APAC e-labeling EWG Position Paper

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List of abbreviations and definitions of terms

abbreviation	definition of term
APAC	Asia Partnership Conference of Pharmaceutical Associations
EMA	European Medicines Agency
FDA	Food and Drug Administration (United States)
HA	Health Authority
HCP	Healthcare Professionals
HL7	Health Level Seven
HSA	Health Sciences Authority (Singapore)
ICH	International Council for Harmonisation
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
JPMA	Japan Pharmaceutical Manufacturers Association
MHLW	Ministry of Health, Labour and Welfare (Japan)
PI	Product Information
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
TFDA	Taiwan Food and Drug Administration

1. Introduction

1.1. What is e-labeling?

Under the COVID-19 pandemic, various e-labeling initiatives have begun worldwide in the healthcare and pharmaceutical fields as part of a wider digital transformation. Through these initiatives, the regulators, industry, healthcare professionals (HCPs) and patients understand that e-labeling will deliver the most updated labeling to HCPs and patients and will improve the accessibility and understanding of approved medical product information, thereby enhancing adherence to medicines and improving patient outcomes. E-labeling also provides an opportunity to deliver personalized, user-friendly information and enhanced features for patients with visual and hearing disabilities. Although there is no universal definition of e-labeling globally, it is widely accepted that e-labeling refers to the product information that is distributed via electronic means.

There are 5 factors to be considered in e-labeling:

1) availability of the latest labeling on a publicly accessible website (e.g., product information available online)
2) accessible through a reader-friendly format (e.g., scanning a machine-readable code);
3) eliminating paper labeling from commercial pack;
4) common electronic standard (e.g., structured content);
5) efficient information flow (e.g., interoperability between systems).

1.2. Definition

Although there is no universal definition of e-labeling globally, the following is the definition of e-labeling in this Asia Partnership Conference of Pharmaceutical Associations (APAC) e-labeling position paper.

E-labeling is the availability of the latest approved product information electronically on publicly accessible website via smart devices. E-labeling would be in a common structured format using global standards to allow efficient and seamless information flow amongst manufacturers, regulators, HCPs, and patients. E-labeling would eventually replace the paper product information leaflet that are placed within commercial packs.

1.3. Benefits and expectation in patients/ healthcare professionals/Industry

The availability of the latest labeling on a publicly accessible website is an important first step in improving patient safety and trust in medicines. The adoption of e-labeling with improved accessibility will enhance the user's experience to navigate around the product information in a more user-friendly manner, and to better understand correct usage as well as the safety and efficacy profile of the drug. Eventual transformation from paper labeling to e-labeling will shorten the lead time to launch new products, improve efficiencies by eliminating the operational steps of inserting paper labeling in packs, and support environmental-friendly practices. In the future, e-labeling can be integrated with the wider

digital healthcare system such as electronic medical records, resulting in greater efficiencies, and opportunities across a wide spectrum within healthcare.

1.4. Global landscape for e-labeling

As shown in Table 1-1, e-labeling has been discussed and implemented in various stages across regions. The research on the electronic standards implemented or planned to be implemented in major markets (Japan, Canada, the EU, and the US) has been conducted by Matsui et al. in 2020. It explains that while each market has independently developed their path forward for digitalization of the labeling, most of them have their sights set on exchanging the labeling information. It would be important to learn from the different countries that the implementation of e-labeling must be planned and implemented in stages.

