

3.6.1 Text of the PI

In PIM, the textual part of the product information is created directly within the authoring tool. Items created directly within the authoring tool are:

- Annex I – Summary of Product Characteristics
- Annex IIa – manufacturer information
- Annex IIb – conditions of the marketing authorisation
- Annex IIc – specific obligations
- Annex IIIa – the labelling
- Annex IIIb – the package leaflet
- Additional information – for example, administrator instructions, analysis and testing specifications, "how to self-inject", instruction sheet, medication record, medical information sheet, patient alert card, patient reminder card, preparation guide, reminder stickers, sticker for final product, tear-off label for final mix

3.6.2 Additional Documents

Additional documents are files which cannot be created using a PIM authoring tool but need to appear in one or more PI documents, for example, JPEG graphics. The authoring tool lets the applicant select the files and indicate where they should appear. The tool then puts the files in the `additional-docs` folder⁴ and creates links to the files in the PI. Items handled in this way are:

- Graphics and images
- Mathematical and chemical formulas

On screen and in PDFs, these items appear to be embedded within a document.

Table 3 shows the allowed formats for additional documents.

⁴ For a listing of the folders in a PIM submission, see Appendix B.

Table 3. Allowed formats for additional documents

Items	Format	Expected File Extension
Graphics and images	JPEG	.jpg or .jpeg
	GIF	.gif
	PNG	.png
	TIFF	.tif or .tiff
	SVG	.svg ⁵
Mathematical & chemical formulas	MathML	.mml ⁵

3.6.3 External Information

External information contains files which will *not* appear in the PI but will be available to the regulators for reference when they review the submission. External information is stored in the `additional-docs` folder and referenced in the envelope of the PIM submission. Authoring tools typically guide the applicant to create the link to external information.

Table 4 shows the allowed formats for external information.

Table 4. Allowed formats for external information

Items	Format	Expected File Extension
External information	PDF	.pdf
	RTF	.rtf






⁵ Not yet supported in PDF files produced by the PIM Review System.

3.7 Virtual Documents

A virtual document combines the text from two or more similar official documents and highlights the differences. Virtual documents make it easier for authors and regulators to spot the differences between different strengths or presentations, but they do not appear in the EPAR. If an applicant provides virtual documents in a submission, they appear in the product structure with pale versions of the document icons.

In the example in Figure 22, there is a virtual outer labelling document at form level. The virtual document combines the text from both of the official outer labelling documents. The differences between the documents are highlighted in grey-shaded boxes.

Figure 22. A virtual document

Product structure			
Product	Form	Strength	Presentation
Virtual Medicine 	film-coated tablets 	5 mg 	30 tablet blister pack 
			10 tablet blister pack 

10-tablet presentation	30-tablet presentation
15. INSTRUCTIONS ON USE For headaches Do not take all 10 tablets at once Do not take Virtual Medicine if you are pregnant or planning to become pregnant	15. INSTRUCTIONS ON USE For headaches Do not take all 30 tablets at once Do not take Virtual Medicine if you are pregnant or planning to become pregnant

Virtual document
15. INSTRUCTIONS ON USE For headaches Virtual Medicine film-coated tablets 5 mg 30 tablet blister pack Do not take all 30 tablets at once Virtual Medicine film-coated tablets 5 mg 10 tablet blister pack Do not take all 10 tablets at once Do not take Virtual Medicine if you are pregnant or planning to become pregnant

Note: Virtual documents are *not* supported in submissions made in versions of the DES before v2.7.



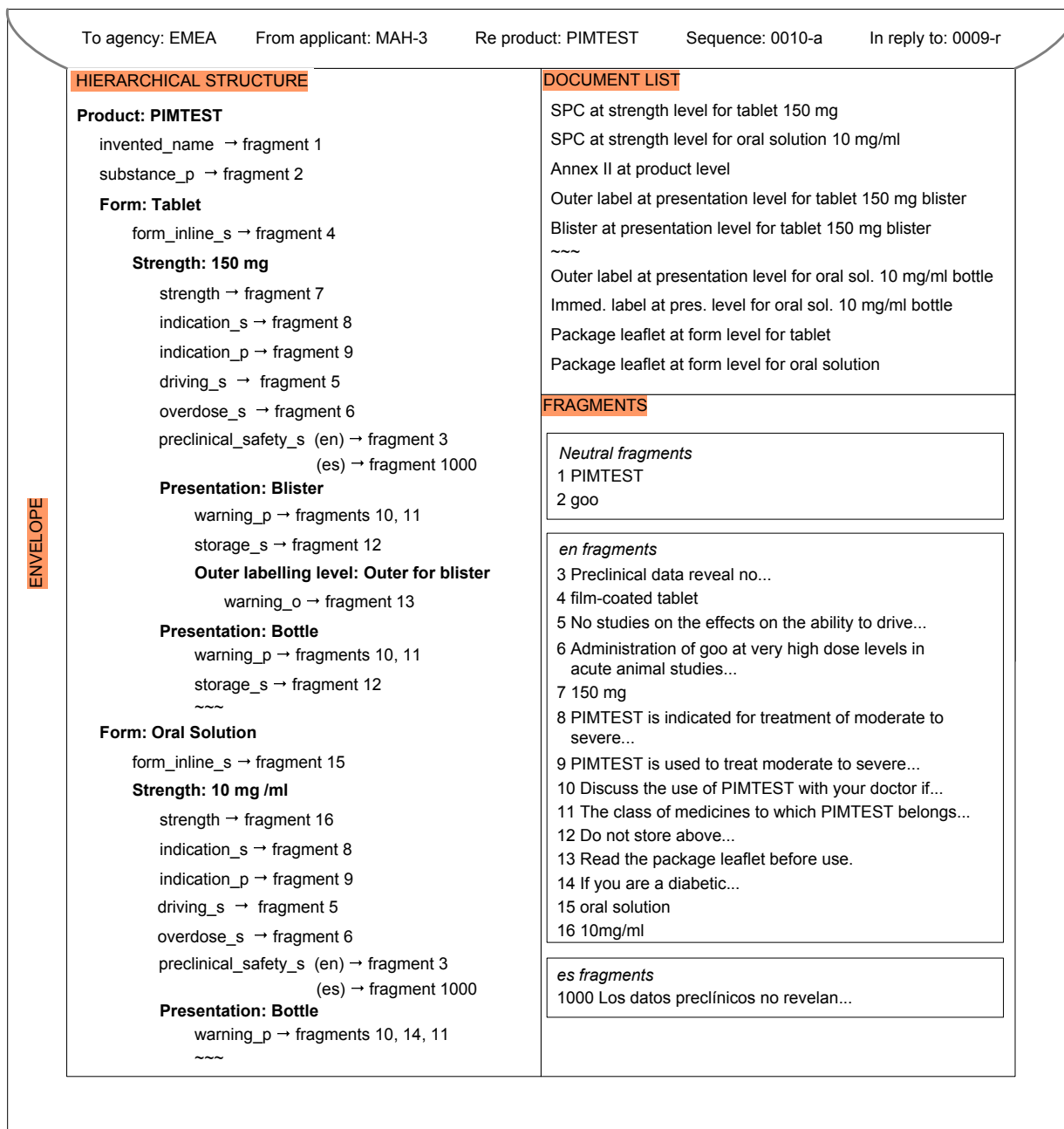
3.8 Summary of the Organisation of a PI Version

