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Association of Pharmaceutical Manufacturers in Estonia

Preliminary analysis of the implementation of the electronic package leaflet (ePIL) in Estonia

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Table of contents

Project info

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Keywords and abbreviations

Found at	Explanation
EMA	European Medicines Agency (EMEA)
EFPIA	The European Federation of Pharmaceutical Industries and Associations
PIL	Package leaflet (also PL, *package leaflet*)
ePIL	Electronic package leaflet (also ePL, *electronic package leaflet*)
QR code	*Quick Response code*
SmPC	*Summary of Product Character*istics (SPC)
ePI	Electronic product information (*EPI*) - includes PIL, SmPC, labelling.
EPAR	Product Information Document *(PID) for* a medicinal product registered centrally in the European Union *(European public assessment report)*
FHIR	*Standard for health care data exchange*
SPOR	Standard for a pharmacovigilance system
Packaging labelling	Information on the inside and outside of the packaging (*labelling*)
GTIN	*Global Trade Item* Number *(*GTIN) used on the sales package gs1.ee
DMC	The two-dimensional code printed on medicines through the medicines authentication system, consisting of black and white squares or dots, is different on each pack and includes the product code, unique serial number, expiry date and batch number of the medicine. (*Data Matrix Code*)
Packaging code	A unique combination of numbers that is not printed on the packaging of medicines or products, but is mandatory for all medicines and products entered in the Estonian Register of Medicines.
Marketing Authorisation Number	A unique number identifying the packaging of a specific product, which must be marked on the outer packaging or, in its absence, on the inner packaging.
SamTrack	Medicines information system in Estonia

Summary

The aim of current project is to carry out a preliminary analysis of the implementation of the electronic packaging information leaflet (ePIL) in Estonia, which consisted of the following activities: 1) mapping of the field in Europe - what models are used in different countries and what are the most important ongoing projects; 2) possible technical solutions - both based on the Estonian Medicines Register and the planned solution of the European Medicines Agency (EMA); 3) overview of legislation and standards; 4) mapping of expectations and needs of Estonian shareholders; 5) creation of a vision of a possible user-friendly visual solution. The project was initiated by The Association of Pharmaceutical Manufacturers in Estonia as a country engagement project funded by EFPIA.

Overview of the current developmental trends of the ePI

The future vision and development of electronic product information (ePI) has become a topical issue in the European Union and worldwide. The aim of the ePI is to improve people's information on the use of medicines through better access to information on medicines, and to reduce the burden on the environment by moving away from paper leaflets. The paper leaflets currently in use are not reader-friendly and their handling is not flexible (e.g. introduction of changes, etc.).

First aim of the project was to give an overview of the current situation by 1) describing initiatives at European level, mainly by the European Medicines Agency (EMA); and 2) assessing the functionalities of medicines information environments developed by EU medicines agencies and third parties.

The main conclusions of the overview are the following:

1) The EMA is in the process of creating a central repository for the creation and management of ePIs, with the possibility to use the corresponding data in different applications planned at API level.

2) the Gravitate Health project is also underway, aiming at the creation of a white paper for an ePI system as well as a corresponding G-lens platform targeting the presentation of product information to the patient.

3) all EU countries have medicine information registers where the package leaflets of nationally registered medicines can be found. In the case of centrally registered medicinal products, the accessibility varies, in some cases the information can be found directly in the national register, in other cases only a link to the EMA register is presented.

4) The usability of the registers varies, but in most cases, they are designed for specialist level search.

5) there are also a few third-party environments, the usability level of which may vary - Spain, Sweden, Norway, and the Netherlands have the most comprehensive solutions. These are either a national register or an integrated solution (the national register directs the user to a third-party register to find the package leaflet). Data retrieval is provided either through a web or mobile application, which offers a number of usability enhancements as well as notification options (e.g., adverse reaction reporting, subscriptions to information on changes to the medicine of interest, videos on general instructions for use, etc.).

6) A few pilots are underway in Europe to examine the possible ePI system - the most widely communicated being the pilot on hospital medicines in Belgium, Luxembourg, and now Estonia, Latvia, Lithuania, and Spain. In Sweden, for example, both EMA and a national solution pilot are running in parallel. In summary, the topic of electronic product information (including ePIL) is currently at the focus, with different countries at very different starting positions, and the EMA key principles therefore emphasise flexibility in the implementation of the system. At the same time, EFPIA underlines the need for a harmonised approach.

Regulations and standards

In terms of regulation in general, the area is regulated at EU level. However, the patient safety issues, for example, are directed at the level of the Member States, to implement specific regulations. In Estonia, there is a register of medicinal products, the data of which are freely accessible online and open to the public. Within Estonia, the "Medicines Act" and the "Requirements for the application for a marketing authorisation for a medicinal product and the fee for the professional assessment" regulate the subject of package leaflets.

A common standard (the 'technical standard') under this topic will ensure that the same data set is used irrespective of the country of destination. The standard defines the rules and provides a model for the uniform use of data in the package leaflet, regardless of the medicinal product or language. In the case of the ePIL, the question is which standard applies for the uniqueness of the packaging (national or international). The regulatory framework and the standards are explained in Chapter 3 of this document.

Stakeholder involvement - expectations and needs

As the implementation of ePIL in Estonia requires the cooperation of different stakeholders, a mapping of stakeholders' expectations and needs was carried out. The result of the mapping exercise is presented in Chapter 5 of the analysis. In summary, the stakeholders see ePIL as an important innovative solution to advance public health. It is essential that patients receive comprehensive, accurate and up-to-date information on the medicines they are taking at the

right time. Patient awareness and patient empowerment are key to effective treatment. At the same time, there are also issues that need to be analysed and decided in advance of the implementation of the system (e.g., avoiding multiple codes on the packaging, ensuring the possibility of printing). It is important to consider the expectations and needs of all parties involved as early as possible.

Technical solution alternatives for the ePIL in Estonia

One of the main objectives of the project was to analyse the alternatives for a possible technical solution to create a way to display ePIL to the user via mobile phone by scanning the code on the packaging. The technical solution alternatives have been presented in two parts: 1) from the base of the Estonian Medicines Register, which would be feasible using the current infrastructure, and 2) from the base of the EMA ePI repository to be created, which would be feasible after the completion of the EMA development, the exact timeframe of which is currently unknown. The technical analysis has been carried out on the basis of the ePI technical standard developed by EMA.

One of the issues that needed to be resolved was the issue of reconciling the nationally used packaging codes (opcode) with the internationally used GTIN codes. The EMA has pointed out that the ePIL could be displayed to the patient using the existing DMC codes printed on the packaging as part of the implementation of the Falsified Medicines Directive. An alternative would be to print an additional QR code on the packaging, which is not supported by manufacturers - mainly for technical reasons (packaging often lacks space) and the presence of two codes on the packaging can also be confusing for the consumer. However, in order to use the DMC code, the packaging would need to be linked to a corresponding record in the database based on the GTIN code, which is currently not available in the pharmaceutical register. The GTIN code will probably also be needed in the future for data matching by the EMA when the ISO IDMP Product Management Service (PMS) solution, also currently under development, is implemented. The analysis identified technical options for obtaining this code (e.g. data set to be generated by manufacturers, data set to be generated by pharmacies during scanning, data set of the The Estonian Medicines Verification System), but each of these options has its limitations.

A further objective of the technical part was to identify possible next steps for the system. The most optimal way would be to start with a pilot project to create an ePIL application with a web-based scanner based on the preferred alternative. During the pilot project, patients would be able to scan the code on the pack and be presented with the existing pack leaflet in a reader-friendly format. The web application can be based on the design created in this project. It is important that, in addition to nationally registered medicines, all centrally registered medicines with different documentation are covered.

The following questions/factors, which are very important for the future, could be tested and analysed through a pilot project:

1) testing the reliability of code scanning through a web application to avoid printing additional codes on the packaging;

2) creating a database linking the GTIN code and the packaging code;

3) testing the manageability of the system - according to the Estonian Medicines Agency, more than 33 million medicine packages are sold in Estonia per year, which can be taken as an expected load on the system;

4) testing the usability of the system;

5) gradually familiarising patients with the use of ePIL - user profiles by medicine;

The pilot would result in a primary service that can be further developed and enhanced - the analysis also identifies a number of technical extensions that can be incorporated if the basic functionality works well.

The role of managing the pilot could be taken over by the manufacturers, with the possibility that at some point it could be taken over as a service by the government. Estimated development needs for the pilot project are approximately € 50 000 - 60 000 for the development of the corresponding web application (project management and other costs of up to 20% may be added), and annual management costs are estimated at around € 20 000. The system could be upgraded in subsequent phases. A more detailed architectural design and analysis is presented in Chapter 3 of the analysis "ePIL technical solution alternatives".

In total, seven different models are described as alternatives to the ePIL technical solution and analysed in terms of advantages and disadvantages. A possible pilot project could be structured in two alternative ways, depending on the preferences of the client. The two models are accompanied by information on the components required and an indicative estimate of the scope of the works (including costs).

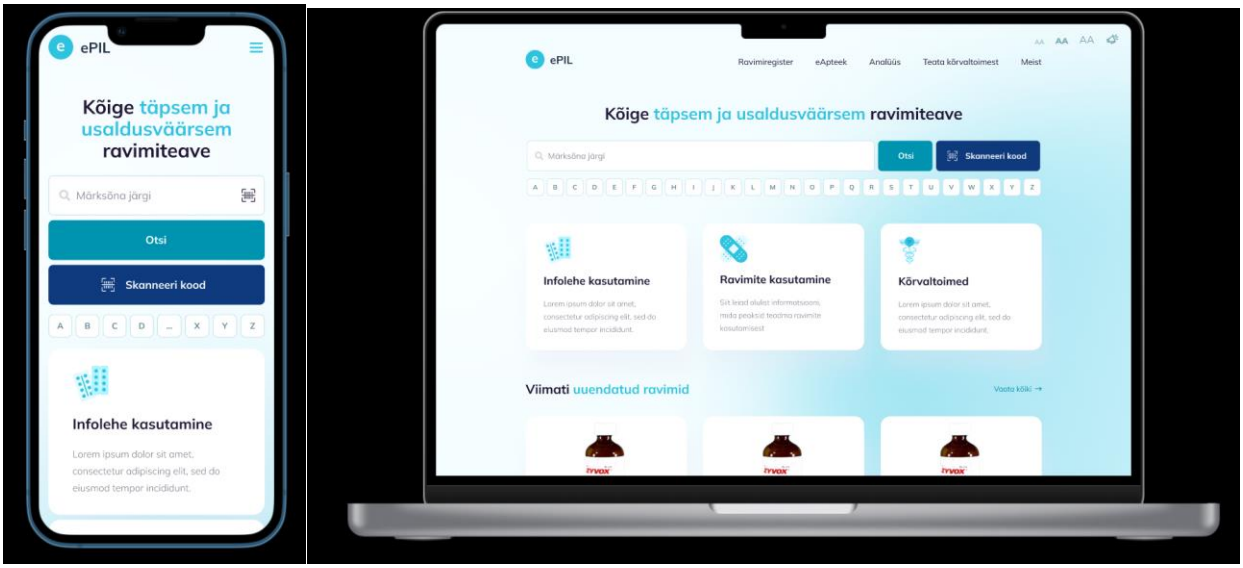
Application design vision

The visual solution has been created with a user-friendly design in mind, where the design supports readability and allows users with different needs to reach the desired result.

The design vision of the application is presented as separate links and is functionally viewable in the Figma environment.

The primary visual solution can be found by scanning the given DMC code (by mobile phone):

On the computer: [▶ Desktop - ePil (figma.com)]



1. Overview of developments in ePI

Introduction

Purpose

The aim of this preliminary analysis is to map the possibilities of ePIL implementation in Estonia and to propose possible ePIL solutions in the European context. The analysis will give an overview of current plans and project directed to the implementation of ePIL at European level and the resulting input to analyse the introduction of ePIL within Estonian context. The project will focus on an ePIL solution from a patient/user perspective, i.e. a package leaflet in a reader-friendly format that would provide relevant information on the medicine used and thereby improve patient awareness, treatment compliance and general quality of life.

Background

The package leaflet is an integral part of the marketing authorisation documentation.[1]

Electronic Product Information (ePI) is the product information (including SmPC, PL and labelling) legally required and authorised for a medical product, presented in a semi-structured format based on a common European standard. ePI contains both structured elements (headings/chapters, vocabulary) and some non-structured elements such as free text and graphics. Documents in pdf or word format are not considered as electronic product information.

The package leaflet provides the consumer with information about the medical product. The printed leaflet is accessible and familiar, but often rather difficult to read, especially when it contains information in several languages. The advantage of a paper leaflet is that it is in a format that the user is used to and is accessible due to regulatory requirements. At the same time, the paper leaflet has several disadvantages: 1) it is difficult to read due to its small print size and complex language; 2) it can be further confusing due to the multilingual nature of the leaflet - information is provided in several languages on one page and it can be difficult to find the relevant content; 3) it is procedurally difficult to change and/or update the information on the leaflet - updating the information is time-consuming and resource-intensive, and readers may not notice the changes made if the medicine is used repeatedly. As a result, information about the medicine does not always reach the consumer, which in turn can have a negative impact on patient safety. Generally, the package leaflet is available with the medicine after purchase, and people become familiar with the characteristics of the medicine only after it has been dispensed. In addition, it is difficult to fold the leaflet back into the packaging after reading. There is therefore a risk of the leaflet being lost or damaged. Printing paper leaflets is also not environmentally friendly.

[1] Conditions and amount of the fee for the variation of the marketing authorisation of a medicinal product and for the professional assessment - the Republic of Estonia, RT I, 08.07.2022, 2

In the Estonian context, the issue of joint markets is also an important topic - the packaging leaflet is often printed in several languages and is therefore large, difficult to read and manage. Procedurally, the leaflet has to be approved by the respective health authorities of the three countries, which makes the production process more time-consuming.

Sirkas and colleagues (2022)[2] conducted a study on the implementation of ePIL in hospital pharmacies and concluded that potential difficulties in the adoption of ePIL would be related to changes in existing processes and achieving clear communication. In addition, potential problems in using the online system to search for product information need to be considered. However, the advantages identified in the article were improvement of the process as a whole, increased awareness (educational aspects), better collaboration and environmental savings.

Medicines information in the European Union

In order to be marketed in the European Economic Area, a medicinal product must have a valid marketing authorisation. Marketing authorisations are issued through central or national procedures. Marketing authorisations granted through the centralised procedure are valid in all EU countries, Iceland, Liechtenstein and Norway. The type of marketing authorisation depends on the type of medicinal product. In the case of a centralised marketing authorisation, the application is submitted directly to the European Medicines Agency and the decision on the marketing authorisation is taken by the European Commission. The granting of marketing authorisations for medicinal products which are not subject to the centralised procedure falls within the competence of the Member States of the European Union. Information can be found on the websites of the national medicines authorities and in the medicines registers.

Medicines information in Estonia

Information on all medicines and their packaging available in Estonia can be found in the medicines register (ravimiregister.ee). The register contains basic information about the medicine, information on the discounts, the limit price in Estonia, the last date of supply and, as separate files, the summary of product characteristics (SmPC), the package leaflet and the text of the package leaflet. Information on centrally registered medicinal products is also available, but in a different format, with all the information on medicinal products in a single file (EPAR - European *public assessment report*). In total, according to the Estonian Medicines Agency[3] , there were 4 452 different packages of medicines (1 400 different active ingredients) marketed in Estonia in 2022, 33.6 mln packages were sold (of which 20.5 mln prescription medicines). In

[2] Sirkas , K , Juppo , A , Miettinen , M & Siven , M 2022 , ' Could paper package leaflet be left out from hospital products?' , Exploratory Research in Clinical and Social Pharmacy , vol. 7 , no. Sept , 100176 . https://doi.org/10.1016/j.rcsop.2022.100176

[3] Statistics on human medicines | Medicines Agency

exceptional cases, medicines that are not authorised in Estonia may be used in the course of treatment (especially in hospital settings)[4] .