Table 1-1: Implementation of e-labeling

	Labeling availability on RA website	**Easy accessibility to e-label (e.g. via bar code)**	**Structured contents of labeling such as XML**	**Eliminating paper labeling from a commercial pack**	**Interoperable e-labeling**
EU	✓	In discussion	In discussion		In discussion
Japan	✓	✓	✓	✓	
U.S.	✓		✓		✓
Singapore	✓	Voluntary		Voluntary	
Taiwan	✓	✓	Pilot underway	Pilot underway	
Korea	✓	In discussion	✓	In discussion	
Malaysia	✓	In discussion		Pilot underway	
China	Some products				

1.5. Asian status on e-labeling initiatives from survey results in 2021

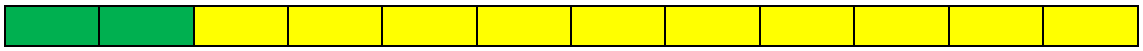
Research on e-labeling initiatives in Asia was conducted in 2021 by the APAC e-labeling Expert Working Group (EWG). A 22-question survey was completed by APAC's 12 member associations and Pharma Group Vietnam in November 2021 to understand the current e-labeling status in 12 markets in the Asian region. Each member association made only one response to the survey. Please see "Status of e-labeling implementation in APAC markets below". It showed that e-labeling initiatives are at different levels of maturity in Asian markets, and that various challenges exist around e-labeling initiatives due to differing approaches being taken. Discussion on e-labeling initiatives is still at early stage in the majority of markets.

Figure 1-1: Status of e-labeling implementation in APAC markets

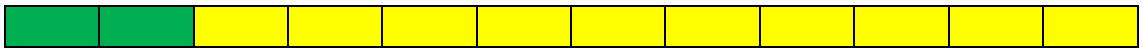
1) Availability of the latest labeling on a publicly accessible website (product information available online)

2) Accessible, reader friendly format, e.g., scanning a code

3) Eliminating paper labeling from commercial pack



4) Common electronic standard, e.g., structured contents

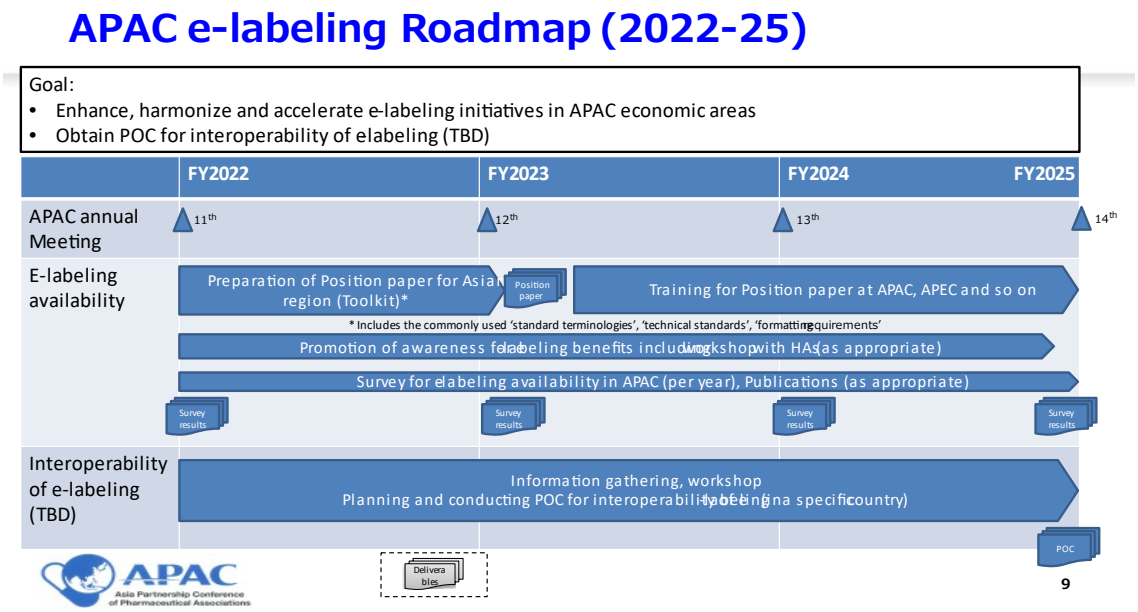


5) Efficient information flow, e.g., interoperability between systems

Implemented
Not implemented

1.6. APAC e-labeling Roadmap

Figure 1-2: APAC e-labeling Roadmap



1.7. Purpose of this position paper

The variety of approaches being adopted in the Asian region introduces complications for e-labeling development. Companies have to comply with national regulations, even though manufacturing sites have been integrated across regions. If the e-labeling regulations are different depending on the markets, it will be difficult and inefficient, and this will bring a negative impact on the implementation on e-labeling. Therefore, it is advisable to develop regional guidance on how to proceed with e-