This chapter has described the following parts of product information:

- The envelope — information about the application
- A hierarchical structure — a way of organising (1) the forms, strengths, presentations, and labelling of a product, and (2) the elements of product information
- Fragments — pieces of product information
- List of documents — a list of documents and virtual documents to be created and what forms / strengths / presentations they apply to

Figure 23 illustrates this way of organising PI. Figure 24 illustrates how PIM combines this information with its own information, such as section headings, to create documents.

Figure 23. Organisation of a subset of a PI version

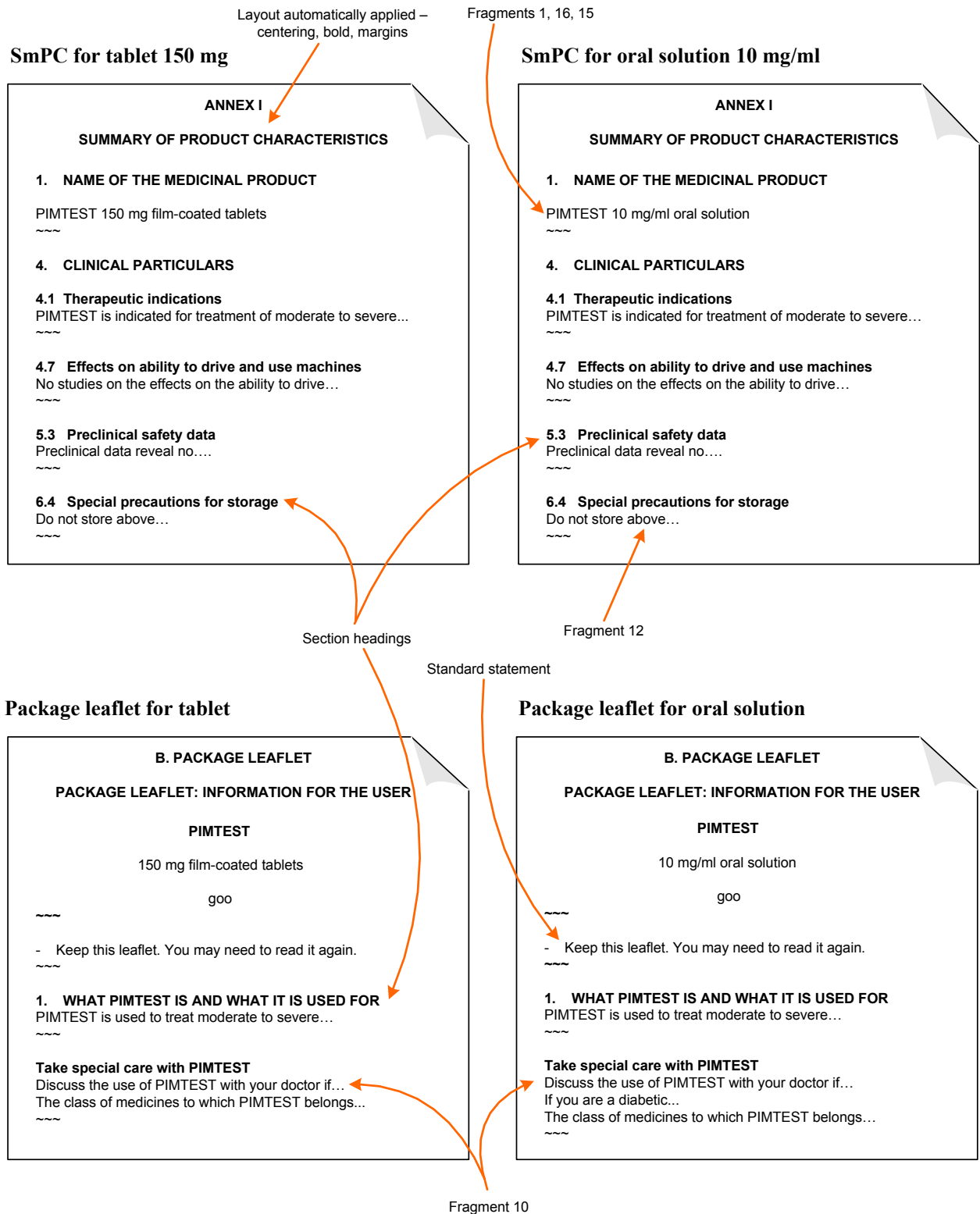


Notes on the diagram:

In the hierarchical structure, the product structure is shown in bold and elements are shown in regular text.