In addition to the National Register of Medicines, information on medicines in Estonia can also be found on other health sector websites. The Kliinik.ee site is said to list information on 2040 medicines, and a search will bring up PIL information in html format with a pdf linked from the drug register (except for centrally registered medicines). Retailers have two information environments: apteegiinfo.ee and ravimiinfo.ee - both PIL and EPAR are available (opens from PIL sheet, Annex 3), information on price and availability in pharmacies is also provided. In addition, the medicines information leaflets can be accessed via the pharmacies' websites (linked from the medicines register) by searching for the relevant medicine.

Methodology

The analysis used the following methodologies: document analysis, semi-structured interview, focus group interview, and technical solution analysis.

The work has been based on the The Association of Pharmaceutical Manufacturers in Estonia's terms of reference and scope of the project (it is a preliminary analysis, i.e. a vision-level mapping of needs, opportunities and constraints).

EMA ePI key principles

Currently, the key principles for electronic product information published by the European Medicines Agency in 2020[5] is the main reference document for the development of the field. These were developed on the basis of consultation with a wide range of stakeholders and represent the guidance of the industry's lead organisations (EMA-HMA-EC) on the implementation of ePI with a view to achieving a coherent pan-European system.

The ePI common standard also defines the technical characteristics of the ePI (including mark-up language, controlled vocabularies and interoperability specifications), it has been endorsed by all interested parties and complies with the five key principles.

The five key principles define how ePI will bring benefits in the area of public health, create efficiencies in regulatory systems, relate to the existing legal framework (complementing the existing packaging leaflet), fit into the European multilingual culture and link to other digital development activities. ePI implementation will not affect the existing legislative framework for PI and will not change the content of PI.

1. Benefits for public health as a whole

[4] Over-the-counter medicines - kliinikum.ee

[5] Electronic product information for human medicines in the EU: key principles A joint EMA-HMA-EC collaboration

1.1. Expand access to information on medicines that is un-biased, up-to-date and regulator-approved.

The ePI supports the provision of the most up-to-date information on the use, benefits and risks of a medicine, while also allowing this information to be updated promptly. This ensures that information is available at the right time and supports informed decisions from the perspective of both the patient and the healthcare professional.

As ePI would be accessible through different platforms, it could also support patient information, adherence and collaboration in the treatment process, due to better information. ePI's structured presentation offers opportunities for personalisation of PI, enabling more effective information retrieval - for example, in the future it would be possible to subscribe to notifications when updates are uploaded for information on a medicine of interest. In addition, it could be possible to provide authorised information through interactive materials (e.g. video or audio) and to report adverse reactions online.

As ePI is handled electronically through machine-readable data, the information could also be linked to other systems such as electronic health record (EHR), e-prescribing, so that the right information reaches the right person at the right time. Better availability of ePI, approved at regulatory level, is a counterbalance to the unreliable and incorrect information that can be disseminated about medicines.

The implementation will aim to create an ePI for all authorised medicines for human use in the EU and ensure a rapid and consistent update of the ePI. It is technically feasible to make the ePI available through various technologies and applications, including mobile phone scanning of information on the packaging (but not required). The 2D DMC (barcode) code introduced under the Falsified Medicines Directive could also be considered for this purpose.

1.2. The introduction of ePI will improve access to information in cases of special needs, such as physical disabilities, learning difficulties or other cases. It would be possible to use a large font size according to the needs of the individual, to adapt the screen, to use screen readers, and so on. Formats used to improve accessibility must include all the information in the PIL.

2. Increasing the effectiveness of regulatory systems

2.1. The implementation of ePI is expected to increase the efficiency of regulatory processes by reducing manual work and the risk of error. The PI currently contains the same information in different sub-elements, which could also be changed automatically in the ePI.

2.1.1. Better availability of information will allow it to be analysed more effectively for different scientific purposes.

3. Compatibility with the existing legal framework

3.1. The implementation and use of ePIs must be in line with current legislation (Articles 58, 59 and 62 Directive 2001/83/EC[6]). As the current legislation does not require the submission of an electronic version of the PI, the use of ePI is not mandatory. ePI is primarily intended to extend the formats in which PI can be made available, not to replace the existing paper version. Paper PIL is particularly relevant for consumers with limited digital literacy or limited access to the internet. In terms of implementation, the PIL could contain information directing the consumer to the ePI (a guide to finding the ePI in paper).

3.2. Open access to regulatory approved information. ePI contains the same information as PI and should be provided on an open access basis. The inclusion of any information, whether for advertising or other purposes, is not permitted.

3.3. The ePI itself does not contain any personalised data. In cases where the need to process personal data arises (e.g. when developing a mobile application), the rules on the processing of personal data must be complied with.

4. Processes, roles and responsibilities for ePI implementation

4.1. In the longer term, the aim is that the ePI format will be used to process information on all medicines authorised in the EU throughout the evaluation process, but in the shorter term, the creation of an ePI is only possible in the final phase. ePI will be made available to users on websites at EMA level and possibly also at Member State level. ePI data will be made available for cross-use in other e-health systems (e.g. e-prescription). ePI will also be accessible to third parties who may make it available to patients and healthcare professionals.

4.2. Flexibility in implementation. The introduction of ePI for all medicines is a challenging task for Member States, so flexibility in the application of the system is essential.

5. EU context

5.1. Multilingual ePI. The ePI for centrally authorised medicines will be available in all official EU languages (plus Norwegian and Icelandic), while for nationally authorised ePIs, the local medicines authority will decide on the language selection. the introduction of ePI will not imply the provision of additional translations compared to the current system. PI may also be needed in some non-EU languages, but this is not currently the focus of the ePI initiative.

[6] DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on the Community code relating to medicinal products for human use

5.2. The ePI initiative is closely linked to a number of ongoing and future eHealth initiatives. It is important to achieve interoperability with other digital health systems, including cross-border prescription, electronic health record (EHR), SPOR (substance, product, organisation and referential) data system, the future veterinary ePI system and the Common European Data Model, etc.

Technical standard

In February 2022, the European Medicines Regulatory Network published a common technical standard - the **EU ePI Common Standard** - for the electronic submission of medical product information in the European Union, based on the principles of Fast Healthcare Interoperability Resources (FHIR). A public consultation was also conducted on this standard, the results of which were published in the Report on public consultation on EU ePI Common Standard.

The main points that were raised regarding the technical standard were 1) data granularity - currently data is presented in QRD (Quality Review of Documents) format, the ePI development documents have also highlighted the use of the SPOR standard - this allows ePI to be displayed section by section, combining the SPOR API and the ePI API. Increasing the granularity and standardisation of data is a future topic, which would allow for further development of user frienfly materials; 2) differentiation of style and content in ePI implementation; 3) filtering of ePI data and incremental update of data at local level; 4) test cases for generating ePIs from existing Word documents; 5) consistency with other projects and FHIR versions; 6) future business processes; 7) technical features and ePI API specification. The exact specification of the ePI API is outlined in a separate document (EMA, 2021)[7] .

The EU's ePI common standard consists of:

- ePI API specification and the related list of ePI API services (Excel),

-FHIR's XML template, based on the QDR model.

A pilot project is currently underway to implement the EU ePI common standard in regulatory processes.

This analysis is based on the principles and standard described above. Use of mobile scanning for ePIL transmission

[7] Electronic Product Information (ePI) Standard and API Specification v1 EMA/531749/2021

Further guidance on the use of mobile scanning in the delivery of the leaflet was issued by the EMA in 2018 at[8] . In accordance with Article 62 of Directive 2001/83/EC, the package leaflet and the package leaflet may contain symbols or pictograms to help clarify the information provided in Articles 54 and 59 (1). The package leaflet and package leaflet may also contain other information that is consistent with the SmPC and is useful to the patient, but any promotional information is excluded. The inclusion of information for mobile scanning is therefore permitted.

In order to add a code, a request must be submitted to the EMA, including details of the material and product information to be linked, together with a precise description of where the technology will be used to refer the patient.

QR vs DMC code

EFPIA has carried out an analysis of the use of the[9] DMC (datamatrix code) in the implementation of the ePI, using the codes on the packaging under the Falsified Medicinal Products Directive as outlined in the EMA Key Principles, which are already present on many serial medicines. EFPIA's analysis aims to foster discussion between the parties involved and to arrive at a solution with a single code on the packaging to avoid confusion. Currently, a number of Member States are working on patient-specific ePI solutions. For example, in Germany and Sweden, the DMC code on the pack is used to link the electronic leaflet to the package. Spain has adopted the DMC code in a recently launched pilot project on paperless hospital medicines.

While the ultimate goal is certainly the publication of all product information, it seems sensible to take a step-by-step approach, with the first step being the implementation of an electronic packaging leaflet as part of the ePI. EFPIA supports the idea that one DMC code, already implemented to date, could be used to provide ePI information. This would avoid the confusion that could arise from printing multiple codes on the packaging. A barrier to the use of the DMC code is that a separate app/software is required to read this code. Discussions have already started on this issue. In the short term, the ePI could also be made available by means of a QR (Quick response) code. Although this would imply an additional code on the packaging, it would not require a separate app to be downloaded to the phone. However, the ultimate goal should remain the use of the DMC code, once the technical issues have been resolved. This would reduce the number of different codes on the pack and ensure clarity for the patient. EFPIA's recommendation is to provide additional guidance on the packaging on how to access the electronic information, i.e. scan the packaging.

[8] Mobile scanning and other technologies in the labelling and package leaflet of centrally authorised medicinal products EMA/493897/2015 Rev.1

[9] POSITION PAPER Implementation of electronic product information (ePI) in the European Region: The use of Data Matrix Codes to enable easy access to ePI. Version: 08 February 2023 (unpublished draft)

The logic behind the preference for the DMC code - this code is present on the packaging of almost all medicines covered by the Falsified Medicines Directive. This serialisation code contains unique information including the product identification number (GTIN), serial number, batch number and expiry date. The GTIN code can be used to link a specific package to a specific medicine leaflet. It has been successfully used in ePI projects in Germany, Sweden and Denmark. Thus, a single code could be implemented for both the verification of the medicine and the reference to the ePI. Such an approach would avoid the need for changes to existing packaging.

In addition, the advantage of using a DMC code is the information on the batch and the expiry date. This will allow for additional enhancements in the future - e.g. expiry reminders, information about possible recalls, adverse reaction notifications that would include batch data. QR codes have the advantage of being widely used, people are already used to scanning QR codes. The use of two codes can be confusing for both the individual and the pharmacy. The additional code takes up space on the packaging, which could be used to improve legibility. At the same time, the development of a specific app and the need for the patient to download it separately is also a major obstacle. EFPIA encourages solutions that allow the DMC code to be read without the need for a specific app, as currently iOS and Android cameras do not read DMC. Therefore, EFPIA recommends a step-by-step solution - use QR codes to link electronic product information to the packaging, if mobile phones allow. Alternatively, some kind of universal (pan-European) technical solution (e.g. an app) could be developed and use DMC codes. This would allow a simpler and harmonised solution. Experience with QR codes: product specific solutions (e.g. vaccines), used for ePI in Singapore, Australia and also in the EU. Experience with DMC: used for ePackaging in Germany, Sweden, Spain, Singapore, South Africa, Poland/Ukraine.

SPOR

The ISO IDMP standard was created with the aim of of establishing a standard for information on medical products to enable the identification and exchange of this information in pharmacovigilance activities (including adverse reactions)[10] . The standard was adopted by EMA under the name SPOR. The aim of the standard is to use standardised definitions for the identification and description of a medical product in order to enable reliable exchange of information, so as to create a common 'product language' that can be used by parties. The implementation of the ISO IDMP standard started in 2012[11] and the process is ongoing, with a possible mandatory implementation in late 2024 or early 2025[12] . The implementation of SPOR is intended to create secure communication about medicines throughout the product lifecycle,

[10] Products Management Services - Implementation of International Organization for Standardization (ISO) standards for the identification of medicinal products (IDMP) in Europe EMA/676106/2019
[11] Commission Implementing Regulation (EU) No 520/2012, articles 25 and 26
[12] What is IDMP? - tepsivo.com

it is not intended to be part of the product information, nor is it designed to meet end-user requirements (accessibility, readability, etc.). The creation of the corresponding online system started in 2017 and the system is being developed and tested in parallel with the ePI system, linking the two in the PLM (Product Lifecycle Management portal).

Interoperability with EMR (electronic medical record). The interoperability of the different systems is currently an ongoing challenge, as much of the data is not clearly structured and therefore there is a lot of 'noise'. Consequently, it is very difficult to achieve a clinically valuable system. Most of the EMR information is based on freely dictated free text, intended to assist doctors in their work. However, there is an active movement towards structuring information on the EMR´s, see the EH4CR project.

EFPIA's view and recommendations for ePI implementation

AESGP, EFPIA and Medicines for Europe have published their own analysis of the ePI five key principles, focusing on a broader vision of how timely, accessible and up-to-date information on medicines can reach patients and health professionals. The benefits of ePI implementation for the patient would be in particular: 1) immediate and timely access to the regulators' approved medicines information; 2) user-friendly information to motivate patients to take a more active interest in their health; 3) mandatory information could be supported by video and audio materials to develop health awareness and safe use of medicines; 4) notifications of changes to the medicines information.

For a coherent implementation of the ePI, it is important to have a clear governance model, as well as a roadmap with clear milestones, to ensure the flexibility to reach a harmonised pan-European solution at a clearly agreed pace. In addition, it is suggested that the first phase of ePI implementation could focus on the electronic submission of PILs and SmPCs.

In addition, the implementation of an ePI will certainly have a positive impact on the availability of medicines through increased efficiency and flexibility. Multilingualism would be possible without the need for relabelling. Positive benefits would also be the potential reduction in packaging size, which is particularly important for the transport and storage of medicines stored at a controlled temperature.

For implementation, pan-European harmonisation is essential - one clear access point for ePIs and a single code on the packaging to avoid confusion for patients and pharmacists. An architectural design is essential that would uniquely guide the patient to the correct approved ePI for the specific product. Patients who are unable to access information electronically should be able to access the same information on paper. Communication is also important to raise people's awareness and readiness for change. It is also important that the ePI is compatible with

other applications and solutions in the field. When implementing an ePI, the paper leaflet should contain a standard phrase to direct the patient/user to the ePI for the given product.

EMA ePI development project

EMA ePI project (summary of the demo video 21.12.2022).

EMA is developing a MVP (minimum viable product) level system for managing ePIs. An MVP-level system means that in the first phase, basic functionalities are developed that are sufficient for the initial use of the system and for the evaluation of its usability. The PLM portal was launched on 4.11.2022 [13] and the second online demo of the ePI online system under development took place on 21.12.2022.

The aim is to create an online environment where ePIs can be created for both new and existing medicines. Once the MVP-level system is ready, it is planned to pilot it in selected four countries (Denmark, the Netherlands, Spain and Sweden).

The new information system will allow the creation of an ePI at the point of application and the updating of information on existing medicines. The MVP will consist of an ePI authorisation portal and will have the following functionalities: 1) enable ePI creation, updating, uploading (FHIR) and downloading in different formats; 2) enable rich text editing - supporting the creation and design of ePIs according to the requirements of the PI; 3) include a repository/server where ePIs will be stored and an ePI application programming interface (API) where ePI data will be made available to different stakeholders (companies, eHealth developers) for websites, etc. The MVP will also provide the possibility to create and update ePIs. Thus, the ePI data will be hosted on a server based on the FHIR standard, for which a corresponding API will be created - HL7 and FHIR are the technical messaging standards used for health data.

In the last quarter of 2022, features were added to the ePI development project to enable a comprehensive user journey for the creation and management of ePI. A number of export functions have been added, the possibility to link ePI to the SPOR system has been created, the user interface has been improved and initial testing of the system has been carried out.

[13] eSubmissions Web UI - ReleaseNotes_2 (europa.eu)

The Product Lifecycle Management (PLM) portal is the "future home" of ePIs, where it is possible to view a list of user-created ePIs as well as to create a new ePI. During the demo, it was shown how to create an ePI for an already existing medicinal product as a variation post-authorisation.