labeling initiatives in the Asian region to have a consistent approach. Asian countries can collaborate further in terms of e-labeling although the guidance will neither be intended to mandate nor to include the implementation plan for each market. The research encourages the close collaboration between health authorities (HA), HCPs, patients, and industry associations in order to move e-labeling initiatives forward in Asia.

2. E-labeling proposal

2.1. Availability of the latest labeling on publicly accessible website

2.1.1. Goal

2.1.1.1. Background and Current Status for Asia as a Whole

The availability of the latest product information on publicly accessible websites can be an important first step in improving patient safety and trust in medicines, and can help accelerate the transformation process from paper labeling to e-labeling. Improved accessibility on public websites enhances user experience by improving navigation around the product information, can increase understanding of the correct usage of medicines, and gives better familiarity with the safety and efficacy profile of the drug compared to more conventional printed labeling materials.

The current availability of labeling information on publicly accessible websites in Asia has been published in the e-labeling survey[1]. Four markets (Japan, Malaysia, Korea and Taiwan) have already published HCP labels for all products (but generics products were out scope in the survey questionnaire) on their Health Authority (HA) websites centrally as of November 2021. On the other hand, 5 markets (Singapore, Thailand, China, Indonesia and Vietnam) have published them partially, while 3 markets (Hong Kong, India, and Philippines) have not published labels on their HA websites. When it comes to patient labels, only 4 markets (Japan, Malaysia, Singapore and Thailand) have published labels on HA websites while the remaining 8 markets (Korea, Taiwan, China, Hong Kong, India, Indonesia, Vietnam and Philippines) have not published patient labels yet. Only Japan and Singapore have set a guideline to have the latest labeling information uploaded to a publicly accessible website based on a defined time frame implemented by the HA. With this information, one can see that while only a small number of markets are publishing in this way today, there is a clear trend for markets in Asia to move this way.

2.1.1.2. Goal

After reading this section, one would be able to understand the different options available on how the latest labeling is being displayed on publicly accessible websites. By focusing on the initiatives that were already conducted by some countries such as Japan and Singapore which both utilized a different approach in showing the latest labeling of drugs on website, one would be able to understand the different tools and methods of communication including the pros and cons that accompany such options.

This section sets out what might be the most suitable approach and option to be taken depending on the situation of each of the Asian markets. Factors such as resource availability, readiness of available platforms for e-labeling to be posted, internet connectivity, and the mechanisms for updating the e-labeling information should be taken into consideration, together with the preference of different

stakeholders such as the regulatory agency, pharmaceutical companies, external platform vendors, and of course HCPs and patients themselves who are directly using the updated labeling information.

2.1.2. Methods

2.1.2.1. Using HA Website as platform

Package inserts are part of the mandatory legal documents of the dossier submitted by Marketing Authorization Holders (MAH) to the HA. One way in which product information is made available to the public is by uploading the latest labeling information to the HA website. HA websites can serve as a central platform where the approved product information can be published within a specific timeframe.

The second step is to create a link to the HA website and establish a “data carrier” on the pack to facilitate access to the information for HCPs and/or patients.

In using an HA website as a national platform, one of the most important advantages is that reliable information can be provided in a single source with high security. Once the product information is approved, it can be easily updated, versioned and maintained according to HA processes. A central trusted platform on an HA website can also offer a linkage to other healthcare systems, thus improving interoperability[2]. Restricted access can be implemented as needed to comply with any local legislation (eg to restrict patient access to HCP labeling, if required by local legislation). HA websites are often viewed as a trustworthy source of information that can serve as a basis for patients to safely access accurate and precise information in a timely and standardized manner. Another benefit of having a single central platform (especially if the format is standardized by the HA), is that it can facilitate the comparison of product information of various drugs for HCPs to make benefit–risk decisions. Lastly, having one central location/host for all product labeling is typically preferred from a patient convenience perspective, especially in the case of polymedicated patients.