Normally, a version has either no translations or all translations. Here, one fragment has been translated into Spanish for illustration.

Figure 24. Creation of documents from user-supplied and PIM-supplied information



4 Lifecycle Information

As described in section 2.6, PIM is based on a 2-way exchange of PI versions between applicants and the Agency during the life of a product. This chapter describes the lifecycle information in more detail.



4.1 Tracking Changes to PI

Each PI version contains not only the actual product information but also lifecycle information, such as:

- The sequence ID
- The ID of the related sequence (unless it is the first version)
- Which fragments are new
- Which fragments have been replaced
- Which fragments have been deleted
- Comments
- Responses to comments

This information enables PIM applications to keep a record of the changes during the life of a product and to match textual changes in a version to comments in a previous version.



4.2 Comments

Reviewing is done by making comments on the PI. Applicants can also comment on their own PI, for example, if they spot mistakes themselves or to justify not implementing a regulatory comment.

4.2.1 Open-ended Comments and Specific Changes

In PIM, comments can be made at several levels:

Table 5. Types of comments

Comment Level	Example
Fragment – with alternate text (and optional reason)	HIV Human Immunodeficiency Virus
Fragment – reason only, with text selected	<i>Rewrite the highlighted phrase to make it more patient-friendly.</i>
Fragment – reason only, with no text selected	<i>What about the photosensitivity side effect?</i>
Section	<i>This section is too detailed.</i>
Document	<i>Amend this PL to reflect the changes in the SmPC.</i>
Instance Applies to the version as a whole, either to just the selected language or to all languages in the version	<i>The quality of the Czech translations is not acceptable.</i>

Section-level comments, document-level comments, and instance-level comments are always **open-ended comments** because they do not propose specific alternative text. The applicant has to decide exactly how to implement the comment, perhaps by changing text in several places.

In a fragment-level comment, the reviewer usually proposes specific **alternative text**. The reviewer can optionally provide a **reason** for a proposed change.

A reviewer can also make a **fragment-level open-ended comment** by creating a **reason-only** comment.

The facility to make open-ended comments is provided to support the way that scientific reviewers work. In the first round, they focus on the Assessment Report. Therefore, they might want to make a section-level comment like “This section must be updated following discussion of question X”. In later rounds, when the questions in the List of Questions have been resolved, reviewers make more use of the facility to comment on specific text in a fragment, e.g. changing one number to another number.

Section-level comments are also useful in another situation. Suppose a scientific reviewer wants to make a comment that applies to only one strength in a multi-strength product — but the text to be commented on is in a fragment which is reused across all strengths. Obviously, the applicant will have to split the text into separate fragments in the next version. Meanwhile, the reviewer can make the comment at section level and explain why.

In Word, the equivalent of making a comment with alternative text is turning Track Changes mode on, selecting some text, and then typing replacement text (or adding or deleting text). The Word equivalent of making an open-ended comment is using the Insert → Comment option.

4.2.2 Information Exchanged with Comments

Both regulators and applicants can provide a reason for any comment. The text provided as a reason is exchanged between applicants and regulators to help the evaluation process but never appears in the published information.

Comments are also classified according to the type of review (Scientific or QRD) and the language. This enables you to work with only the comments relevant to your role. Again, this information is exchanged between applicants and regulators but never appears in published PI.

4.2.3 Example of an Exchange of Comments

This section shows an example of an exchange of comments (in a schematic way, not as it looks on screen).

Here is the original text in the first version from the applicant, which has sequence ID a-0000:

```
PIM EX2 is indicated as part of antiretroviral combination therapy for
the treatment of HIV infected adults and children.
```

Regulator version r-0002 contains the following comment:

```
PIM EX2 is indicated as part of antiretroviral combination therapy for
the treatment of HIVHuman Immunodeficiency Virus infected adults and
children.
```

Reason:	Define the term “HIV”.
Type:	Scientific
Language:	en
Comment ID:	id67

The next version from the applicant, a-0001, contains the following comment:

PIM EX2 is indicated as part of antiretroviral combination therapy for the treatment of **Human Immunodeficiency Virus (HIV)** infected adults and children.

Reason:	It is proposed to have both the full term and the abbreviation.
Type:	Applicant
Language:	en
Comment ID:	com4
Referenced comment:	id67 in r-0002

In this example, both parties have provided a reason for their comments. Reasons are optional if replacement text is provided but can be used to explain the reason for a proposed change.

However, it is recommended that applicants *not* use comments just to say ““We agree and have made the requested change”; if the applicant has made a change exactly as requested by the regulator, there is no need to comment.



4.3 Post-authorisation Procedures

4.3.1 Baselines

In the first submission in a post-authorisation procedure, the related sequence is the **baseline**. The baseline is the version that received the most recent positive opinion from the CHMP or that was adopted at the most recent Commission Decision.

4.3.2 Exchanges for Acknowledgement of Procedures that do not Involve a Decision

In some post-authorisation procedures, such as a Type I variation or an Article 61.3 Notification, the application is deemed accepted if there is no response from the Agency within a certain time. When **tacit approval** happens in the Word-based process, there is simply no response from the Agency. In PIM, an acknowledgement is needed in order to establish a new baseline for subsequent procedures. So, there is an additional regulator version in the PIM process, purely for the purpose of acknowledging an application which has been approved without any exchange of comments. This is a regulator version in which the only change is the change of status (e.g. Approved).



5 Rules that PIM Can Validate

This chapter gives an overview of the validation of PIM submissions.

5.1 Automated Validation

A submission is automatically validated when:

- An applicant runs the validation feature in their authoring tool (if applicable)
- An applicant runs the validation function of the PIM Data Validation Engine (PDVE)
- The Agency validates the submission in the PIM Review System when importing it

Examples of the types of checking performed during the automated validation are:

- The folder structure in the submission is correct.
- All mandatory elements of product information are present.
- References to previously exchanged versions are correct.
- A response to a comment refers to a comment made in the related version.
- Each presentation appears in one and only one SmPC document.
- External information is in either PDF or RTF format.