Summary of the EMA ePI demo video 22.03.2023

Over the period of Q1 2023, work has been done on the main features, tests have been carried out and user stories have been created. A QRD-based stamp in 26 languages has also been created, which provides input to the ePI authorization portal. Work has been done on the NCA pathways, with the addition of elements for the role of the regulator (ePI validation, publication to FHIR repository, etc.). On the API side, an ePI query function has been added. The demo will demonstrate the addition of NAP (nationally approved product) to the ePI system, ePI signing and ePI validation and publication by the regulator. After publishing, it is also possible to *unpublish*. The next period will be devoted to the planning and implementation of the pilot project. In the next phase the ePI will be linked to the SPOR Master data.

The Gravitate Health project

Gravitate Health - a digital health information journey

Gravitate Health is a public-private partnership organisation with 40 members in Europe and the US, with the University of Oslo in a coordinating role, Pfizer representing the pharmaceutical industry, and funding from the Innovative Medicines Initiative (IMI). Gravitate Health's mission is to create digital information tools that patients can use in their own healthcare pathways - patient empowerment, patient responsibility and safe use of medicines. Gravitate Health's vision states that a patient is engaged in his or her care process when he or she has access to understandable, relevant, reliable and evidence-based information that meets his or her specific needs, health status and competence. The aim is to propose a Gravitate Lens (G-Lens) solution for presenting ePI information to the patient. The Gravitate Health project started on 01.11.2020, has a total duration of 5 years and a budget of €18.5 million. The project will result in a White Paper, a document containing recommendations on ePI implementation strategies. The project will create an open source platform based on the HL7 FHIR standard and conduct pilot studies of the G-Lens application to assess whether the G-Lens functionality supports the patient (providing access to health information, understanding, engagement, educational materials). Involvement of all stakeholders, communication is important. In the longer term, the project will result in the sharing of experiences, communication, strategies for stakeholder involvement, the application (G-Lens IT infrastructure) and documentation (documentation, guidelines, standards) that will be created during the project.

The project consists of eight work packages:

WP1 - Identifying user needs. Using a design thinking model to create a functional design of a G-lensi solution. An information model for the ePI will be created, user scenarios and key performance indicators (KPIs) will be defined to validate the digital solution during the pilot project.

WP2 – Involvement. Input from all user groups (patients, citizens, health professionals) at all stages of the project. A variety of methods will be used to incorporate the users' perspective, including the organisation of hackathons and interoperability demos aimed at engaging SMEs as well as industry stakeholders.

WP3 - Creating the G-lens platform. The creation of a technological solution is at the core of the Gravitate Health project - the platform to be developed will integrate IT infrastructure and services using a modular and flexible layered architecture (data, services, presentation).

WP4 - End-user tools. Access to information and services. APIs and interactive solutions with G-lensi functionality will be implemented. End-user prototypes (at the minimum viable product level) will be developed for web and mobile apps, through which patients can access reliable medical information as well as educational materials, allowing end-users to improve their access, understanding, adherence to the treatment regime, safer use of medicines, health awareness, habit change, etc.

WP5 - Bringing all components together in a holistic way. ePI data, HL7 standard, regulatory, ethical components and legislative view and consistency with other standards and systems in the field.

WP6 - Evaluation and validation. Multi-faceted evaluation will be carried out through the different phases of the project - prototype testing, MVP and mock-ups testing, proof-of-concept pilot studies.

WP7 – Sustainability. In this phase, a sustainable implementation plan will be created, including recommendations on how the open source platform solutions developed under Gravitate Health could be implemented into the digital health ecosystem, providing a long-term view on how G-lens could be a dimension for each medical product, as well as providing additional risk minimisation and efficient use of medical products.

WP8 - Coordination and management. Gravitate Health project management, collaboration with partners, consortium level decision making, communication, involvement, etc.

Hospital medicines ePIL project

On 1 January 2022, a joint ePIL project for hospital medicines[14] started in Estonia, Latvia and Lithuania, where it was possible to apply for a waiver to remove the printed leaflet from the packaging of medicines used in hospital settings. The necessary drug information is available to the user in the drug register. The aim of the project is to assess the impact of the waiver on the retrieval and safe use of medicines and the availability of hospital medicines. Marketing authorisation holders were invited to participate in the project, which is now in its second year.

In Belgium and Luxembourg, the ePIL pilot project[15] was launched in 2018 by the Belgian and Luxembourg pharmaceutical associations in collaboration with local medicines authorities and hospital pharmacy associations, with the agreement of the European Commission. In 2022, an analysis of the results was presented in a 24-month summary. To facilitate the process, all Belgian and Luxembourg hospitals participated in the project (so that MAHs would not have to supply both leaflet and nonleaflet medicines at the same time). In the first phase of the project, 12 products (from 10 manufacturers) were focused on, in the second phase 42 products (from 18 manufacturers). The results showed that, in terms of handling of medicines, 33% of pharmacists saw a positive impact and 64% saw no impact; in terms of time, around 25% saw a positive impact, 2% felt a negative impact and 73% saw no impact. The largest positive impact was seen in waste management, where nearly 90% of users observed a positive impact and about 10% did not notice a significant impact. The overall conclusion of the project was that 98% of pharmacists felt that the absence of paper PIL did not have a significant impact on their work processes. In total, 409 511 products were transmitted without paper PIL. In summary, it was concluded that ePIL is as effective and secure in communicating information as paper PIL in hospital settings. The use of an electronic version either has no impact at all or has a positive impact on work processes and time use. The third (and final) phase of the project started in August 2022 and will run until 2025 - the aim is to validate the results on a wider sample (involving more products) and to compare the results with similar projects started in the Baltic States and Spain to support possible legislative changes at European level.

In summary, there are several projects underway at EU level related to the development of an electronic product information system, but the exact form and timing of their realisation is not yet certain.

[14] Haiglaravimite ePIL projekt algas 1. jaanuaril 2022 | Ravimiamet
[15] rr-april-2022-e-pil.pdf (pharma.be)

2. Models in European countries for making available information on medicines

All medicines registered at EU level can be found in the central database of the Union Register of medicinal products. In all EU countries, the PIL is available as a pdf or word file on the **local** Health Authority website. In some cases, the information field to search for a medicinal product can be found directly on the home page of the local medicines authority, in other cases it is rather difficult to find. In most cases, it is possible to search through several information fields (active substance, ATC code, manufacturer). In most cases, it is possible to open the **PIL and the SmPC via a separate link** that opens on a separate page. In some cases the file does not open in a separate window but is automatically downloaded to the user's device. In terms of accessibility, it is possible to implement the solutions offered by the browser (font enlargement, text reading - functions depend on the program used and are provided that the user can find the corresponding options on the page). In many cases, a link to the adverse reaction information is provided with the information on the medicinal product. A more comprehensive solution is offered by the **Spanish** system, where there is a mobile phone app to display the package leaflet via the code on the product. The **barcode** on the pack has to be **scanned** and this can be used to open the PIL for a particular medicine on the phone, as well as the SmPC, both open as html files structured by titles.

In addition, in a number of countries, information on PILs republished by **third parties** is also available. In most cases, the information is presented in a click-by-heading style html format. Among the third party solutions, accessibility features are the most commonly found. In addition, it is possible to store information on medicines of interest, to receive notifications of updates, to check the availability of medicines in pharmacies. **Sweden, Norway** and the **Netherlands** can be considered as the most functional sites. In the Swedish system, it is possible to view the PIL through the barcode on the packaging using the app, while the Dutch and Norwegian pages allow access to PIL information through the mobile version of the website, which has a barcode reading function on the home page.

In addition, **US**, **Japanese** and **Canadian** models were included in the current review. The Japanese model can be considered as one of the most successful in ePIL implementation, as **from August 2021 only electronic leaflets will be used for prescription medicines**, with the corresponding technical solution and communication. The US medicines site is a very important benchmark in terms of drug information, as their drug information database is the **most visited in the** world. Canada, on the other hand, has taken an important role **in standardising** PI information.

The table in Annex 2 shows the PIL information sheets found during the review, with an indication of the publisher and a description of the functions. In several cases (e.g. the Netherlands, Norway and Sweden) **the national authority and third party pages are also integrated.**

More advanced approaches in providing ePIL information

The following are more detailed descriptions of solutions in some countries where, a more advanced (third-party) system is in use or where other interesting developments are taking place. Due to the large amount of information on the subject and the different languages in which it is presented, it is possible that some third party pharmacovigilance websites have not been described.

Sweden

On the Swedish Medicines Agency's website lakemedelsverket.se you can find drug information, where SmPC opens as a pdf file, but when opening the PIL the user is redirected by a link to fass.se. This is the website of the Swedish Medicines Association, which contains PIL information in html format. In addition, information about the packaging, availability in pharmacies, pictures of how to correctly split the tablet and other graphical information is provided. Information for health professionals (SmPC) is also available. All the information can also be presented in audio and, if necessary, in a large font and high contrast version to ensure accessibility. The site also has an API to link this information to other databases. A mobile app has been developed, with separate versions for patients and health professionals. You can search for a medicine by starting to type the name of the medicine or you can search by scanning the barcode or 2D code found on the packaging.

In 2023, a pilot project on ePI will be carried out in Sweden to analyse the possibilities of using the XML format to better structure information and achieve machine readability (see also developer information). The aim is to analyse further possibilities, e.g. adding search functionality and combining with additional eHealth data, parallel to participation in the EMA ePI project.

Sweden has also developed a separate strategy document[16] to support the uptake of ePI, which has been developed with the involvement of all key stakeholders with the aim of better structuring product information so that it can be implemented in an even wider and more integrated way.

Belgium

[16] Strukturering och digitalisering av svensk produktinformation Förstudierapport från Läkemedelsverket (*Strukturing and digitalisation of Swedish product information. Study report from the Swedish Medical Products Agency*). 24.01.2019

The website of the Belgian Medicines Agency has a search engine database for finding information on medicines, basededonneesdesmedicaments.be, which opens the PIL in pdf format. Healthcare professionals can find the PIL in four different places.

On the Pharmaceutical Industry Association website, there is a package leaflet for the general user linked to E-Compendium (e-notice.be). On this website it is possible to search for a drug leaflet by name and then links to the different packs/forms of the given medicine will open, after selecting a specific pack the page will open in html format, the text is structured according to the topics of the PIL, in addition the price of the medicine is indicated. The page has a print function. On the home page there is a link to the adverse reaction reporting environment. In addition, there is a video with general information on targeted use of medicines and a link to vaccination schedules. There is a separate page with a place to search for research on medicines, which opens the SmPC. You can choose between French, Dutch and German. In addition, the General Association of the Pharmaceutical Industry is running the above-mentioned e-PIL pilot project for hospital medicines (The e-PIL Pilot Project | pharma.be).

Netherlands

The Dutch Medicines Agency's website www.geneesmiddeleninformatiebank.nl provides a central search box where you can enter the name of the medicine, search by additional information and search by complaint. The site is in Dutch, with English available at the bottom of the page. Clicking on the link with the name of the medicine will open a page with a note that it is an approved product. Links to the SmPC and PIL are included. In addition, there is a link to a separate page for healthcare professionals www.farmacotherapeutischkompas.nl with the html version of the information and the content of the SmPC. The page also links to the adverse reaction database https://www.lareb.nl (where adverse reactions can be searched for as well as reported). There is also a link to www.apotheek.nl, where it is possible to search for medicinal products, the information is in html format and accessibility requirements have been taken into account (it is possible to change the size of the text, the text can be read aloud). It is also possible to search for information by complaint. General information on the use of medicines, regulations, etc. is also provided. There are also videos with more general instructions, e.g. how to take tablets, how to use a nasal spray, etc. Apotheek.nl is an initiative of the Royal Dutch Society for the Promotion of Pharmacy.

Ireland

Medicines information can be searched for and found on the local Health Products Regulatory Authority (HPRA) website Find a medicine (hpra.ie), which opens PIL and SmPC documents as pdf files. In addition, information on medicines can be found on www.medicines.ie, which is managed by the Irish Pharmaceutical Healthcare Association. The home page has a central search bar -

searching by name will bring up the different versions of the medicine and selecting the appropriate one will open the SmPC and PIL, with the dates of approval. On the page it is possible to search for medicines by active substance. In terms of accessibility, an option to change the text size has been added in a prominent place. In addition, there is a link to adverse reaction reporting. The options for increasing the size of the font to ensure accessibility are clearly visible.

France

The package leaflets can be found on the database of the local medicines authority, where they are available as PIL and SmPC files. In addition, the package leaflets are also available on the website of a private company www.vidal.fr, which is part of the Vidal group. When searching for a medicinal product, information is displayed which differs in part from the structure of the PIL (additional information (e.g. interactions) can be accessed by membership). For ease of use, there are instructions on how to download the app on your phone and view the drug information there. In addition, it is also possible to search for medicines by active ingredient, search for international analogues. The site has a separate news section and login search facilities. In the accessibility section, links to increase the fund are highlighted. According to the information on the website, vidal.fr is visited by more than 5 million people a month and is the leading site for information on medicines in France.

Denmark

The electronic package leaflets are available on Indlægssedler.dk, managed by medicin.dk, which is owned by Dansk Lægemiddel Information A/S (DLI A/S), which in turn is part of the Pharmaceutical Industry Association Lægemiddelindustriforeningen (Lif). The package leaflet opens in html format, the information is linked under the headings, with a link next to it to information for health professionals (SmPC). Pictures of specific tablets are attached. As an innovation, there is information on the possibility to scan the code from the package to display the leaflet on the phone. It is also possible to download a separate app to read the leaflets on the packaging, which requires an internet connection to work. However, it is also possible to download the app min.medicin.dk for offline use. Medicin.dk also offers an API, which can be used to bring a party interested in the drug information into their information systems. API - Medicin.dk. In addition, the site has videos with information about medicines.

Norway

In Norway, the system is structured as a collaborative model between the Local Medicines Agency (NCA) and the pharmaceutical manufacturers (the Norwegian Pharmaceutical Compendium - Felleskatalogen), who have set up a system for the submission of validated ePILs by regulators. The Norwegian Medicines Agency website opens a separate page, Legemiddelsøk, where it is possible to search for medicinal products by name, as well as select from an

alphabetical list. The PIL is provided as a link to another environment in Medisin - Felleskatalogen. The PIL opens in html format, with the option to open SmPC via the link. The information is grouped by titles with links, with the option to select a reading icon. Side effects can be searched for separately and a link to report side effects is provided. Information on the price of the medicine is included. Felleskatalogen is part of The Norwegian Pharmaceutical Compendium, a private company belonging to the Norwegian Pharmaceutical Industry Association. In addition, the leaflet contains information on interactions.

Spain

The local medicines office website (aemps.gob.es) provides a link to the medicines information page CIMA Centro de información de medicamentos, where you can search for medicines by name. The PIL opens via a link on a separate page as html text, next to the PIL there is a link to the SmPC. There is also a link for reporting adverse reactions. Separately, it is possible to register and save medicines of interest to receive updates. Videos are provided with general information, also available in sign language. Although the brochure states that a code can be scanned from the packaging to access the information, no description of how to do this can be found on the website. It is possible to download an app to use CIMA. For health professionals, the link opens another environment for more specific information. The Spanish ePI project started in 2015 as a pilot project in collaboration with three Marketing Authorisation Holders (MAHs) and by 2017, ePIL was available for 85% of nationally authorised medicines. The created environment also allows the exchange of information between MAHs and the local medicines office, where the system shows the status of the submitted document. In addition, Spain is actively involved in the piloting of EMA solutions, both for the implementation of the hospital medicines[17] and the ePI system.

Germany

On the website of the Federal Institute for Drugs and Medical Devices, www.bfarm.de, there is a link to the medicines information page www.pharmnet-bund.de - this page contains information for patients/public as well as a section for partners (for companies to submit information). There is a separate Arzneimittel-Informationssystem (dimdi.de) database for searching for a medicine - it contains different information on the medicine searched for, but does not lead to a specific PIL document. There is also a page of the private company Vidal MMi Germany GmBH, where, in addition to other health information, you can also find package leaflets, which open as pdf files and can also be used via the app.