On the other hand, the control, features, and ownership of the website as a single platform is dependent on HA specifications, which might leave less flexibility from the MAH’s perspective. Other potential challenges for the HA include the need to maintain the platform over the long term and implement appropriate security measures to protect from cyber-attack. Offline availability of labeling should be taken into account when planning this.

2.1.2.2. Using Company or External Vendor as a platform

If information technology (IT) restrictions or other resource constraints exist at the HA, there are two possible interim solutions that can be considered:

First is use of company platforms or websites which may easily be used to implement e-labeling. Some benefits include:

- The e-label is updated and managed internally by the MAH, hence there is no need for a 3rd party vendor which can incur additional cost for technical and maintenance services.
- Company is accountable and has full control
- Uploading of latest product information will be faster since it will be in real-time and implementation will be streamlined

Second option is to hire a third-party vendor with the following benefits:

- Cost and resources can be shared through industry partnership and collaboration
- Minimal risk for company since a third party will maintain the system
- More centralized platform for HCPs and patients

Platforms utilizing company website or external vendor provide flexibility and functionality which has the possibility of simultaneous distribution to stakeholders[3]. It enhances the accessibility to the labeling by establishing a tailored platform.

Although it does not create unnecessary burden to authority, provision of safeguards and security is crucial for establishing a trustworthy source and maintaining reliability of compliance information by pharmaceutical industry and/or external vendor. Different platforms trigger variance and inconsistency in the management of e-labels. It also creates difficulties to standardize and harmonize the formats.

The use of multiple platforms may have increased compliance risk, but it also has increased access options and flexibility to users and in turn can be used to enhance the system.

2.1.3. Tools

2.1.3.1. Using HA Website as platform

One of the options to obtain the latest labeling on publicly accessible website is by using the Health Authority's website. An example is the Japan Pharmaceuticals and Medical Devices Agency (PMDA) with the implementation of e-label following the amendment of the Act on Securing Quality, Efficacy and Safety of products including Pharmaceuticals and Medical devices (Pharmaceutical and Medical Devices Act) whereby the product information should be browsed in an electronic way on the website of PMDA. The act also specifies the obligation of the MAH to make prior notifications of package inserts before the start of marketing and at the time of their revision[4].

Japan PMDA adopted the following method of communication and notification in which the MAH is required to submit the e-label to PMDA using SGML or XML and PDF format. The e-label will then undergo evaluation and confirmation by PMDA. If the e-label is accepted by PMDA, MAH will receive the confirmation from PMDA and the e-label will then be published in PMDA homepage.

However, if modification of e-label is required, PMDA will request MAH to make the necessary changes and resubmit again for confirmation.

HCPs and patients can access the published e-label in PMDA homepage.

The Taiwan Food and Drug Administration (TFDA) is another example where the HA website is used as a central platform for labeling information. In 2006, the first generation of the "Drug License Online Search System" was established which became the central platform for labeling information in Taiwan. This contains PDF files of drug e-labeling for new application and labeling changes approval.

TFDA also established the second generation of Drug License Online Search System which aims to create a structured drug e-labeling where MAHs are expected to follow the format established by TFDA. Although e-labeling is not yet implemented in Taiwan, there is an active ongoing pilot project where MAHs are invited to participate by using the newer operational platform, with eventual creation of a structured e-labeling format.

2.1.3.2. Using Company or External Vendor as a platform

When it comes to Asian markets are utilizing MAH or External Vendor sites as a platform, one can immediately think of Singapore as a primary example.

The Health Sciences Authority (HSA) is taking a phased voluntary approach to facilitate the implementation of e-labeling in Singapore. Presently, e-labeling is applicable to prescription-only-medicines (POM) and complementary health products[5]. MAHs must ensure the hosting platform (e.g., website of individual companies or external vendor) has the necessary IT infrastructure and back-up system, to ensure that the most updated e-label can be obtained by the end-users in a timely manner.