5.2 Manual Validation

Some manual validation is needed, for the following reasons.

- **Paging problems can only be spotted by humans.**

The most common examples are tables that do not fit on an A4 page. A table that is too wide for A4 not only gets truncated on printouts but additionally causes a horizontal scroll bar to appear in the PIM Review System. Since horizontal scrolling makes reviewing awkward, the Agency manually checks for such problems after a submission has been imported into the system.

- **Humans can check whether a submission is as expected.**

Before opening a submission for review, the Product Team Leader checks that the submission is as expected, for example:

- Does the information in the envelope correctly describe the submission?
- Are the expected languages in the submission?
- Is the product structure as agreed with the applicant?

Therefore, an applicant submission can still be rejected even if it passes all the automated validation checks. However, rejection is much less likely if applicants follow these guidelines:

- Check all the PI, including the envelope.
- Generate PDF files to preview the layout and then correct any formatting problems before submission.
- Follow any recommendations given at pre-submission meetings.

Applicants will find further guidance on best practices for PIM submissions in *PIM Guidance for Applicants (Centralised Procedure)*. The Agency's staff will find further guidance on PIM validation procedures in *PIM Review System: Procedures for the EMEA (Centralised Procedure)*.



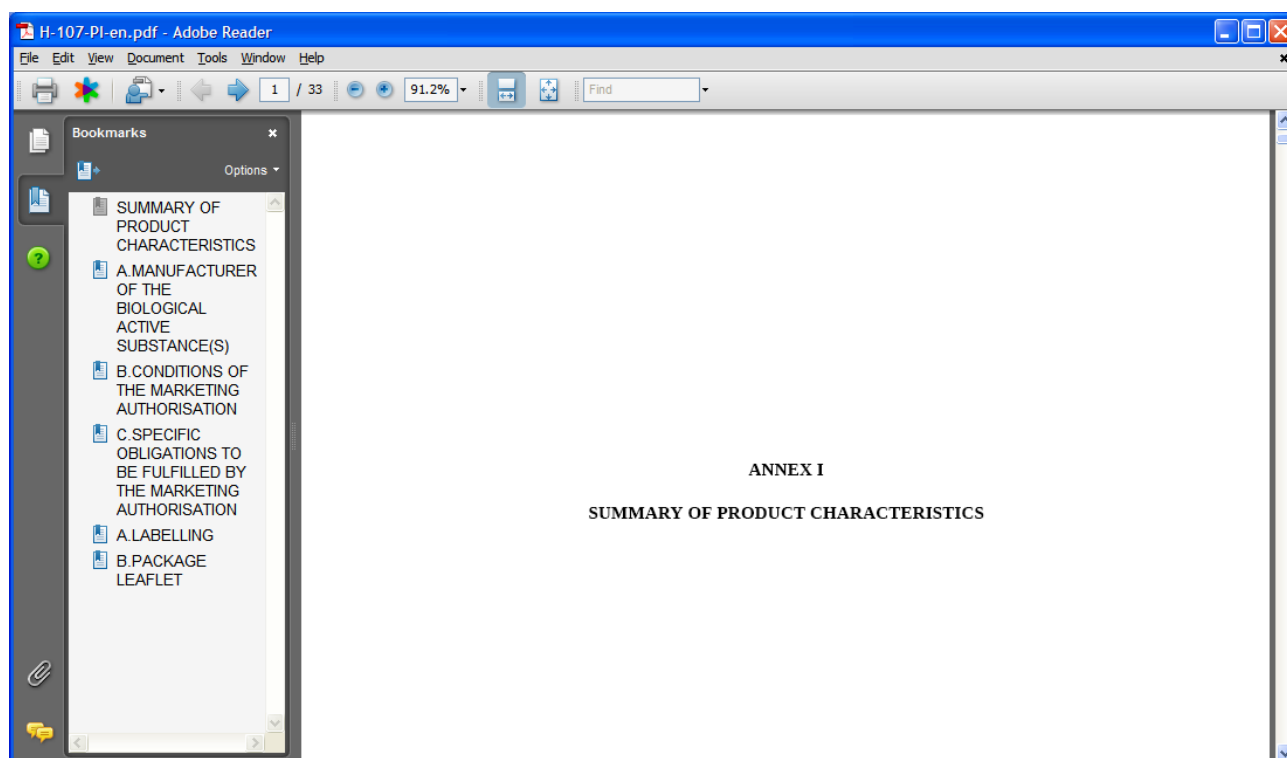
6 Views of PI that PIM Can Generate

PIM applications can generate various views of product information, initially for review and ultimately for publication. This chapter describes these views.

6.1 The EC PDF

The EC PDF is the product information part of the European Public Assessment Report (EPAR), that is, all the PI documents for a given language in a single PDF file. The PIM Review System creates the EC PDF on request from the Agency's Product Team Leader. Figure 25 shows an example of an English EC PDF file.

Figure 25. An EC PDF file created by the PIM Review System and displayed in Acrobat Reader



For applicants, authoring tools (including the LAT) typically have a facility for generating a preview of the EC PDF, and so does the PDVE. This facility is useful for people with a PI coordination role at applicant companies. Since it is the EC PDF that is transmitted to the European Commission for the Decision, it is important that PI coordinators can check in advance what the EC will see. If the formatting is not right, the applicant can change the proposed PIM submission to get the desired format (by adding a "keep with next" instruction to a fragment, for example).

Because the EC PDF is automatically generated by the PIM Review System, there is no longer any need for applicants to manually generate EC PDF files (a process which involved adding bookmarks, styles, and properties to the Word files and then manually converting the files).

Nonetheless, applicants still have some control over the order of documents in the EC PDF. The order of documents is defined by applicants in their authoring tools. For example, an applicant can choose to present SmPCs in increasing order of strength.