[17] La AEMPS impulsa un proyecto piloto sobre el acceso a la información electrónica de medicamentos de ámbito hospitalario y supresión del prospecto en papel. (The AEMPS promotes a pilot project on the access to electronic information of hospital-based medicines and discarding of the paper package leaflet) MUH, 15/2021

United Kingdom

Datapharm is a leading provider of medical information in the UK. The company has been operating for almost a quarter of a century with the aim of providing medical information through technology-driven solutions to the healthcare sector and also from a scientific perspective. Datapharm has created the platform https://www.medicines.org.uk/, which contains up-to-date, accessible information on medicines licensed in the UK. The EMC website features over 10 000 medicines from more than 300 pharmaceutical companies, approved at either UK or European level. Entering a medicinal product will bring up a search result with a link to the SmPC or PIL. The PIL opens as a pdf file. The page provides links to search for possible medicines with the same active ingredient and ATC code, to view changes, to save the medicine of interest and also a link to report adverse reactions.

Japan

The Pharmaceuticals and Medical Devices Agency (PMDA) website has a link on the front page to find PI information, which opens a self-service search facility at https://www.pmda.go.jp/english/search_index.html. There are links to resize the text. According to the information on the website, the inclusion of paper package leaflets in prescription medicine packages will be discontinued from August 2021 (read more: Electronic Package Inserts). In the case of over-the-counter medicines, package leaflets will continue to be available. There is a separate guide on the website on how to find the leaflet - you should use a phone tip to read the code on the pack. It was decided to use the GS1 *barcode*, based on the GS1 standard[18] . However, if the patient still needs a paper copy of the leaflet, they can obtain it as follows: "紙媒体の添付文書情報が必要な場合は、各社の医薬情報担当者や情報提供窓口から提供させていただきます。" which means " *If package insert information in paper is required, it will be provided by the respective company's medical information officer or information contact.*"[19]

Canada

Health Canada's website provides a separate link to the Drug Product Database (DPD), where you can search for drugs by various attributes - in the absence of a free search field it is quite difficult to find a drug, for a product there is a link to a *Product Monograph in* pdf format (which is similar in content to SmPC information). It is therefore primarily a database aimed at the specialist level, not for finding patient information. At the same time, Canada has invested in bringing the

[18] GS1 Digital Link helps deliver valuable e-leaflet information to healthcare providers and patients. *GS1 Healthcare Reference Book 2021-2022*.
[19] Information found and translated in consultation with the Embassy of Japan in Estonia.

information on medicines into a machine-readable format, so that it is easier to process electronically.

USA

On the U.S. Food & Drug Administration (FDA) website, you can first find videos with general information on how to take medicines, and then links to find information on: 1) Find a Medication Guide - Medication Guides (fda.gov) - on this page you will find the medicines sorted by name and you can also subscribe to receive notifications of changes to the medicine of interest - when you open the information on the medicine you will see a pdf file with SmPC level of detail in a separate window; 2) The FDA website also provides a link to MedlinePlus - where you can enter the name of the medicine in the search engine and then you will see PIL style patient information in html text grouped under headings. In addition, the FDA also has a link on this page for finding and reporting adverse reactions, and a link to instructions on what to do with medicines you don't use. *MedlinePlus* is based on the NIH's National Library of Medicines database and also contains a variety of other patient-oriented information. In 2021, the site was visited by 418 million users more than 888 million times.

3. ePIL architectural design baselines

In order to describe the architectural design and interoperability of the ePIL, both the technical solution and the governance model need to be assessed, in particular from the point of view of the technical development and management of the system.

The governance model for ePIL is rather complex, involving pharmaceutical manufacturers, the European and local medicines authorities, the Health Insurance Fund, and medicines users. At present, the governance model has not been finalised.

The European Medicines Agency (EMA) has developed initial broad guidelines for the implementation of the ePIL technical solution. At the moment, the package leaflet is available through the local and EMEA registries in pdf format (and on-pack with each medicinal product). ePIL data is partly structured but not machine-readable (or standardised). The longer term goal could be to bring the data in the product information leaflet into a machine-readable format. This would increase the usability of such information for the patient (as well as cross-use across systems).

Implementation of the ePIL architectural solution

Given that the final governance model is still being developed, it would be reasonable to break down the implementation of the technical solution into phases.

The first step could be to make existing information available to the patient in pdf format (which would also build up the habit of displaying the leaflet in code, for example on the phone, while still being more user-friendly than a paper leaflet). At the same time, the paper version of the leaflet would remain in use (as there may always be situations where the electronic version is not available). Such a solution can be easily and quickly implemented and does not require extensive development. Manufacturers would be required to include a corresponding 2D code (which is already being added) on each package, which would include a standard reference to the Register of Medicinal Products. The reference must include a unique identifier for the medicinal product, which can be used to either locate the corresponding leaflet in pdf format or, where structured information is available, to display information on the medicinal product in a user-friendly format.

If, as a first step, a solution has been implemented to scan the corresponding code on the packaging to display the current information in pdf format, the concept itself can be considered to have been implemented. As a next step, it will be possible to solve the problem of converting the information into a machine-readable format and replacing the information already in pdf format with that already in machine-readable format, which will allow the information to be better structured and displayed in a format that best meets the patient's needs.

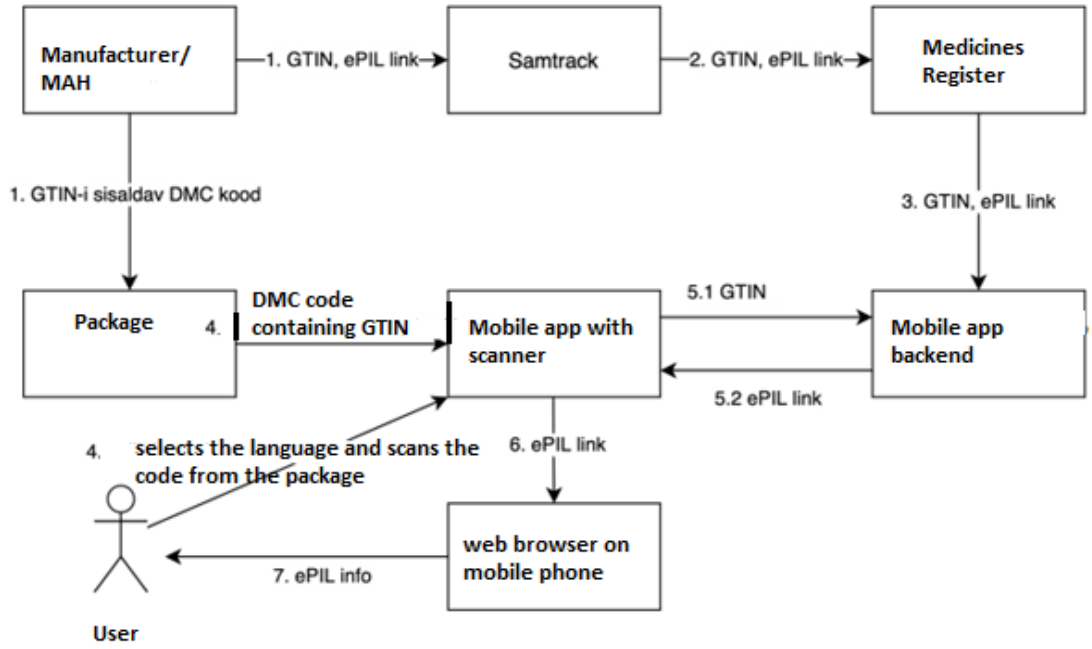
Future solutions

From the point of view of the interoperability of ePILs, the linking of the relevant information with the digital prescription data (managed by the Health Insurance Fund) should be considered, in particular with regard to administration. The latter information is important for the patient, but at the same time there is nowhere for the patient to check it immediately. This is information for the individual patient, which needs to be personalised (it is personalised information). However, concrete technical solutions can be considered only after the technical side of the solution/entity at European level has been precisely developed and the governance model agreed in Estonia. As a complementary option, the electronic availability of expiry date information for the patient in the safety element could be considered in the future.

ePIL technical solution alternatives

Alternatives based on the Estonian Medicines Agency's Register of Medicinal Products and DMC code.

Alternative 1 - Product code (GTIN) in the Medicines Register + scanner *backend*



1. *A Datamatrix* (DMC) code containing the GTIN (product code) will be added to the packaging by the manufacturer or marketing authorisation holder for REKS. The link to the ePIL and the GTIN are registered by the manufacturer when the medicinal product is registered with the Agency, and by the Agency in the Agency's information system Samtrack. The ePIL links are updated in Samtrack as necessary.
2. Data on Samtrack are regularly entered in the Medicines Register.
    a. The GTIN is currently missing from the Register of Medicinal Products.
    b. ePIL links will be entered in the Medicines Register.
3. *The backend of the* mobile application synchronises the data from the Pharmaceuticals Register over the X-road on a weekly basis, keeping only the ePIL links and the GTIN code.
4. The user selects a language in the mobile app and scans the package with the DMC code containing the GTIN.
5. The mobile app extracts the GTIN from the DMC code and sends the language and GTIN code to *the backend* and receives back the ePIL link in the desired language.
6. The mobile app opens a package leaflet on your mobile device using the ePIL link.
7. The user can access the ePIL information.

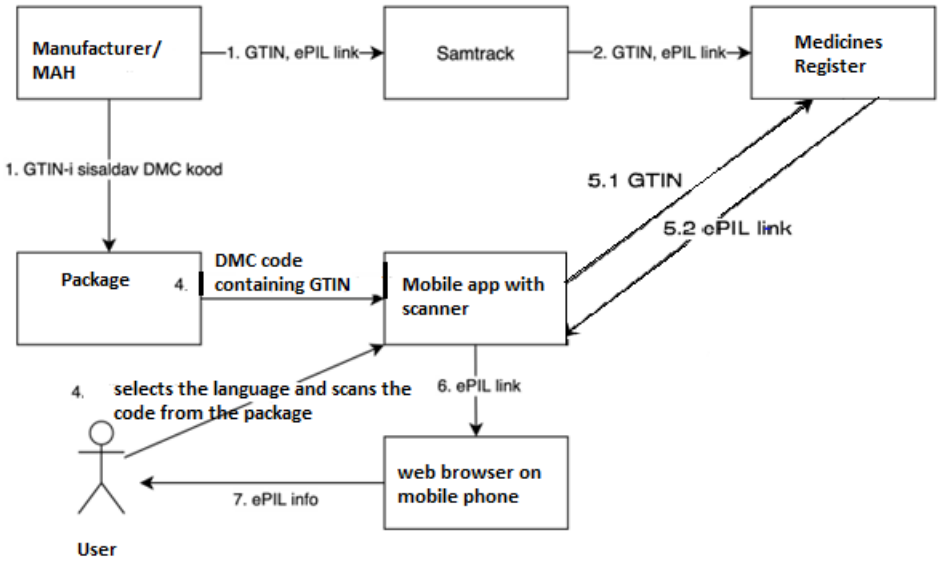
Strengths of the alternative:

1. DMC codes containing the GTIN already on the packaging can be used.
2. The ePIL links in the Medicines Register can be used and will be maintained.
3. The solution is not very dependent on the availability of the Medicines Register - the synchronisation of the Medicines Register can be repeated if it fails immediately.

Weaknesses of the alternative:

1. To register GTINs, the national medicines information systems Samtrack and the Medicines Register need to be developed.

Alternative 2 - Product code (GTIN) in the Medicines Register, Medicines Register is the scanner *backend.*



Basically the same as the previous one, but instead of developing a separate *backend, a* service will be developed for the Medicines Register to query the ePIL link based on language and GTIN. Step 3, the synchronisation of the *backend* and the RR will be omitted. Step 5, the query will be done in the Pharma Register.

Strengths of the alternative:

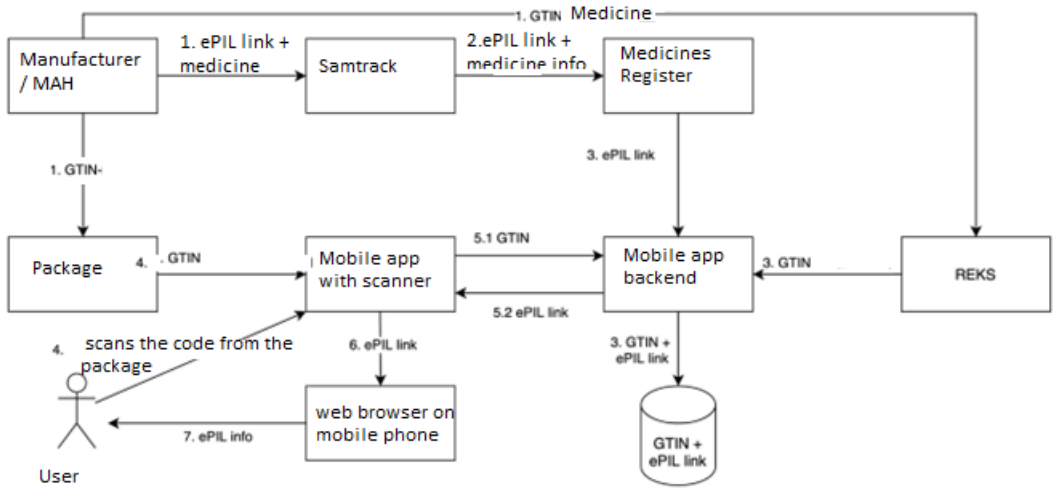
1. The DMC codes containing the GTIN already applied to the packaging for REKS can be used.
2. The ePIL links in the Medicines Register can be used and will be maintained.
3. There is no need to develop the *backend of the* mobile app separately.

Weaknesses of the alternative:

1. To register GTINs, the national medicines information systems Samtrack and the Medicines Register need to be developed.
2. A new service must be developed for the Medicines Register.

3. The solution is highly dependent on the availability of the Pharmaceutical Register .

Alternative 3 - The scanner *backend* finds the GTIN and ePIL links using REKS and the Medicines Register.



1. The DMC code containing the GTIN (product code) will be added to the packaging by the manufacturer or marketing authorisation holder for REKS purposes. The manufacturer registers the product information and the links to the ePIL in three languages (Estonian, Russian, English) at the time of registration of the medicinal product with the Medicines Agency, which registers them in the Agency's information system Samtrack. The ePIL links are updated in Samtrack as necessary.
2. Samtrack is regularly entered into the ePIL and the Medicines Register.
3. *The backend of the* mobile application synchronises data from the Medicines Register and REKS over the X-road on a nightly basis. The drug information base is matched with the REKS and the drug registry data and the scanner backend, keeping only the ePIL links and the GTIN code. The following Medicines Register and REKS data will probably be used for matching.

Register of medicines	REKS (https://eur-lex.europa.eu/legal-content/ET/TXT/HTML/?uri=CELEX:32016R0161&from=EN Article 33)
Title	name of the medicinal product, common name
pharmaceutical form.NameEstonia	Medication form
active ingredients. active substanceYhik active substanceYhikusYhik size yikusuurusYhik	Ingredients

packingLiik - { 'Specialtyfood', 'MyygiloagaRavim', 'MyygiloataRavim', 'MyygiloaConditionalRavim'}	type of pharmaceutical package
quantityPackage	Size of medicine pack

4. The user selects the language in the mobile app and scans the package with the DMC code containing the GTIN.
5. The mobile app extracts the GTIN from the DMC code and sends the language and GTIN code to *the backend*, and receives back the ePIL link in the desired language.
6. The mobile app opens a packaging leaflet on a mobile device using the ePIL link
7. The user can consult the ePIL information.