MAHs are responsible to ensure that the e-labels published in the hosting platform are aligned to the most up-to-date product information approved by HSA. MAHs are given 30 days from the date of the approval of the revised label to be updated in the hosting platform.

2.1.4. Communications (How should we implement each option including communication)

2.1.4.1. Using HA Website as platform

Japan and Taiwan are some examples where HA Websites will be utilized as the platform for labeling information. In this position paper, we will provide an example on how Japan implemented and communicated e-labeling initiatives with the focus on the availability of labeling information on the HA website.

In Japan, submission of the package inserts to the Ministry of Health, Labour and Welfare (MHLW) became mandatory in November 2014[2]. Package inserts for prescription drugs had been posted on the website before this submission, but the posting became company's duty not the company's efforts. In December 2019, an amendment of the Act on Securing Quality, Efficacy and Safety of Products

including Pharmaceuticals and Medical Devices (known as the Pharmaceuticals and Medical Devices Act or PMD Act) was stipulated and was enforced from August 2021 to have a smoother transition to e-labeling in Japan.

This was communicated in various forums such as international conferences, release of regulatory guidance and notification and even through conducting seminar or a meeting with various stakeholders such as HCPs and pharmaceutical trade organization.

2.1.4.2. Proposed Position B (Using Company or External Vendor as a platform)

On the other hand, for labeling information that is not being maintained in a central HA website mentioned in the option above, the following communication and implementation plan should be considered.

First, in using the company website as a platform, the following are taken into consideration.

- The e-label should be managed internally by MAH for document version control.
- The newly approved/registered e-label is published and available with PDF or structured format of labeling (XML) on the company website in a timely manner agreed with HA.
- The company is responsible for ensuring compliance with local law and regulation, importantly the accuracy of the approved/registered version and timeline until publishing completion.

For those MAH using the external vendor website as a platform, the method is partially different from using the company website.

- The e-label is managed by the MAH for document version control.
- The newly approved/registered e-label is transferred from the MAH to the external vendor via the secured platform in a timely manner and then published and available with PDF or structured format of labeling (XML) on the external vendor website in a timely manner as agreed.
- The MAH is still the owner and responsible for ensuring compliance with local law and regulation, importantly the accuracy of the approved/registered version and overall timeline until publishing completion on the external vendor website.
- Monitoring and evaluation as a tool for oversight of the external vendor operation is essential to ensure compliance.

After the user's connectivity to either MAH or external vendor website via any available pathway (e.g., scanning QR code, etc.), the end-user will be able to access the newly approved/registered e-label as available on such website. This is to promote rapid accessibility of the latest product information via reliable source so that adherence and ultimately patient outcomes can improve[6].

2.1.5. Expectations (Recommendation)

2.1.5.1. Using HA Website as platform

The challenge in managing HA system is to ensure information is updated in a timely manner. This will require additional resource which might prove challenging for both the HA and MAH. Upon approval of PI, there is a need for both parties to ensure that the latest product labeling information is also available on the website. This will enable HCPs and patients to access the most accurate and up to date product information which both HA and MAH are accountable for.

2.1.5.2. Proposed Position B (Using Company or External Vendor as a platform)

This option might reduce the HA effort to maintain the product information. However, this will require high investment, which will become a burden for low-middle size company, especially local company.

Over-all, if there will be no resource constraint from the part of the HA in a particular market, it would be more advisable to use HA website as the central platform to better maintain the consistency of the format of the product information. The consistency in the format in the product information accessible to the end-users would also mean better usability, convenience and understanding which is the end goal of e-labeling. The consistency early on when it comes to labeling information might also lead to better operability functions in the future. Thus, this point should be highly considered when a particular market is deciding which option to follow.