6.2 Views of PI during Product Evaluation

During the evaluation process, you may want to view individual documents or focus on the changes in the product structure or in individual documents. Depending on the software application you are using and your role, you may be able to see the following views of PI.

- **Individual documents**

All PIM applications let you display individual documents on screen or save them as PDF files. Viewing an individual document is useful for authors or reviewers of the particular part of product information contained in that document.

- **Virtual documents**

PIM applications that support DES 2.7 will let you view any virtual documents in a submission. Viewing a virtual document is useful for authors or reviewers who need to spot the differences between different strengths or presentations.

- **Custom PDF files and HTML files**

PDF files and HTML files are useful for any reviewer who does not have access to the PIM Review System (such as external experts) or who wants to work offline.

The PIM Review System lets users generate PDF files to meet various requirements: just a selected document or all documents; just a selected language or all languages; with or without comments and tracked changes.

For applicants, authoring tools typically also support the creation of PDF files.

- **List of comments**

Some PIM applications let you view a list of the comments on a version.

Figure 26. A list of comments in the PIM Review System

	ID	Group	Author	Visibility	Status	Comment Type	Reason	Date
<input type="checkbox"/>	j418800	EMEA	emea_ptl	Personal	Draft	Instance	Please follow the advice given at the pre-submission meetin ...	2009-09-15
<input type="checkbox"/>	j418900	EMEA	emea_ptl	Personal	Draft	Section	Expand this section.	2009-09-15
<input type="checkbox"/>	j419100	EMEA	emea_ptl	Personal	Draft	Document	Units of measurement in all sections should be standardised ...	2009-09-15
<input type="checkbox"/>	j419000	EMEA	emea_ptl	Personal	Draft	Fragment	Make the shelf life consistent with the data.	2009-09-15
<input type="checkbox"/>	j419200	EMEA	emea_ptl	Personal	Draft	Fragment		2009-09-15

5 comment(s) shown

- **Summary of applicant responses to comments**

When a new applicant version arrives, the PIM Review System provides a view that lists each comment from the previous regulator version and indicates whether there is an applicant response.

Figure 27. Part of an "Applicant Responses to Comments" document in the PIM Review System

PIM Review System
Simulation Product - EMEA-H-C-XXX

Applicant responses from "**Response to LoQ (Day 121)**" (0001-a)
to regulator comments from "**LoQ (Day 120)**" (0002-r)
Language: en

Generated on 29-04-2008 01:18:40

Section 4.3

Regulator comment: id161800 EMEA (DE) Scientific ⚠

Reason: Add renal impairment.

Section 4.4

Regulator comment: id161904 EMEA (DE) Scientific

Reason: Extend the section

Fluid retention

Applicant response: com1010

Reason: Section extended as requested.

Finally, if fluid detention is observed for more than 2 months, the drug should be withdrawn immediately.

- **Comparisons of versions and tracked changes**

The PIM Review System can automatically create various views of PI for regulators. For example, during the review of the Day 121 submission, it will highlight which documents have changed since the first submission. When viewing a changed document, reviewers can ask the PIM Review System to:

- Show the Day 121 text as submitted by the applicant
- Highlight differences between the Day 121 text and the previous regulator comments (that is, any comments not implemented by the applicant, or changes that were not asked for, or responses to open-ended comments)
- Highlight differences between the Day 121 text and regulator comments added in the current (post-Day 121) review

In translated documents, the PIM Review System can show English text and the corresponding translated text side by side, as shown in Figure 28.

Authoring tools typically also have facilities for comparing versions.

Figure 28. A side-by-side view in the PIM Review System of English and Portuguese text

The screenshot displays two parallel text views within the PIM Review System interface. The left pane shows the English version of section 4.2, 'Posology and method of administration'. The right pane shows the Portuguese version of the same section. Both panes include a toolbar at the top with options like 'View: Text', 'Search', and 'Track Changes'. The Portuguese text includes a comment box for 'New Regulator Comments' with the text: 'id163800 PT "Apply italics format." ms2_qrd_1 EU Regulator Draft QRD'. Below the main text, there is a section for 'Crianças e adolescentes' (Children and adolescents).

- **Snapshots of PI versions**

A snapshot is a frozen copy of a PI version at a particular time. The PIM Review System can take snapshots of PI, and authoring tools may also provide a snapshot facility.

In the PIM Review System, a snapshot can include just the scientific comments, just the QRD comments, or both. It can include just the English PI or all languages. A PI coordinator at an NCA can take a snapshot to ensure that there is a record of their own organisation's comments before consolidation of comments at EU level. A QRD member at an NCA can take a snapshot to ensure that there is a record of the QRD comments on the translation they are responsible for. A snapshot can later be opened and viewed the same way as any other version but cannot be edited. If an NCA needs to have a copy of a PI version within their own national boundaries for legal reasons, the NCA can download the snapshot.

- **Product structure**

All PIM applications can show a view of the forms, strengths, and presentations for a product and the documents associated with each level of the structure. There are examples of product structure views in Figure 17 and Figure 18.

When a new applicant submission arrives, the PIM Review System can highlight any changes in the product structure since the last submission, for example, the addition of a new strength.

- **Envelope**

Most PIM applications let you view the envelope. Figure 29 shows an envelope in the PIM Review System.

Figure 29: A PIM envelope in the PIM Review System

View PI version envelope

Des Version: 2.7

Application : EMEA-H-C-XXX

Submission : Initial MAA

Inn: theINN

Applicant: MAH-3

Procedure: Centralised
Day 1

ECTD Sequence: 0000

Product ID: 725

Agency: EMEA

Invented Name: LP Medicinal Compound

PIM Sequence : 0000-a

Status:

ATC Code : COXK00X

Related Sequence(s): -

Source Sequence(s): -

Description: Initial Authorisation Procedure
(EMEA-H-C-XXX)
Start of the procedure



Appendix A: Using the PIM Viewer and PI Examples

Several examples of PI versions are available on the PIM website. You can download these examples and then view them in the PIM Viewer. The following table shows what features are used in each example.