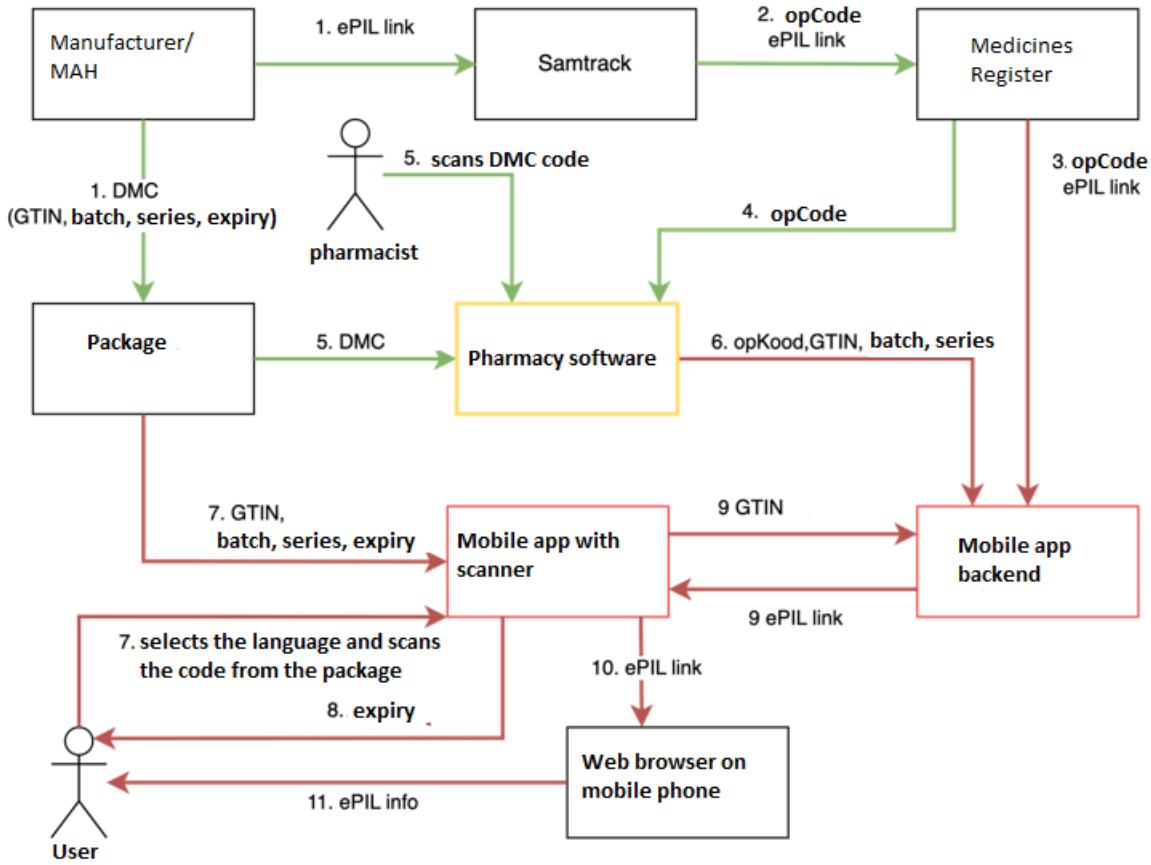
Strengths of the alternative:

1. The DMC codes containing the GTIN already applied to the packaging for REKS can be used.
2. The ePIL links in the Medicines Register can be used and are maintained.
3. Compared to the previous alternatives, there is no need to additionally develop national information systems (Samtrack and the Medicines Register).

Weaknesses of the alternative:

1. The automatic matching of medicines based on the information in the Medicines Register and the REKS may not be accurate and the system may not be able to find ePIL links corresponding to all GTIN codes. Continuous manual post-matching may be necessary.

Alternative 4 - The pharmacy links the DMC code (GTIN, batch, series) of the package to the Pharmacy Register package code.



1. The GTIN (product code), the batch, serial number and the *Datamatrix* (DMC) expiry code will be added to the packaging by the manufacturer or marketing authorisation holder for REKS purposes. The manufacturer registers the ePIL link when registering the medicinal product with the Agency, the Agency registers it in the Agency's information system Samtrack. Samtrack generates a packaging code for each medicine pack. The ePIL links are updated in Samtrack as necessary. (This is already being done)
2. Data on Samtrack are regularly entered in the Medicines Register. (This is already being done)
    a. Packaging codes.
    b. ePIL links for three languages.
3. The backend of the mobile app synchronises the data from the Medicines Register over the X-road on a weekly basis, keeping only the ePIL links and the opCode (thus updating the ePIL links so that the patient receives the latest version of the ePIL).
4. Pharmacies regularly synchronise the data in the Medicines Register, including opCodes. When a prescription is dispensed, the opCode of the Pharmacy Register goes to the prescription centre.
5. The pharmacist scans the DMC code when the pack is sold to check the authenticity of the medicine from REKS.

6. After the authenticity check is successful in REKS (after deactivation of the package) and the opCode is added to the package in the Prescription Centre, the pharmacy information system adds the GTIN, batch, serial, opCode read from the DMC code to the mobile app backend.
7. The user selects the language in the mobile app and scans the DMC code from the package.
8. The mobile app will display the expiry date of the packaging from the DMC code (especially if the expiry date has already passed).
9. The mobile app finds the GTIN, batch and series from the DMC code and sends the language and GTIN, batch and series to the *backend* and gets back the link to the ePIL in the desired language.
10. The mobile app opens a package leaflet on your mobile device using the ePIL link.
11. The user can consult the ePIL information.

Strengths of the alternative:

1. DMC codes containing the GTIN already on the packaging can be used.
2. The ePIL links in the Medicines Register can be used and will be maintained.
3. The solution is not very dependent on the availability of the Medicines Register - the synchronisation of the Medicines Register can be repeated if it fails immediately.
4. The DMC code on the packaging and the link to the ePIL can be linked exactly.
5. There are two pharmacy information systems in Estonia and it is not necessary to develop many information systems to realise the alternative.
6. The DMC code of the packaging will only be placed in the public mobile app *backend* after the packaging has been sold and deactivated in REKS, so there is no fear of the codes being re-used for authenticity checks.
7. Allows for further development so that the dosage of the medication can be read from the prescription centre (or can be added to the backend pharmacy software if the dosage is not changed in the prescription centre after dispensing).

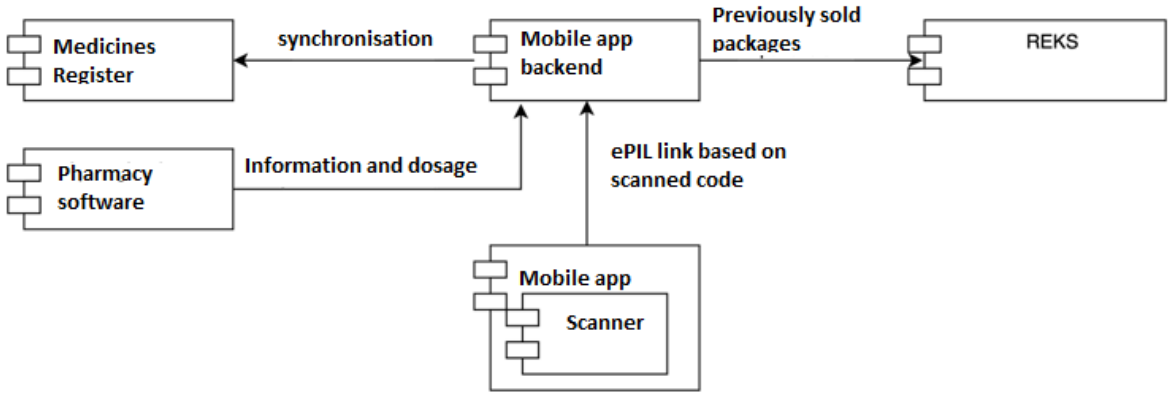
Weaknesses of the alternative:

1. Requires a separate mobile app that users must download.
2. Developers of pharmacy information systems may not come up with an idea and realise it, or they may charge a very high price to realise it, even though the development is not very large.
3. The ePIL cannot be displayed when scanning DMC codes of packages sold before the system is started.

Alternative 4 + developments needed for alternative 3 and their cost estimation.

By combining Alternatives 4 and 3, the best overlap between DMC code and ePIL can be achieved. In addition, it is also possible to obtain dosage information linked to the packaging from the pharmacy software.

Solution Component themselves and their cost estimates

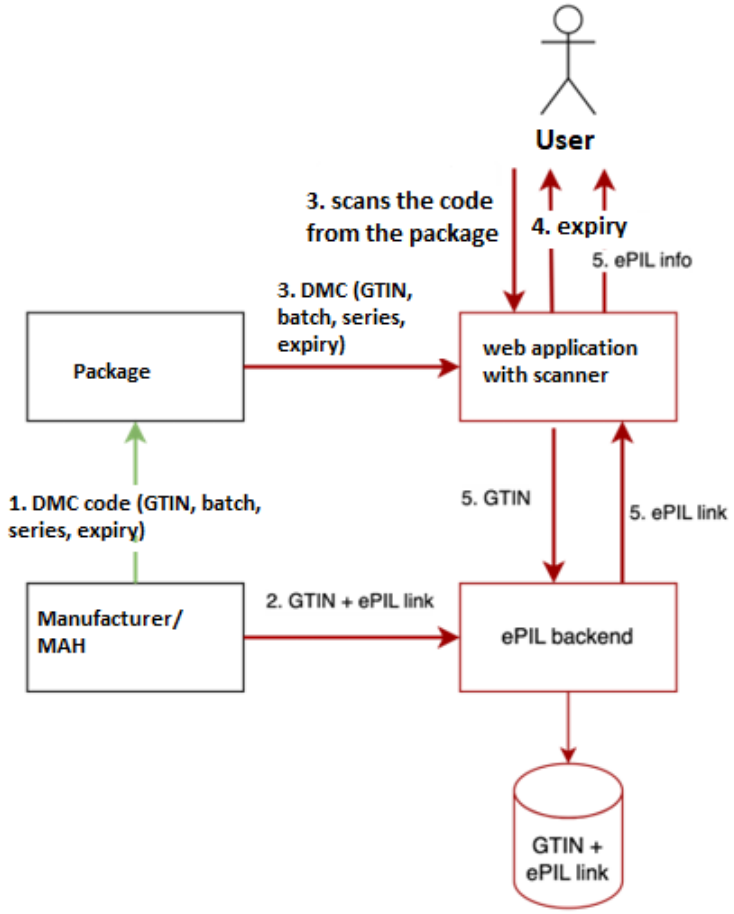


Title	Purpose and need for development	Cost
Medicines Register	Links to ePILs can be obtained from the Medicines Register; the Medicines Register Synchronisation X-Road Interface is available here https://ravimiregister.ee/?pv=PublicHelp There is no need for development.	0
Mobile app *backend*	Finds the ePIL link based on the DataMatrix code scanned from the package. Development is needed: • Regular uploading of changes from the Medicines Register to the *backend* database, need to synchronise at least opCode, drug name, ePIL links. • A web service whereby pharmacy software can transmit the GTIN, batch, series (and could also transmit the dosage) of the package sold as read from the DMC code (the pharmacy or software will also need to be authenticated/authorised!). • A web service that allows the mobile app user to read the ePIL link (and dosage) based on the scanned DMC code. • If the DMC code is not in the database, the *backend* could try to find it in the REKS system (REKS should have a service for this).	30 000 €
Mobile app	Allows you to scan the DMC code from the package, the expiry date detected and display the ePIL (and dosage) using the *backend* service. For example, the Google Machine Learning Kit https://developers.google.com/ml-kit/vision/barcode-scanning can be used to scan DMC code.	20 000 € Android 20 000 € IOS

Pharmacy software	In the pharmacy's software, after the prescription is dispensed, you can get the DMC code scanned for REKS, the Medicines Register opCode (and the dosage of the medicine) registered when the prescription is dispensed. The sending of this information to the backend *of the* mobile app needs to be developed.	10 000 € per software
REKS	When the system goes live, people will have in their hands the packs they bought before the launch, for which pharmacies have not sent DMC codes to the *backend of the* mobile app. REKS is the only system with deactivated DMC codes. Does REKS have a technical interface to read them?	?

Alternative 5 - Manufacturer sends GTIN and ePIL link to ePIL *backend*

A separate **ePIL application** will be developed (GTIN database will be created) + a **web application** with a scanner.



1. The GTIN (product code), the batch, serial number and the Datamatrix (DMC) expiry code will be added to the packaging by the manufacturer or marketing authorisation holder for REKS purposes. (This is already done)

2. The manufacturer will add the GTIN and the related (Estonian) ePI link to the ePIL *backend*. The *backend* stores the link in the database.
3. The user scans the DMC code from the package. To do this, the user must first go to a web application page with a web browser, and the browser will load an application with a scanner to read the DMC. When using the application for the first time, the user must allow the application to use the camera on his/her computer or mobile phone. The web application extracts the expiry from the DMC code and displays it to the user.
4. The web application also extracts the GTIN from the DMC code and finds the link to the ePIL in *the backend* and displays the ePIL information to the user via the link.

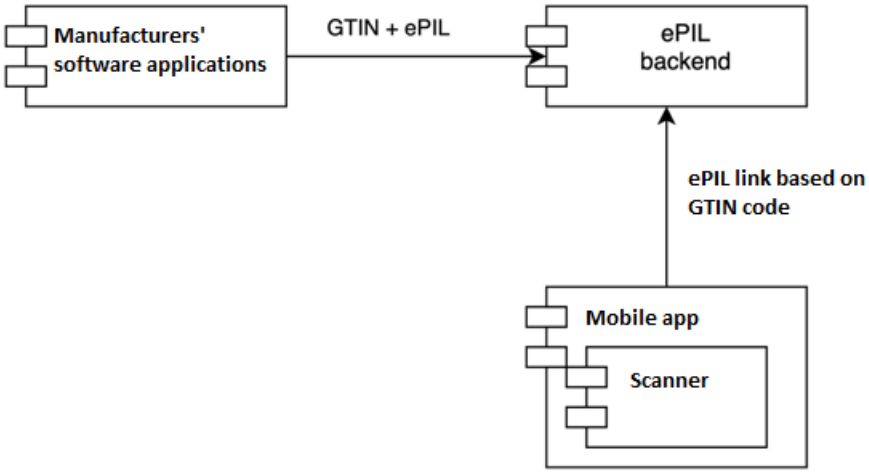
Strengths of the alternative:

1. DMCs containing GTINs already applied to packaging for REKS can be used.
2. The DMC code on the packaging and the link to the ePIL can be linked exactly.

Weaknesses of the alternative:

1. Obtaining GTIN + ePIL links for all medicines from all manufacturers can be a very lengthy process. It is likely that when the system is launched, there will be many packs that when scanned with the GTIN code, the pack will not be found.
2. When used in a web browser, there may not be as good a DMC code scanner as is available for mobile apps.

Components needed for the solution and their cost estimation



Title	Purpose and development needs	Cost
ePIL *backend*	Finds the ePIL link based on the DMC code scanned from the package. Development needs:	25 000 €

	• For manufacturers, a GTIN + ePIL upload service and possibly a user interface. The service will need to include producer authorisation. • A web service that allows a web application user to read a link to an ePIL based on the GTIN found in the scanned DMC code.	
Web application scanner	Allows you to scan the DMC code from the package, the expiry date detected and display the ePIL using the backend service. In order to scan DMC code, it is necessary to find a scanner that works in a web browser (e.g. a freeware scanner that integrates with web applications and supports the formats supported: https://github.com/mebjas/html5-qrcode#supported-code-formats. It is certainly necessary to test the quality of the scan before deployment).	25 000 €

Service maintenance costs

The infrastructure costs of the solution are likely to be marginal, less than €1000 per year. The higher cost is likely to be the cost of providing user support and technical assistance and keeping it up to date. It is estimated that the cost could be in the order of €20 000 per year, unless a separate organisation needs to be developed.