If a particular HA would then decide to give flexibility to MAH to use their company platform or third vendor platform, the HA should clearly lay out the guideline, rules and even the format that each MAH should adhere in order to avoid inconsistencies and variances in the format of product information. Having a uniform format early on will also be useful in the future in case HA would then decide to migrate into a central repository since format is already standardized.

Lastly, it is also recommended to confirm the following points regardless of whether the latest e-labeling product information will be uploaded via central HA platform or using company/external vendor platform. First, is to ensure that there is one-stop and single source of e-labeling in order to assure the latest and reliable information is being utilized by the end-users. Second, HA from each market should be able to clarify the deadline by when the latest e-labeling information will be uploaded and available to publicly accessible website similar to what was being implemented by Japan and Singapore. This will ensure better compliance from MAH and better-quality assurance of the labeling information that the HCPs and patients will access.

2.2. Accessibility, reader-friendly format

2.2.1. Goal

2.2.1.1. Background

Access to the most updated product information in real time is essential in ensuring the optimal use of medicines and patient safety[7]. The provision of user/reader-friendly access to product information is an important element of e-labeling where the label is linked directly via a machine-readable code accompanied by a human-readable format, printed on a pharmaceutical product packaging. This allows the end-users (e.g., healthcare professionals, patients, consumers, caregivers) to access product information electronically and in real time, thereby enhancing user experience as compared to the traditional paper leaflet.

In a survey conducted by APAC in November 2021, only 2 markets in the region have started to use GS1 barcodes to provide access to e-labels, 1 market is dependent on the choice of the company, while 4 markets are currently discussing with their health authorities on the accessibility format to be used. In Japan, the pharmaceutical law was amended to introduce e-labeling in December 2019 and was enforced on August 2021 that the paper labeling has to be removed from the commercial pack with two years transition period. The users can access the latest labeling by scanning the GS1 barcode printed on the outer and inner packaging using a mobile application[8]. In Taiwan, the first label online search system established in 2015, utilized a smartphone based GS1 barcode scanning, called “Medicine Scan APP”. In August 2019, the Health Sciences Authority (HSA) of Singapore issued a guidance for e-labeling. This is on a voluntary basis and is implemented in a phased approach where prescription-only medicines (POM) are eligible. Companies who wish to implement e-labeling may print the Uniform Resource Locator (URL), Quick Response (QR) code, or other machine-readable code on the outer packaging of the pharmaceutical product[6].

In the European Union (EU), the current legal framework allows the provision of mobile scanning technologies for the purpose of providing information in the outer and immediate packaging and the package leaflet, for centrally authorized medicinal products. It is required however, that the URL of the platform hosting the product information must always be displayed in the labeling and/or package leaflet along with the mobile technology feature[9].

Pharmaceutical serialization in Asia is also starting to progress. Serialization is one of the existing systems that electronically provides information on medicines using unique codes. The system is to give unique numbers to each packaging unit of a drug to prevent counterfeits from entering the supply chain. Certain level of interoperability among system is required to track and trace, and the GS1 standard is widely adopted in many countries for the serialization system. According to the survey in Asia, China, Indonesia, Japan and Korea already have regulations for pharmaceutical serialization

with machine readable code. Taiwan and Malaysia are in planning stage for a pilot, while India, Philippines, Singapore, Thailand and Vietnam are still in discussions. In Korea, it was mandated by the government that all pharmaceutical product labeling system must have a unique serial number to the minimum distribution package which allows traceability at all stages of the supply chain from manufacturing to use[10].

2.2.1.2. Objective

The objective of this section is to describe the e-labeling accessibility formats widely used in Asia and present each format's benefits/pros and risks/cons. This will provide markets in the region the information that they need to assess the most suitable format that they can adopt, considering their respective markets' available technology, internet connectivity and end-user's preference, among other factors.

2.2.2. Methods

A review of the widely used e-labeling accessibility formats in Asia was made and the results are presented below, with the benefits/pros and risks/cons of each format summarized in Table 2-1.