Table 6. Features in the PIM examples

Feature	PIM EX1	PIM EX2	PIM EX3	PIM EX4	PIM EX5	PIM EX6
File type	ZIP	TGZ	ZIP	TGZ	ZIP	TGZ
Number of PI documents Per language, including additional docs.	21	16	17	10	13	7
SmPC, Anx2, Outer, Blister, Immed, PL Number of docs. per PI type	5/1/5/4/1/5	3/1/5/2/3/2	3/1/6/2/2/3	1/1/2/1/4/1	2/1/5/0/3/2	1/1/2/1/0/1
Flexible PI generation With reference to more than one level	-	-	Blister	-	SmPC, Outer, Immed, PL	-
Repeated labelling levels More than one labelling level for a presentation	-	-	-	Immed	Outer, Immed	
Multilingualism Languages used	EN, ES, FR, IT	EN	EN	EN	EN	EN, FR, DE, SV
Additional documents	-	-	-	-	-	Annex III A
Combination product More than one substance	-	-	-	-	-	Yes
Combined pack More than one strength in pack	-	-	Yes	-	-	-
Custom heading	PL sect. 2a	-	PL sect. 2b	-	-	-
Images	Yes	-	Yes	-	Yes	-

Downloading and viewing a PIM example:

- Go to the DES Documentation page on the PIM website, <http://pim.ema.europa.eu/des/docs.html>, and download the example you want to view.
- Uncompress the example file and store it on a hard drive.

All the examples are supplied in a compressed format — some in ZIP format and some in TGZ format. Most computers already have software that can “unzip” a ZIP file, e.g. WinZip. There is a link on the web page to free software that can uncompress TGZ files.

- Open the `pim.xml` file by double-clicking or pressing Enter.

The product information appears in a new window within your default web browser.

Notes: If your browser displays a message saying that the XML file cannot be displayed, you have either tried to open it while it is still stored within a ZIP or TGZ archive or you have moved the file away from the folder structure it came with.

If the file opens in a different program than the PIM Viewer (that is, if it doesn't look like Figure 7), another program has been associated with the file type XML on your computer. You can change the association in Windows Explorer (using the Tools → Folder Options menu). Or you can right-click the file, choose the Open With option, and select your web browser as the program.

Viewing a real PI version:

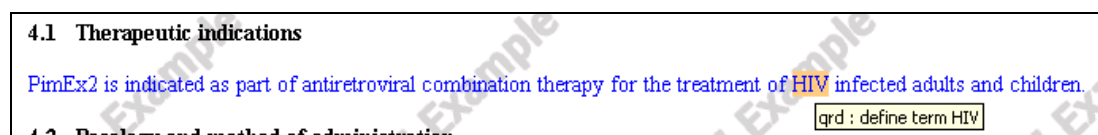
You can use the PIM Viewer to view a real PI version created by an authoring tool or the PIM Review System (though remember that it is not a substitute for an authoring tool or the PIM Review System). The `pim.xml` file will be in a folder at the export/download location, and this file must be opened *from the unzipped folder structure* (in the same way as for the examples).

Limitations of the PIM Viewer:

The PIM Viewer has some limitations. As the name implies, it can only be used to view a version, not to make changes. Other limitations are as follows.

- Although the format of documents in the PIM Viewer is very similar to that in the PDF files created by the PIM Review System, it might not be exactly the same, especially with regard to complex formatting such as tables and formulas. For example, a long table or image may get truncated in the PDF file, but truncation never happens in the PIM Viewer.
- Because the PIM Viewer displays the documents within a web browser, it cannot show where page breaks will occur in the PDF file.
- The presence of a comment is indicated by highlighting the text affected by the comment. To see more information, you need to hover the mouse over the highlighted text. Then a tool tip appears containing the type of comment and the reason, as shown in Figure 30.

Figure 30. A comment in the PIM Viewer



- If the version is a delta (a pre-DES 2.7 version that contains only the changes since the last version), only the changes are displayed.

Supported web browsers:

The PIM Viewer has been tested with the following web browsers:

- Internet Explorer V6
- Internet Explorer V7
- Firefox V2⁶
- Netscape V8⁶
- Opera V9⁷
- Safari V3⁷

⁶ Doesn't handle shortcuts for special symbols, such as ` ` and `λ`

⁷ Can display product structure only; cannot display documents.



Appendix B: Files and Folders in a PI Version

A PI version is provided as an archive file (compressed file), in either the ZIP format or the TGZ format. The name of the archive file must be in a standard format. You don't have to remember the format because your software will automatically name the file when you "export" a version. But in case you are curious about the file names you may see, the format is:

```
131-pim-x-nnnn-var.ext
```

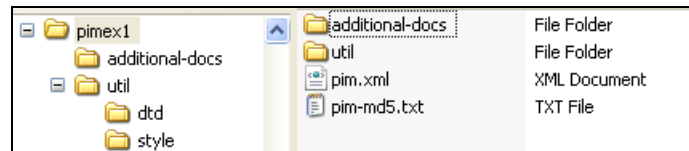
where:

131	indicates that the file belongs to section 1.3.1 of the CTD
pim	indicates that the file contains PIM data
x	is one of the following: <ul style="list-style-type: none"> a for an applicant version r for a regulator version
nnnn	is a sequence number (four digits)
var	in an applicant submission, optionally contains a free-form description of the submission (lowercase, no spaces)
ext	is either "zip" or "tgz" to indicate the type of compression

For example, the submission for PIM Example 1 is named `131-pim-a-0031-pimex1.zip`.⁸

When uncompressed, the archive must have the folder structure shown in Figure 31 (where `pimex1` is the just the name of the folder where the example archive has been extracted).