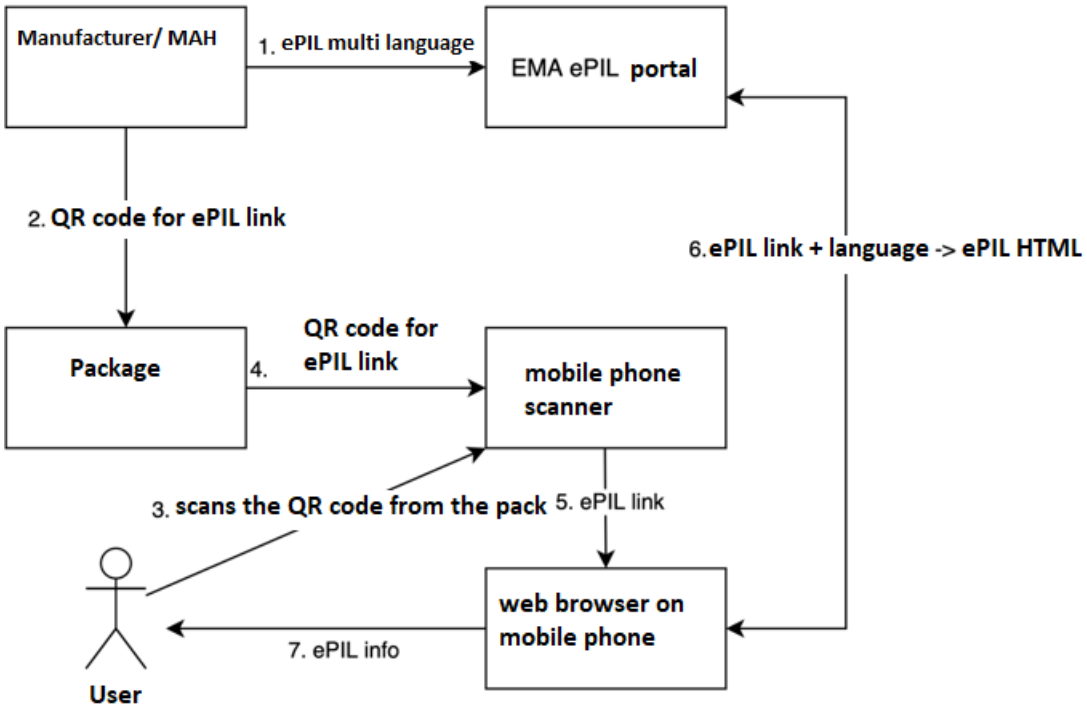
Extension possibilities

1. **Functionality of ePIL in English and Russian.** If there is a desire to display ePILs in Russian and English in addition to Estonian, the ePIL backend would need to be interfaced with the Medicines Register, where the Medicines Agency maintains the ePIL links in these languages. For interfacing with the Medicines Register, it would be good to have a GTIN there, or manufacturers should also add a link between the Medicines Register drug card or packaging code (opCode) and GTIN to the backend. Estimated cost around €20 000.
2. **Dosing.** After scanning the packaging, it would also be possible to immediately display the dosage of the medicine as indicated by the doctor on the prescription on the basis of which the packaging was purchased. For this purpose, the ePIL *backend* would need to be interfaced with pharmacy information systems, which would transmit the GTIN, batch and series, and the dosage that was on the prescription to the *backend* after deactivation and purchase in REKS. Cost estimate €20 000 for the ePIL *backend* and €10 000 for the web application per pharmacy software.
3. **Who is the medicine for?** Once the packaging has been scanned, it would also be possible to display who the medicine is for. To do this, in addition to pharmacies, ePIL should be interfaced with the Backend Prescription Centre. To use this feature, the scanner would need to authenticate themselves (for example with a Smart-ID or

Mobile-ID) and, if they have power of attorney, would be able to query the prescription centre by the prescription number for whom the prescription was written. The previous point also requires the pharmacy to transmit the prescription number to the ePIL backend. Cost estimate €40 000.

Alternatives based on the EMEA ePIL solution

Alternative 1 ePIL portal link as QR code on the packaging



1. The manufacturer or marketing authorisation holder adds the ePIL to the EMEA portal and gets a link from there (For example, the link for the test medicine Karvea is https://ema-dap-epi-tst-fhir-web.azurewebsites.net/View/7fe951af-7180-4ef9-9cfe-6075f88ed612/en/e6011a2f-a30c-415e-ab8b-5c0dae098475).
2. The manufacturer or marketing authorisation holder will add the link as a QR code to the packaging (a second code will appear on the packaging in addition to the REKS code).
3. The user selects the language in the mobile app and scans the package with the DMC code containing the GTIN.
4. The mobile browser should be able to send the information in the preferred language to the web server, in addition to the link (https://www.w3.org/International/questions/qa-lang-priorities) The server will return the ePIL information of the medicine behind the link in the appropriate language.
5. The user can consult the ePIL information.

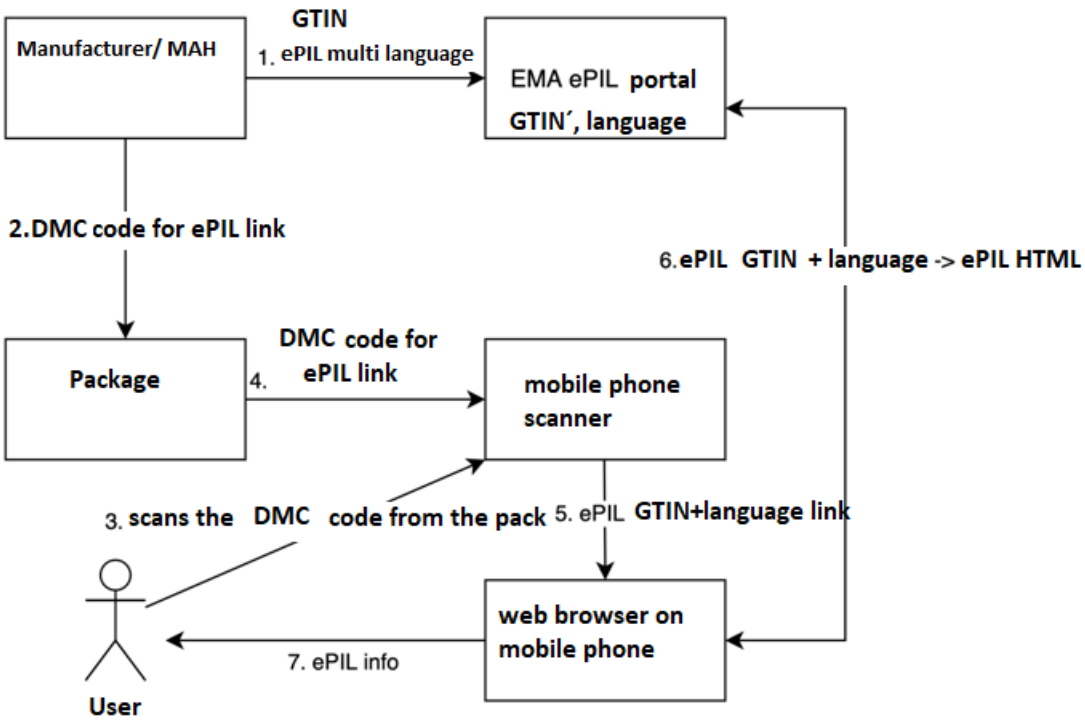
Strengths of the alternative:

1. Can use the ePIL information system being developed by EMA.
2. You can use the QR scanner already on your phones, which can open links in a web browser.

Weaknesses of the alternative:

1. The packaging is small and the new QR code may not fit.
2. A person can scan the REKS code and not understand why the link does not open.
3. It is not known when the ePIL information system being developed by EMA will be ready, and it is likely to take some time to enter all the information on medicines and generate ePILs.

Alternative 2 ePIL portal links by GTIN, scanning from DMC code to GTIN



1. The ePIL and GTIN will be added to the EMEA portal by the manufacturer or marketing authorisation holder. The portal generates links to medicines by GTIN and language.
2. DMC code containing the GTIN (product code) will be added to the packaging by the manufacturer or marketing authorisation holder for REKS.
3. The user selects a language in the mobile app and scans the package with the DMC code containing the GTIN. The mobile app extracts the GTIN from the DMC code and generates an ePIL URL link using the language and GTIN code.
4. The mobile app opens an ePIL with a link to a browser on a mobile device, which displays the ePIL information.
5. The user can access the ePIL information.

Strengths of the alternative:

1. DMC codes containing GTINs already applied to packages for REKS can be used.
2. Can use the ePIL information system being developed by EMA.

Weaknesses of the alternative:

1. Requires a separate mobile app.
2. Sets the conditions for the ePIL information system links (GTIN and language).
3. It is not known when the ePIL information system being developed by EMA will be ready, and it is likely to take some time to enter all the information on medicines and generate ePILs.

4. Regulations and standards

Introduction

This sub-section of the analysis focuses on the regulatory framework and the standards to be applied (in particular, which standard is optimal to apply) in the preliminary analysis of the ePIL project.

This sub-section provides an overview of the legislation related to the ePIL project in general, leaving aside any details that may further affect the implementation of the project. Regarding regulation, it should be noted that in general terms the area is regulated at EU level. However, there is some scope for Member States to implement specific regulations, in particular with regard to the safety of medicinal products.

In addition, there is a public register of medicines in Estonia, the data from which are freely available online. This national information system should be considered as one of the solutions for the publication of the factsheet. In the relevant register, leaflets are available in pdf format, but above all it is important to have a unique identifier as a basis for making the correct product leaflet available to the customer.

The standards chapter gives an overview of the options currently available for implementing a product identifier. The chapter outlines three existing options for reaching the published factsheet. All of them have certain limitations. Each of the proposed solutions requires either a regulatory and/or a technical change. In addition, a change in packaging (i.e. the inclusion of a real coding scheme to make the fact sheet available via an identifier) is required.

Legal framework

This chapter reflects the main legislation governing the creation/implementation of ePIL. Depending on the solution (choice of identifier, substantive organisation), further analysis should be carried out to identify the changing/changing regulation(s) in all aspects.

1.1 Justice beyond the European Union

- **Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (hereinafter also referred to as the *Directive*).**
  The Directive provides definitions and a framework, including for package labelling, packaging, serialisation, leaflets, etc. The Directive allows the use of package identifiers more widely than just for checking the authenticity of the packaging of a medicinal product (leaving this to national discretion).

1.2 The Estonian internal legal framework on the Package Information Leaflet

- **Medicines Act**
  Defined as a framework law that mandates sub-regulations. Among other things, the identifiers of the authenticity of a medicinal product are regulated at the level of the law. Within the framework of this project, the existing package identifiers (in particular the GTIN of the package) are one of the solutions to create a system. As the law in question does not define these identifiers in detail, a change in the law would in any case be necessary to implement the solution. Among other things, the Medicines Act should also refer to the permissibility of using these identifiers.
- **Requirements for a marketing authorisation application for a medicinal product and fees for a professional assessment**
  Regulates the prospectus and information to be submitted when applying for a marketing authorisation. Important for the content of the leaflet.

1.3 Relevant defined terms from the Directive

- immediate packaging - product packaging or other type of packaging in direct contact with the medicinal product.
- Outer packaging - packaging in which the primary packaging is placed.
- Labelling - information on the front or outer packaging.
- Leaflet - a leaflet that accompanies the medicine and contains information for the user.

1.4 Mandatory nature of the leaflet

The Directive imposes an obligation in Article 58 to include a package leaflet on all medicinal products, except where the information provided for in Articles 59 and 62 appears directly on the outer or immediate packaging.

In addition, the Directive provides that Member States may exempt from the obligation to provide a package leaflet where the medicinal product in question is not intended to be supplied to the patient for self-administration.

1.5 Medicines advertising

Advertising of medicinal products is defined in the Directive as advertising of medicinal products to the general public, to persons authorised to prescribe or supply them (including visits by pharmaceutical sales representatives, supply of samples), inducements to prescribe, etc. A situation in which additional information (supplementary material), data on human health or diseases is requested, provided that there is not even an implicit reference to medicinal products, is not considered as advertising.

Standards

The issue of electronic packaging leaflets was raised for a systemic view in 2017 when the European Commission published a report on the subject, highlighting the need for a common standard and model.

1.6 Nature of the standard

A common standard (the 'technical standard') under this theme will ensure that the data set is used on the same basis regardless of the country of destination. The standard defines the rules and provides a model for the uniform use of data in the package leaflet, regardless of the medicinal product or language.
In essence, the requirements of a technical standard can be set on a country-by-country basis, but it is many times more optimal to implement an internationally accepted/established standard. Standards can be managed by a technical solution, but can also be regulated by legislation (i.e. there is no need for a separate standard management or central organisation).

The standard aims to:

- Create a machine-readable database
- Provide users of the standard with unchanged rules and requirements
- Optimise costs for producers, regardless of destination, by implementing an international standard.
- Use the standard to ensure that the correct information page opens for the searched/referenced medicinal product.

1.7 Options for standardising factsheet data

In the leaflet section, a distinction must be made in the definition of the standard:

a) Standardisation of packaging structure.
b) The packaging uniqueness standard to be used for the electronic reference.

The use of a technical fiche is ensured by a standard of uniqueness, i.e. what is the data to be applied to find a specific package, what are the rules and requirements for the data fields and who are the central administrators.

In the first phase of ePIL implementation, it is important to find possibilities for a unique standard, given Estonia's national possibilities, but bearing in mind that the vast majority of packaging in Estonia is of the multimarket type, and a significant proportion of unauthorised packaging (for which the language requirements are different).

1.7.1 *Content standardisation of the packaging structure*

The implementation of the ePIL project does not require the harmonisation of the content structure of the newsletter. The requirements for the leaflet are laid down

at EU level in a directive and have been transposed by each Member State, and may also have specific national requirements where appropriate.

The content structure is not a prerequisite for the success of a project, as long as the digitally displayed input complies with the format. The format, in turn, can be provided by the unit/institution that manages/maintains the newsletters in question.

1.7.2 *Standard for uniqueness of packaging*

For the whole solution to work, a machine-readable, unique identifier (referring to a specific product, not to a specific package) must be used to identify the package. ePIL projects will in any case require the creation of the technical infrastructure to allow the customer/patient to view the digital package leaflet. However, the cornerstone of the technical solution is the unique identifier of the packaging used to identify the specific product. This sub-chapter only gives an overview of the currently known options for the implementation of a unique identifier and the possibilities/disadvantages of implementing these options.

In Estonia, there are three known ways of uniquely identifying packaging:

a) By package code

- Numbering in Estonia, managed centrally.
- Only an Estonia-centric solution.
- This code is not physically present anywhere on the packaging, so it would only be associable as separate new information.

Table 1. Pros and cons of implementing the packaging code. The following table shows the advantages/disadvantages of implementing a packaging code as a component of an ePIL project.

Pros	**Cons**
Existing code in the Estonian Pharmaceutical Register	The code is specific to Estonia
No change in national regulation needed to implement the code	The code is not visually visible on the packaging, i.e. it cannot be used by customers/patients
Allows you to make an Estonian-only central solution	MLH/manufacturers are not aware of this code as it is created by the Pharmaceuticals Register
The code is applicable to a specific product	Cannot be applied to multi-market packaging across the Baltics

	Requires separate labelling/encoding of packaging, i.e. additional printing/adhesive costs

More information on the packaging code:
The Pharmaceuticals Register contains the packaging code[20] , which is a six-digit number, plus a check digit, which is the last digit of the cross-sum of the six-digit packaging code. The packaging code is a unique combination of numbers that is not printed on the packaging of medicines or products, but is mandatory for all medicines and products entered in the pharmaceutical register.

- The packaging code will be issued once and will not change over time.
- A package code will be assigned to each unit pack size of the medicinal product after the marketing authorisation has been granted.
- The package code is issued by the Agency when a marketing authorisation is granted (or a new pack size is added).
- The packaging code is assigned to an unauthorised medicinal product after a specific authorisation has been granted.

b) The product code number of the medicine packaging or GTIN code.

The use of this product code, the GTIN code, would ensure a solution with a high international coverage, which is likely to be used in any downstream EU-level solution.

Unique Product Identifier (also known as GTIN; PC code) - is a code, as referred to in Article 4 of the Delegated Regulation[21] , which allows the identification of at least the name, the common name, the pharmaceutical form, the quantity of the active substance, the size of the pharmaceutical package and the type of the medicinal product bearing a unique identifier (hereinafter referred to as "product code"). This is one of the four elements for verifying the authenticity of a specific package as regards the authenticity of a medicinal product. The ePIL project is only appropriate to assess the possibilities of using the product code, insofar as it is sufficient to refer to a specific product, but at the same time generic enough to avoid excessive data loading/modification obligations for manufacturers.

Today, the GTIN code is not identifiable in the Estonian Medicines Register and this information can be found visually on the packaging or by scanning the product during the authenticity check. In Estonia, this information is held by the EtMVS database managed by the Estonian Medicines Authenticity Control SA. The initial data on the GTIN code is uploaded there by the manufacturers of the medicinal products.