Figure 31. Contents of a PIM archive file



You don't have to remember the details of this folder structure. An authoring tool will automatically create the required folder structure within the archive file when the applicant exports a version. Likewise, the PIM Review System automatically creates the required structure when the Agency exports a regulator version. But, in case you are curious about the folders you may see, the structure is:

<code>pim.xml</code>	File at the top level containing PI conforming to the DES
<code>pim-md5.txt</code>	File at the top level used by the system as a check on the validity of the contents of the <code>pim.xml</code> file (checksum)
<code>additional-docs</code>	Folder present only if there are additional documents (e.g. graphics)
<code>util</code>	Folder with two subfolders: <ul style="list-style-type: none"> <code>dtd</code> Components needed by the PIM Viewer (structure definition) <code>style</code> Components needed by the PIM Viewer (display definition)

⁸ For submissions in a DES version before v2.7, the "a" or "r" comes after the sequence number, e.g. 0000-a, and there is no free-form text at the end.



Glossary

This glossary defines terms as they are used in this guide.

additional documents Files which cannot be created using a PIM authoring tool but need to appear in one or more [documents](#), e.g. graphics or formulas.

additional information Information within a PI [version](#) containing information additional to labelling or package leaflets, e.g. an alert card.

applicant An organisation that submits an [application](#).

application A request for authorisation to market a medicinal product (initial marketing authorisation application) or for a post-authorisation procedure such as a variation. The lifecycle of an application consists of a [sequence](#) of PI [versions](#) exchanged between the [applicant](#) and the [European Medicines Agency](#).

AR Assessment Report. A report written by a regulatory agency about a [submission](#).

ATC code Anatomical, Therapeutic, Chemical code. A classification system for drugs, maintained by the WHO.

baseline The [version](#) of [PI](#) for a given product that can be used as the starting point for another [application](#) relating to the same product. The version of PI that received the most recent positive opinion from the [CHMP](#) or that was adopted at the most recent Commission Decision.

Centralised Procedure A procedure for the authorisation of medicinal products, for which there is a single [application](#), a single evaluation and a single authorisation* allowing direct access to the single market of the European Community. The single scientific evaluation is made by a review team which is led by a [Rapporteur](#) and [Co-rapporteur](#) (both [CHMP](#) members) on behalf of all EU member states. Applications are submitted directly to the European Medicines Agency. * Except the EEA states, which share the single evaluation but grant a separate marketing authorisation within 30 days of the Commission Decision.

CHMP Committee for Medicinal Products for Human Use. A committee responsible for preparing the European Medicines Agency's opinions on all questions concerning medicinal products for human use, with membership taken from each of the EU member states, the EEA-EFTA states Iceland and Norway, and co-opted experts.

comment An annotation on the [product information](#) within a [version](#) consisting of proposed replacement text and/or a reason, along with an indication of the source of the comment (scientific review, QRD review, or applicant) and the language.

Co-Rapporteur In the [Centralised Procedure](#) for human medicines, a second member of the [CHMP](#) contributing to the scientific assessment of an [application](#).

CTD Common Technical Document. An internationally agreed definition of the contents and format of the information to be submitted to regulatory authorities in the three ICH (International Conference on Harmonisation) regions of Europe (EU and EEA), USA and Japan.

custom heading A [section](#) heading in product information that an applicant has replaced with an alternative heading.

Data Exchange Standard An [XML](#)-based standard for the 2-way exchange of [product information](#) and [lifecycle information](#) regarding medicinal products for human use, modelled on the [QRD templates](#) and designed on the principle of holding any piece of information only once and allowing its use as many times as necessary to create the required [documents](#).

DES See [Data Exchange Standard](#).

document One occurrence of one type of [product information](#), e.g. the outer labelling for a given [presentation](#) of a given product.

EC PDF The [product information](#) part of the [EPAR](#), consisting of all the PI [documents](#) for a given language in a single PDF file.

eCTD Electronic Common Technical Document. An interface for industry-to-agency transfer of regulatory information facilitating the creation, review, lifecycle management and archival of electronic submissions. See also [CTD](#).

element A part of [product information](#), predefined in terms of its level in the [hierarchical structure](#), which types of [documents](#) it can appear in, its location within documents, whether it is mandatory or optional, and whether or not it can be repeated. Example: the indications in SmPCs. The text for an element is held in one or more [fragments](#).

European Medicines Agency The agency of the European Union responsible for coordinating the scientific resources put at its disposal by the competent authorities of the member states for the evaluation and supervision of medicinal products. It is based in London.

envelope Information within a PI [version](#) about the [application](#), e.g. applicant name and application status.

EPAR See [European Public Assessment Report](#).

EudraNet European Drug Regulatory Network. A virtual private network of computers, managed by the European Medicines Agency.

European Public Assessment Report (EPAR) A set of documents published (or updated, in the case of post-authorisation procedures) at the time of the Commission Decision for any product that has been evaluated via the [Centralised Procedure](#) and received a positive opinion from the [CHMP](#). It contains a summary for the public of the grounds for the CHMP opinion, a list of all authorised presentations, the scientific discussion, and the procedural steps taken (all in English only), together with all the [product information](#) (in all official EU languages).

external information A file referenced in the [envelope](#) of a PI [version](#) containing information that will not appear in the PI, e.g. a letter or form.

form Abbreviation for "pharmaceutical form".

fragment A piece of product information, such as a paragraph of text, a table, or a link to a graphic, which may be reused in multiple documents. Synonymous with template in the DES Specification.

HTML Hypertext markup language. A text description language that is used for electronic publishing, especially on the web.

hierarchical structure A way of organising both the [product structure](#) and the [elements](#) by assigning them to specific levels in a hierarchy. The levels are product, form, strength, presentation, outer labelling, blister labelling, and immediate labelling.

instance A synonym for [version](#). An instance-level [comment](#) applies to the whole version, either to just the selected language or to all languages in the version.

ICH International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

LAT See [Light Authoring Tool](#).

lifecycle information Information used to support regulatory activities during the life of a product (initial MAA and post-authorisation procedures), including [sequence IDs](#), [comments](#), and information about changes to [product information](#) and [product structure](#).

Light Authoring Tool A single-user software application for authoring submissions in accordance with the [DES](#).

LoQ List of Questions. In the [Centralised Procedure](#) for human medicines, a document authored by the [CHMP](#) and addressed to the [applicant](#) at Day 120.

MAA Marketing Authorisation Application.

MAH Marketing Authorisation Holder.

migration The process of establishing a [baseline](#) in PIM for an authorised product for which product information has previously been managed using Word documents.

national competent authority A national body that administers drug regulatory activities.

NCA See [national competent authority](#).

neutral text Textual [product information](#) that is the same in all languages, e.g. the invented name.

open-ended comment A [comment](#) at [section](#) level, [document](#) level, or [instance](#) level, or a [reason-only comment](#) on a fragment.

PDVE See [PIM Data Validation Engine](#).

PI See [product information](#).

PI version See [version](#).

PIM Product Information Management. A system introduced by the European Medicines Agency with the aims of (1) Increasing the efficiency of the management and exchange of product information for all parties involved in the evaluation process by structuring the information and exchanging it electronically, and (2) improving the quality and consistency of the published product information. It consists of the [Data Exchange Standard](#) and software applications that conform to the standard, namely, authoring tools (including the [Light Authoring Tool](#)), the [PIM Review System](#), the [PIM Data Validation Engine](#), and the [PIM Viewer](#).

PIM Data Validation Engine A software application that validates PI versions, creates PDF files, and displays PI in [HTML](#) form in a web browser.

PIM Review System A software application hosted by the European Medicines Agency and used by staff at the Agency and [national competent authorities](#) for reviewing PI [versions](#).

PIM Viewer A software application that transforms PI [versions](#) into [HTML](#) for viewing in a web browser.

presentation The pack in which a medicinal product is marketed, including a description of the form and the quantity of the contents. Each presentation is authorised with its own authorisation number under the Centralised Procedure.

product information The contents of the following documents: Annex I – Summary of Product Characteristics, Annex II – manufacturer information, conditions of the marketing authorisation and specific obligations, Annex IIIa – the labelling, and Annex IIIb – the package leaflet.

product structure The definition of the forms, strengths, presentations, and labelling of a product.

product team leader A project manager from the European Medicines Agency responsible for handling a procedure.

PRS See [PIM Review System](#).

PTL See [product team leader](#).

Quality Review of Documents A working group composed of representatives from Member States' National Competent Authorities, the European Commission, and the European Medicines Agency. This group provides assistance to the Agency's scientific committees and to companies on linguistic aspects of the [product information](#) for medicines.

QRD See [Quality Review of Documents](#).

QRD templates Templates for [product information](#) in Microsoft Word format, available in both "clean" and annotated form and maintained by the QRD working group.

Rapporteur In the [Centralised Procedure](#) for human medicines, a member of the [CHMP](#) appointed to co-ordinate the scientific evaluation of an application.

reason-only comment A fragment-level comment in which the Reason field is filled in but no alternate text is provided.

section A part of a document identified by a heading in the QRD templates, e.g. the "Therapeutic Indications" section of the SmPC or the "Before you Take X" section of the Package Leaflet.

sequence ID A means of identifying a [version](#) within a specific product.

SmPC Summary of Product Characteristics.

snapshot A frozen copy of a PI [version](#), including [comments](#) placed on that version.

style sheet A file in a special format that defines the layout of a type of [document](#) and thus makes the PIM data readable in a familiar layout.

submission A [version](#) sent by the applicant to the European Medicines Agency for review or approval.

validation The process of checking a [version](#) against the PIM data validation rules, carried out by the PIM Review System when an applicant submission is imported.

version A set of [product information](#) and [lifecycle information](#) at a specific time during the life of a product, i.e. an applicant version, a regulator version, or working version.

virtual document A document used only in the authoring and review process which combines the text from two or more similar official documents and highlights the differences.

XHTML Extensible hypertext markup language. An XML-based markup language designed to replace HTML.

XML XML Extensible Markup Language. A flexible way to create common information formats and share both the format and the data on the World Wide Web, intranets and elsewhere.



Related Information

This section lists other sources of information related to PIM and the Centralised Procedure.

PIM

- General news about PIM. <http://pim.ema.europa.eu/index.html>
- PIM Guidance for Applicants (Centralised Procedure). <http://pim.ema.europa.eu/guidance/docs.html>
- PIM Migration Guidance. <http://pim.ema.europa.eu/datamigration.htm>
- PIM Data Validation Engine (PDVE) User Manual <http://pim.ema.europa.eu/pdve/docs.html>
- Light Authoring Tool User Manual. <http://pim.ema.europa.eu/lat/docs.html>
- PIM Review System user manuals. <http://pim.ema.europa.eu/prs/user-docs.html>
- PIM Review System quick reference cards. <http://pim.ema.europa.eu/prs/quick-reference.html>

Centralised Procedure

- Committee for Medicinal Products for Human Use (CHMP). <http://www.ema.europa.eu/htms/general/contacts/CHMP/CHMP.html>
- EMA implementation of electronic-only submissions and eCTD submission: questions and answers relating to practical and technical aspects of the implementation. http://www.ema.europa.eu/htms/human/raguidelines/dossier_format.htm
- EPARs for authorised medicinal products for human use. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125
- EudraLex Volume 2 – Pharmaceutical Legislation: Notice to Applicants. http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/index_en.htm
- Human medicines – EMA pre-submission guidance. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000157.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058002251f
- Human medicines – EMA post-authorisation guidance. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000166.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580023399
- QRD guidelines for human medicinal products. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000204.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058002d4ee
- Scientific guidelines for human medicinal products. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000043.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800240cb