[20] Medicines Act §80
[21] COMMISSION DELEGATED REGULATION (EU) 2016/161, Article 4(a)

- The Directive allows the application of package identification to be extended on the basis of a decision by a Member State.[22]
- Identification of packaging required at EU level
- Currently in use in packaging authentication, each serialised package carries this information in 2D code and physically printed on the package.
- The GTIN code is not currently used in the Estonian Pharmaceutical Register.
- Implementation in Estonia would require an amendment to the Medicines Act, which would allow the use of the package identifier to be extended.
- Requires implementing legislation for the Medicines Act defining the management of the GTIN code in Estonia (i.e. who is the provider of the input data, what stage of the marketing authorisation application, etc.).

[22] Directive Article 54a(5): Member States may extend the scope of the unique identifier referred to in Article 54(5) to any medicinal product subject to prescription or reimbursement for reimbursement or pharmacovigilance purposes. Member States may use the information contained in the system of records referred to in paragraph 2(e) of this Article for reimbursement, pharmacovigilance or pharmacoepidemiological purposes. A Member State may extend the scope of the infringement tool referred to in point (54) of Article 54 to any medicinal product for patient safety purposes.

〉 In principle, GTIN should be added to the pharmaceutical register. The data in the Register of Medicinal Products are public. All the data on the website are accessible without restriction. [23]

Table 2. Advantages and disadvantages of product code implementation. The following table shows the advantages/disadvantages of implementing a product code (GTIN/PC) as a component of an ePIL project.

Pros	**Cons**
International, existing codification	Assumes that Estonian national legislation would regulate its use, in addition to the authenticity check of packaging
Existing unique code in the 2D code printed on the packaging	
Printed on the packaging, i.e. visually visible to the patient/client	The code is the same for the multimarket package, i.e. the language selection solution is needed[24]
Does not require manufacturers to print an additional code on the packaging	The 2D code on the packaging does not yet allow customers to use it to identify the packaging[25]
Presumably a code base on which to build future international solutions requiring packaging identification	The product code is not recognised in the Pharmaceutical Register, it should either replace the currently existing packaging code or an additional record should be created. Developments in the Pharmaceutical Register
Other countries have implemented the same code in ePIL projects	For non-serialised medicinal products that have been imported into Estonia (i.e. the packaging does not have a GTIN/PC code and/or the data have not been uploaded to the NMVS systems), it is not possible to use it
	Separate assessment requires the same application of the "Baltic procedure" for multimarket packaging as hitherto

[23] Medicines Register Statutory Regulation: 01.11.2022 revision. §13

[24] In the Estonian example, the multimarket packaging in use in the country is so-called Baltic packaging, i.e. the product code on the packaging is the same throughout the Baltics.

[25] This comment means that in2023, smart devices in common use will not be able to read the 2D *data matrix* codec without an additional application. To the extent that technical solutions may support this in the future, it can also be assumed at this stage that the package leaflet would open by scanning the existing code there, based then only on the product code of the package.

c) Identification of the packaging by marketing authorisation number

One of the ways of identifying the packaging is the marketing authorisation number. It is a unique number for a specific package, which must be marked on the outer packaging of the product or, in its absence, on the inner packaging.[26] This solution has been proposed by the representatives of the Estonian Medicines Agency. The corresponding number is available in the Register of Medicinal Products.[27]

To the best of our knowledge, no other ePIL solutions have used this code. In addition, there are bottlenecks, e.g. centrally authorised packaging and how to differentiate between them in the future.

Table 3. **Pros and cons of implementing a marketing authorisation number for a medicinal product.** The following table shows the advantages/disadvantages of implementing a marketing authorisation number as a component of an ePIL project.

Pros	Cons
Each product with a marketing authorisation has a corresponding code.	Cannot be used for medicinal products without a marketing authorisation
The code is known to the pharmaceutical registry	Cannot be used for foreign language packaging
Also applicable to veterinary medicines	The code is in human readable form only, i.e. it does not exist in machine readable 1/2D code
	Requires separate labelling/encoding of the packaging, i.e. additional printing/adhesive costs
	Separate assessment requires the same application of the "Baltic procedure" for multi-market packages as hitherto
	As the marketing authorisation number can be located on both the outer packaging and the inner packaging, it is not known if/where the code list can be easily displayed to the customer or if a digitally readable code can be added

[26] Requirements for a marketing authorisation application for a medicinal product and fees for the professional assessment. Version: 01.11.2022, §4

[27] Statutory Regulation on the Register of Medicinal Products. Revision: 01.11.2022, §9(5)(2).

Proposals for implementing the ePIL project

These proposals are based primarily on legislation, the experience of other countries and standard solutions:

1. The ePIL solution should be built with perspective, i.e. it should not be central to the Estonian standard.
   E.g. apply the product code, not the national packaging code. Note that a solution built on the basis of a national code may be ineffective in a cross-EU solution, i.e. the solution may have to be redesigned after a short period of time.
2. It is appropriate to use a code that already exists on the packaging and is visible to the customer/patient.
   E.g. product code, sales authorisation number*[28]
3. Implement solutions already built in a similar way in other countries in the ePIL project.
   For example, in Spain, a system based on product codes has been set up and is structured around hospital medicines.
4. Evaluate separately the possibilities for a digital reading of the existing product code in the 2D code on the ordinary packaging.
   One option is to create an ePIL project based on a product code number in a 'human readable' format, but given that the same code is also digitally readable in 2D (but requires certain scanners and solutions), it could be easily available on every person's smart device in the near future.
5. Implement the ePIL project in at least two stages, starting with hospital medicines and moving on to retail medicines. To some extent, Estonia (Baltic States) has already started this approach.
6. The possibility to agree on a unique identifier for the packaging (e.g. if GTIN is chosen) already now, at least across the Baltics, will also allow to solve the language differentiation of the packaging. Even if other countries don't implement it, the basic rules/requirements would be in place transnationally.

[28] * with the exception that it cannot be applied to foreign language and unauthorised packaging.

5. Mapping the expectations and needs of Estonian stakeholders

The implementation of the EPIL project will require the cooperation and input of a number of stakeholders, so it is key to involve everyone as early as possible. To this end, individual and group discussions were held with representatives of different organisations. In the pre-analysis phase of the project, it is only the partners relevant at the conceptual level of ePIL that are involved, while in the implementation phase the range of actors involved may be extended.

Key players in Estonia

Ministry of Social Affairs

The formulation and implementation of pharmaceutical policy falls within the competence of the Ministry of Social Affairs - with the aim of supporting the improvement of patients' quality of life and the extension of healthy life expectancy through the rational use of effective, high-quality, safe and affordable medicines. The main directions of development in this field are agreed in the Population Health Development Plan 2020-2030 and the Medicines Policy 2030.

Agency of Medicines

The manufacture of medicines (including the inclusion of a package leaflet) is regulated in Estonia by the Medicines Act. Licensing and supervision of the manufacture of medicinal products is carried out by the Agency of Medicines, based on uniform EU rules. The labelling and package leaflet of medicinal products marketed in Estonia must be in Estonian, but exactly the same information may also be provided in another official language of the European Union. The Baltic States have a common assessment procedure for the labelling of medicinal products for human use, which aims to improve the availability of medicines and facilitate the creation of multilingual packaging. The package leaflet is one of the documents in the summary of product characteristics (SmPC) that is submitted when applying for, renewing or varying a marketing authorisation. This document shall be submitted in Word format in the current format, and in the case of changes, the changes to the current document shall be indicated using the 'track changes' function.

Pharmacies

Pharmacies sell medicines at retail, with advice on the appropriate use of medicines. There are general pharmacies, hospital pharmacies and veterinary pharmacies in Estonia. General pharmacies, represented by the Estonian Association of Pharmacies, are one the main stakeholders in this project. In Estonia, general pharmacies are also allowed to operate online pharmacies. The Internet pharmacy must comply with international requirements and must demonstrate this by displaying a logo on its website. Before confirming an order in an

internet pharmacy, the pharmacist is obliged to provide free advice to the customer and to draw attention to the need to read the leaflet on the packaging.

Health Insurance Fund

The main task of the Health Insurance Fund is to organise national health insurance, providing people with access to the healthcare, medicines, cash benefits and medical equipment they need. The focus of this project is the digital prescription service under the Health Insurance Fund. The aim of the digital prescription service is to improve the quality of medical care - the digital prescription system provides added value to the patient, but also improves the efficiency of the healthcare process as a whole.

Pharmaceutical manufacturers

The Association of Pharmaceutical Companies is a non-profit organisation representing pharmaceutical companies operating in Estonia. The mission of the Association is to guide the dynamic development of the Estonian pharmaceutical market, including the promotion of innovation. The Estonian Medicines Manufacturers Association is a member of EFPIA.

Method

Discussions were conducted as unstructured interviews, but the following questions were used as background:

- What is the overall vision for the electronic packaging leaflet?
    - How important is this issue, what opportunities do you see?
    - How does the topic of the e-Newsletter fit in with overall developments and strategic plans, legislation?
    - What are the opportunities to add value to existing services?
    - What could be the ideal impact of an electronic packaging leaflet on the stakeholders in the Estonian healthcare system - a vision for the future?
- What are the most important target groups - what are their needs and objectives?
- Which existing systems and processes would be affected by this change? What risks do you foresee in implementing or delaying this project? How complex does a possible change to an ePIL seem?
- What could be the roles and responsibilities of the parties involved in developing, implementing and maintaining this system? What could be the role of third parties - how could the different actors contribute? What changes would this bring to the collaborative process between the parties?
- How would you see the need to communicate this issue? What aspects should be considered?

- What could be the technical side - both the development and the management side - and the opportunities and constraints that this could bring? What are the potential risks and obstacles?
- What legislative and/or economic aspects should be considered?
- Which features should definitely be on this system, which ones can be, which are less important?

Results from

The results of the discussions are presented in the table below.

ePIL implementation opportunities and needs/risks Views of the parties
Ministry of Social Affairs
Ministry of Social Affairs welcomes developments in the preparation of a technical solution for electronic product information, including an electronic package leaflet, and its availability to patients. As noted in the analysis, there is also a trend at EU level towards Member States being able to decide to use an electronic package leaflet instead of, or in addition to, a paper leaflet, where appropriate technical solutions exist and where there is a willingness on the part of society to do so. One of the key principles of the pharmaceutical policy framework document "Pharmaceutical Policy 2030" is to support the rational use of medicines. This objective is underpinned by patient health-related competences such as accessing, understanding, analysing and applying information to their behaviours. We believe it is essential that information on treatment and medication is communicated in a way that is understandable to the patient and with the level of detail required. When implementing innovative virtual services and e-Help tools (including the electronic package leaflet), it is important to ensure that the necessary digital solutions are available for the different target groups of users. Where appropriate, the development of digital skills should be encouraged. We consider it important to move forward on this issue and are ready to contribute to further reflection, including the preparation of a possible pilot study.
Agency of Medicines
Facilities The Agency's strategy 2023-2026 identifies electronic product information as a key focus for increasing medicines awareness, where the dissemination of evidence-based information on medicines will help to support medication adherence and appropriate use of medicines. One

of the pillars of the strategy is "Value-added information on medicines", and under 1.1.3 it states that "Medicines information is available in different environments in a user-friendly way, information is easy to understand for all target groups, guidance is specific and practical." Developments in ePILs are also included under this topic, which is an important target also as a result of the project initiated by the European Medicines Agency. In the future, one possibility for implementation would be to display a package leaflet on the Patient Portal for prescription medicines and to send the relevant information to the patient by e-mail when the prescription is dispensed. In the first phase of the development of electronic product information, there is no need for significant legislative changes as long as the leaflet is available in physical form on the packaging. The target groups for electronic product information are all people who come into contact with medicines. Electronically managed information on medicinal products is also very important for healthcare professionals, with pharmacists also being an important stakeholder.

The ePIL would be a good way to include different information materials for patients, to keep up to date with changes in the information on medicines. It is important to have a coherent communication between the parties and the patients, and between the parties themselves. Involvement of patient representative associations is also an option. In terms of functionalities, there is a good opportunity to link adverse reaction reporting to the ePIL solution. Information on supply shortages could be communicated together with SmPC as information for health professionals.

Risks/Limitations

The realisation of an electronic package leaflet is an important change, which will require changes to the pharmaceutical register, which currently does not provide information on a package-by-package basis. Centralised medicines do not have a package leaflet separate from the full product information, but as one long file, and a separate technical solution is needed to display the package leaflet. Solutions where someone would have to extract the information manually are certainly not appropriate, as this would be a huge additional burden. At present, one of the possible codes that could be linked to the package code is the marketing authorisation number, i.e. it could be the code that identifies the medicinal product, but there are limitations here. ePI development is very much dependent on the EMA's plans, with manufacturers also being key players - the Medicine Agency itself is more of a user in terms of technical developments. Based on experience, we have seen that EMA solutions will be implemented for centrally registered medicines first and for national medicines at a later stage. ePI is a broad topic and requires cooperation between different parties. The technical development part does not only depend on the Medicines Agency. The Agency will support third parties wishing to exchange information on medicines from the medicines registry, however, it is a requirement that the information on medicines must be automatically updated

from the registry base (no transmission of outdated information is allowed), patients must always have access to the most up-to-date evidence-based information.

Health Insurance Fund - Medicines and Medical Devices Department

From the point of view of the Health Insurance Fund as a funder of health care, developments towards the introduction of an electronic information leaflet on the packaging of medicines are positive. It does not conflict with the Health Insurance Fund's strategic plans, but rather supports them through a more holistic approach to patients. However, the issues directly related to the creation, implementation and management of the ePI remain outside the focus of the Health Insurance Fund.

We see a significant positive impact of ePILs in relation to the Green Paper. Considering the total volume of pharmaceuticals sold in Estonia every year, the elimination of the paper leaflet could save the environment significantly. Therefore, it would be welcome if the introduction of ePILs were accompanied by a legal possibility to dispense with paper leaflets.

As the Medicines and Medical Devices Department of the Health Insurance Fund is also involved in the sales process of medicines, we have seen the impact of paper leaflets on logistics and supply - from this point of view, it would also be good if the system became more flexible**.**

Estonian Association of Pharmacies

Facilities

Focus on increasing knowledge - from the pharmacy perspective, it would be very positive if the leaflet could be made more easily accessible and understandable for patients. It is very important to guide patients to actually read the leaflet, to make people aware that it contains very important information for their health, to increase general awareness and responsibility for their health. Counselling is very important in pharmacies and innovations that contribute to this are welcome.

Developments at the European level suggest that the electronic packaging leaflet will be introduced in the future, offering opportunities as well as challenges for all parties involved, but at the moment processes are still ongoing at the legislative level, the final outcome of which is not clear.

Risks/Limitations

Most importantly, the information should be accessible even where there are limitations and take into account the skills and capabilities of all user groups. The model should be thoroughly developed and tested before implementation to ensure that all user groups are covered, i.e.

can access the information they need. The time of the Covid-19 showed that for many people even printing a corona pass was difficult.

It is important that the workflow does not become more complicated for pharmacies, nor does it increase the administrative burden (printing). It is important to develop the system as a whole, taking into account the work processes and responsibilities of all parties (including the legislative perspective). Pharmacists cannot take responsibility for ensuring that information on medicines reaches the patient; this responsibility must be thought through in a systematic way. The issue of format should also be thought about in advance - currently the PIL is about 30 pages A4 (central medicines even longer), there could be a better solution to this, should there be a need to print anything at all.

It is important to ensure the security of the information - e.g. avoiding online advertising, not storing search terms.

The app should be easy for patients to use and reliable - thoroughly tested for ease of use and security. The transition should also be seamless, so that people get used to and comfortable using the electronic version.

Association of Pharmaceutical Manufacturers

Facilities

There is a clear direction for the future adoption of ePIL in Europe, and this fits well with the pharmaceutical industry's view and principles of innovation. It is essential that patients are able to find up-to-date information on their medicines quickly and conveniently - the latest version of the package leaflet without any time delay. In addition, the readability of the package leaflet would be improved. The electronic format would make the leaflet more attractive to the public as a whole - increasing awareness and improving health behaviour.

In order to create the habit of using electronic information, it would also be conceivable to include the relevant information on the package leaflet, with a recommendation to search for information e.g. in the pharmaceutical register (e.g. a corresponding sentence in the QRD). The habit of scanning e.g. QR codes is very widespread and, if the opportunity exists, some people may, if only out of interest, scan the code on the medicine package and thus become familiar with the PIL.

It is the responsibility of the person taking the medicine to check the information. Thus, the ePIL project targets all people who use medicines. People's needs, in what form and at what point in time they need the information, vary widely - the important thing is that they can get it. Another important target group is health care professionals - the information for them should also be in a reader-friendly format (PIL and SmPC may contain different information, health care professionals usually read both).

The new solution should be able to give access to the package leaflet on both mobile phones and computers. It is important that the information is searchable, enlargeable, readable on a mobile phone, listenable, well-structured, and in a printable format on a computer. In addition, there could be the possibility to include videos with general instructions for use and instructions on waste management of medicines. The code could also be used to inform the patient of the expiry date of the medicine, and the possibility to report adverse reactions using the code.

Certainly, the change in the requirement for paper PILs/creation of alternatives would have a positive impact on the availability of medicines, which is a critical issue for Estonia as a small country. In the longer term, the introduction of ePILs may reduce the administrative burden as a whole.

Risks/Limitations

It is difficult to estimate what proportion of people would start using ePIL, but also how much PIL is currently read. How can we get the message across to people that they should always read the leaflet before taking a medicine? Clearly, effective communication and patient education (which RTL is also doing) is needed when implementing ePIL so that people know that they need to look for information on medicines and where to find it - it takes time to get used to new solutions.

The interest and responsibility for the development of ePIL as a system should lie first and foremost with the state, which could play a leading role - the initiative and the courage - in setting up and managing the ePIL system. As a whole, this will benefit the patient and, in the longer term, the environment. Collaboration and involvement is essential, with manufacturers able and willing to contribute to the development of the system as one party to the process, for example in the form of a PPP (private ***public partnership***), prototype testing, etc. In the future, the system should be free of charge for all and should not be in an app format, but as user-friendly as possible. If there is a common goal, cooperation can always be made to work.

Certainly, the implementation of ePIL needs to be well thought through. We can see that in the start-up phase of the system, this project may be more of an additional work and cost and complicate processes, but the transition from one system to another is always difficult, good communication between the parties involved will help.

All in all, all the key players see the implementation of ePI and ePIL as offering a number of opportunities for patients - accessibility, better information about their treatment, additional information to improve treatment outcomes. At the same time, the different stakeholders also point to limitations stemming from both the current situation (the data composition of the

Pharmaceutical Register) and the possible future distribution of responsibilities (e.g. obligation to print, packaging labelling). These issues can be addressed in the different phases of the project when planning the next steps to move forward on this issue - the issue of data content needs to be addressed at the outset of a potential pilot project. In terms of printing, low-maintenance printing machines based on thermal printers widely used in healthcare (e.g. eHealth project) could be implemented[29] .

All parties agree that the ePI project is an important change with a number of positive opportunities to improve the system, but that it will require good cooperation and input from all parties to make it work.

[29] Computer workstations and communication solutions for ambulances
https://karellkiirabi.ee/Dokumendid/Juhendid/EKiirabi/eKiirabi_seadmed.pdf

Annex 1: Information on the summary of product characteristics

Requirements for the marketing authorisation[30]	**Packaging of drugs**[31]	**Homeopathic preparations**[32]
Goods and services	**Droogid (herbal)**	**Homeopathic medicines NOTE: Leaflet is not required if information is printed on the packaging.**
Name of the medicine	Name of the drug packager or general pharmacy	Name of the homeopathic preparation
Strength of the medicine	Name of the drug in Latin and Estonian	List of active substance(s) in Latin or Estonian
Name of the pharmaceutical form and, where appropriate, whether the medicine is for infants, children or adults.	In the case of a mixture of drugs, the name and quantity of each drug in a single package.	Quantitative content of active substance followed by the degree of dilution
If the name of the medicinal product is fictitious and the product contains only one active substance, the name of the active substance must be added.	Total quantity of drug or mixture of drugs in the package (grams)	List of ingredients
Full qualitative composition of active substances and co-formulants and quantitative composition of active substances	Collection time for packaged drugs	Form
All pharmaceutical forms and their mass, volume or number of doses	Indications, in the case of a mixture of drugs listed in the Annex, indication for each drug.	In the case of a homeopathic preparation in measured doses, the number of units contained in the package

[30] Requirements for a marketing authorisation application for a medicinal product and fees for the professional assessment. 01.11.2022 version; State Gazette: https://www.riigiteataja.ee/akt/129102022018?leiaKehtiv

[31] Conditions and procedures for the handling of drugs, labelling of packaging and list of drugs . 04.03.2011 version; State Gazette: https://www.riigiteataja.ee/akt/885901?leiaKehtiv

[32] Conditions and procedures for applying for marketing authorisations for homeopathic medicinal products. 01.11.2022 version in State Gazette: https:**//www.riigiteataja.ee/akt/875059?leiaKehtiv**

		(tablets, capsules, etc., liquid solution, suspension), the total volume of the liquid shall be indicated.
Pharmacotherapeutic group or type of action in a form easily understood by the patient.	Instructions for use, preparation methodology	The words "homeopathic preparation"
Name or business name of the marketing authorisation holder (+ location)	Dose when used	Name of the marketing authorisation holder
Name of the other marketing authorisation holder	Frequency of administration (if necessary, specify times)	Manufacturer
Name or business name (+ location) of the manufacturer responsible for the release of the batch.	Route of administration	Special warnings if necessary
In the case of a second marketing authorisation, add the name or business name (location) of the repackager.	Warnings about possible side effects, if applicable	List of excipients in a homeopathic preparation that may affect the efficacy and safety of the preparation.
Name or business name of the marketing authorisation holder's representative in Estonia (+ location).	Contraindications	Daily dose for use
Indications	Use in children, pregnant women, breast-feeding, elderly people or people with co-morbid conditions.	Route of administration
Contraindications		Route of administration, if necessary (for external preparations, indicate whether it can be administered to mucous membranes, instructions for administration).

Precautions for use of the medicine, if necessary	Duration of treatment, when to stop treatment and a warning.	Frequency of administration
Interactions with other medicines	Specific warnings and notes on use, storage, etc., where appropriate.	Availability date
Other interactions (e.g. with alcohol, tobacco, food) that may affect the action of the medicine.	Availability date	Information on storage
Special warnings	Batch number	Warning "Do not use after expiry"
Administration dose		Special conditions for conservation, where appropriate
Route of administration		Visual signs of deterioration, where appropriate
Frequency of administration		Date on which the package leaflet was updated
If necessary, specify the time when the medicine can or must be taken.		
Duration of treatment		
If, depending on the nature of the medicine, it should be restricted, instructions on what to do in the event of an overdose (e.g. symptoms, what to do in case of emergency) or if one or more doses are missed, noting or referring to the risk of adverse drug reactions, if appropriate.		

Annex 2: Models of PIL submission in different countries

Country	Institution	Type of organisation	ePIL - web environment	Information provided - national medicines	Format to use	Information provided - central medicines	Accessibility features	Additional features
Austria	Austrian Agency for Health and Food Safety GmbH	Medicines Agency	Register of proprietary medicinal products (basg.gv.at)	PIL, SmPC	Downloadable pdf	No show	no	no
Belgium	Agence fédérale des médicaments et des produits de santé	Medicines Agency	basededonneesdesmedicaments.be	SmPC, PIL	Downloadable pdf	EPAR, Annex 1 separately, redirects to EMA database	no	no
	Algemene Vereniging Van De Geneesmiddelenindustrie www.pharma.be	General Association of the Belgian Pharmaceutical Industry	e-notice.be	PIL (SmPC can be found with a separate search)	html (by chapter)	PIL in html format	no	no
Bulgaria	Bulgarian Grug Agency	Medicines Agency	Registrar of therapeutic products (bda.bg)	PIL	Pdf	No show	no	no (no search option, only alphabetical)

Estonia	Estonian Medicines Agency	Public authority	medicinesregister.ee	PIL, SmPC	pdf opens in a new window	Redirects to EMA database pdf	no	Package leaflet EST, RUS, ENG
	Confido Healthcare Group OÜ	Private company	clinic.ee	PIL	html, pdf	Can't find the newsletter	no	Articles on searchable topics
	Pharmacy Information Technology	Private company	druginfo.ee	PIL	Pdf	Redirects to EMA database, EPAR opens from the right page	no	
	Hansasoft OÜ	Private company	pharmacyinfo.ee	PIL	Pdf	Redirects to EMA database, EPAR opens from the right page	no	
Spain	La AEMPS	Medicines Agency	.:: CIMA ::. Centro de información de medicamentos	PIL, SmPC	html, pdf option	SmPC, PIL, EPAR html	General information in sign language	Picture of the packaging, picture of the tablet, adverse reaction notification, notification of changes, app to scan the code

Netherlands	Dutch Medicines Authority CBG Dutch Medicines Authority MEB	Medicines Agency	www.geneesmiddeleninformatiebank.nl	PIL, SmPC	Pdf	EPAR link to EMA database, link to apotheek.nl and lareb.nl	no	Link to report adverse reactions Patient information link Apotheek.nl
	de Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie	the Royal Dutch Society for the Promotion of Pharmacy.	www.apotheek.nl	PIL, medicine in brief	html (by chapter)	PIL in html format	*Dark mode, increase font, read aloud*	Mobile phone app, possibility to scan the code from the packaging, *Find pharmacy*
Croatia	Agency for Medicinal Products and Medical Devices of Croatia HALMED	Medicines Agency	Medicinal Products Database | Medicinal Products .: HALMED	SmPC, PIL, Public assessment report	pdf (download as file)	EPAR link to EMA database	no	no
Ireland	Health Products Regulatory Authority (HPRA)	Medicines Agency	hpra.ie	SmPC, PIL, Public assessment report	Pdf	Link to EMA general search page, EPAR does not display directly	no	*Follow medicine*
	Irish Pharmaceutical Healthcare Association (IPHA)	Irish Pharmaceutical	www.medicines.ie	PIL, SmPC	pdf	No find	Increasing the fund	Link to report adverse reactions

		Healthcare Association						
Iceland	Lyfjastofnun - Icelandic Medicines Agency	Agency for the Evaluation of Medicinal Products (ima.is)	serlyfjaskra.is	PIL, SmPC	Pdf	EPAR link to EMA database	no	-
Italy	Italian Medicines Agency	Medicines Agency	Search medicine | aifa.gov.it	PIL, SmPC	The link does not open	no	Repeated cookie notification	-
	Edra S.p.A	Private company	Codifa - L'Informatore Farmaceutico	Free text (not PIL structure)	Html	no	Advertisements page	-
Greece	National Organisation for Medicines	Medicines Agency	Product search (eof.gr)	PIL, SmPC	pdf (downloadable)	Reference to the EMA register (not a direct link)	no	no
Cyprus	Pharmaceutical Services, Ministry of Health	Ministry of Health	Pharmaceutical Services - eServices (moh.gov.cy)	PIL, SmPC	doc (downloadable)	Reference to the EMA register (not a direct link)	no	Search for medicines information on the front page easy to find
Lithuania	State Medicines Control Agency	Medicines Agency	VVKT - Medicines	PIL, SmPC	pdf (downloadable)	Reference to the EMA register (not a direct link)	no	Visible link on front page

Malta	Malta Medicine Authority	Medicines Agency	Medicines Authority (gov.mt)	PIL, SmPC, Public Assessment Report	pdf (downloadable)	No find	no	
Norway	The Norwegian Medicines Agency	Medicines Agency	Legemiddelsøk - Legemiddelverket (legemiddelsok.no)	SmPC, PIL - felleskatalogen.no saidile	SmPC as pdf in a separate window	SmPC linked to EMA database, PIL linked to felleskatalogen.no	See felleskatalogen.no	
	The Norwegian Pharmaceutical Compendium	A subdivision of the Pharmaceutical Industry Association	www.felleskatalogen.no	PIL	Html	html	Audio - reads out the full page	Picture of the medicine/tablet, link to adverse reaction reporting, interaction analysis.
Poland	e-Zdrowia Centre	Public authority	RPL (ezdrowie.gov.pl)	PIL, SmPC	pdf (downloadable)	No find	no	no
Portugal	Serviço Nacional de Saúde	Public authority	Infomed (infarmed.pt)	PIL, SmPC	pdf in a new window	Linked to EMA database separately for PIL and EPAR	no	no
France	L'Agence nationale de sécurité du médicament et des produits de santé	Medicines Agency	Authorisation - Accueil (sante.fr)	PIL, SmPC	Html	Reference to the EMA register (not a direct link)	no	no

	Vidal France	Private company	www.vidal.fr	Free text (not PIL structured)	Html	No	Yes, size of fund	Link to report adverse reactions; interactions link; app
Romania	Agenția Națională a Medicamentului și a Dispozitivelor Medicale din România	Public authority	NOMENCLATOR - ANMDMR	PIL, SmPC	pdf in a new window	Reference to the EMA register (not a direct link)	no	no
Finland	FIMEA	Medicines Agency	FimeaWeb	SmPC, PIL	pdf in a separate window	Direct link to the EMA register EPAR	Suitability 75+ (colour coded)	
	Pharmaceutical Information Centre	Private company	Pharmaca Fennica	PIL (SmPC in a separate environment)	Html	html	no	App
Germany	Federal Institute for Drugs and Medical Devices	Public authority	www.pharmnet-bund.de	Does not open	-	-	-	-
Germany	Vidal MMi Germany GmBH	Private company	Yellow List Pharmindex Online | Yellow List (gelbe-liste.de)	PIL, SmPC locked	PIL as pdf	No find	no	App
United Kingdom	Electronic Medicines Compendium	Private company	www.medicines.org.uk	SmPC, PIL	pdf, html	Opens in html format	Yes, print in large text	no

Denmark	Danish Medicines Agency	Medicines Agency	www.produktresume.dk	SmPC	doc file in a separate window	Redirects to the EMA search page	no	no
Denmark	Lægemiddelindustriforeningen (Lif)	A subdivision of the Pharmaceutical Industry Association	indlaegssedler.dk medicin.dk	PIL (link to SmPC environment)	html (linked by topic)	html	no	Leaflet app; guide; educational materials
Czech Republic	The State Institute for Drug Control	Public authority	www.sukl.eu	PIL, SmPC	Pdf	Direct link to the EMA register	no	no
Slovakia	State Institute for Drug Control (SIDC)	Public authority	www.sukl.sk	PIL, SmPC	pdf in a new window	Direct link to the EMA register	no	no
Slovenia	Republika Slovenija Ministrstvo za zdravje	Public authority	http://www.cbz.si	PIL, SmPC	pdf in a new window	Direct link to the EMA register	no	no
Hungary	The National Institute of Pharmacy and Nutrition (OGYÉI)	Public authority	National Institute of Pharmacy and Food (gov.hu)	PIL, SmPC	as a doc file in a separate window	Direct link to the EMA register	no	no
	Pharmindex by Vidal Next Ltd.	Private company	https://www.egeszsegkalauz.hu	Free form information	Html	Free form information	no	no
Sweden	Swedish Medical Products Agency	Medicines Agency	Swedish Medical Products Agency | Start	Link to fass.se page				

			(lakemedelsverket.se)					
	Läkemedelsindustriföreningens Service AB, LIF - the trade association for the researching pharmaceutical companies in Sweden	A subsidiary of the Pharmaceutical Manufacturers Association	www.fass.se	PIL	html (with links to categories next to it)	html	Enlarge text, *Read aloud* (all or selection), *Print large*	Tablets to scale; Find a pharmacy by medicine; Side effect reporting; *Tablet identification*; app with code scanning;
USA	U.S. Food & Drug Administration FDA	Medicines Agency	Medical Encyclopedia: MedlinePlus	Patient Package Insert (PPI)	Html		no	Side effects database; Overdose telephone
Japan	Pharmaceuticals and Medical Devices Agency (PMDA)	Medicines Agency	https://www.pmda.go.jp/english/search_index.html					
Canada	Health Canada	Medicines Agency	Drug Product Database - DPD					