2.2.2.1. Uniform Resource Locator (URL)

The Uniform Resource Locator (URL) is a human-readable format which refers to the website address where the e-label is uploaded. This format does not require a device or application for access but entails the user to manually encode the URL text in a suitable web browser to gain access to the e-label and/or e-label platform. The manual nature of the URL is prone to encoding errors by the user and can lead to inconveniences in accessing the information. The URL may also pose a challenge during printing on the packaging material especially if the text is long or the space is limited. In markets where the URL is required to be printed along with the machine-readable code, lengthy URLs are not advisable and the name chosen for the URL should be meaningful enough to allow proper identification of the product[9]. In Singapore, short URL links are preferred by the regulatory authority[6].

2.2.2.2. Quick Response (QR) Code

The Quick Response (QR) Code is a two-dimensional (2D) code that can carry large quantities of information and can be read omni-directionally at faster speeds as compared to other codes, due to the position detection patterns located at the three corners of the symbol[11]. There are two types of QR Codes: the first is the Static QR Code that contains an embedded URL with a fixed destination which means that the URL is part of the QR Code pattern hence is not editable, while the second type is the Dynamic QR Code that contains an embedded "short URL" that redirects the user to a destination website URL, also called "long URL". The short URL remains the same, but the long URL may be changed even after the QR code has been generated. Advantages of the Dynamic QR Code include easier to scan since pattern is less dense, can be password protected, and can provide scan tracking

and analytics[12]. Since its introduction in 1994, the QR Code is the most familiar and widely used machine-readable code format which may be scanned by almost all mobile devices. It does not also require a specific application for scanning. However, for products that already utilize codes such as GS1 barcodes for other purposes such as serialization, printing a separate QR code for e-labeling alone may result in an additional code on the packaging and can lead to possible confusion for end-users or space constraint issues. Thus, use of multiple codes should be avoided. In the EU, inclusion of multiple mobile technology features or codes is not recommended, and features that will be included should not compromise readability of required information[9].

2.2.2.3. GS1 Barcodes

GS1 is an international organization that develops and maintains a system of supply chain standards and barcodes that provide automatic identification and data capture. GS1 barcodes such as the 2D DataMatrix and the DataBar are machine-readable code formats that usually contain other unique product information such as the Global Trade Item Number (GTIN), serial number, batch number, expiry date, etc[13]. In addition to the ability to provide more information as compared to the QR code, the GS1 barcodes may already be printed on the secondary packaging for products in markets that require serialization, therefore using these codes for linking to the e-label can fulfill both serialization and e-labeling purpose without printing an additional code that may confuse the users. However, the GS1 barcodes require a specific application to access the contained information.

Table 2-1: E-Labeling Accessibility Formats

Format [a]	Benefits/Pros	Risks/Cons
URL http://www.example.com/filename.html	• No need for specific devices or applications.	• It takes some time to reach to the e-labeling due to manual encoding. • Challenging to print if long text or packaging has limited space.
QR Code	• Almost all mobile devices can scan the code without specific applications. • It can be scanned anytime, anywhere using mobile devices.	• Need additional printing of QR code to the packaging with prior codes for other purposes such as serialization, which may cause confusion for end-users. • Some people are not too familiar with mobile devices.
GS1 Barcodes 	• Existing GS1 barcode for serialization on the secondary packaging can be utilized for e-labeling as well. • It can be scanned anytime, anywhere using mobile devices.	• Need specific application for scanning. • Some people are not too familiar with mobile devices.

[a] Overview of all GS1 barcodes. https://www.gs1.org/docs/barcodes/GS1_Barcodes_Fact_Sheet-overview_of_all_GS1_barcodes.pdf

2.2.3. Tools

For markets planning to implement e-labeling, it is recommended that pilot studies and transitory periods be conducted to assess the most feasible e-label accessibility formats that may be adopted by both industry and the regulatory authorities. This is to ensure that the value of accessing the e-label will be maximized within the technological infrastructure available to the end-users.

In Japan, the latest labeling has to be posted on the PMDA website for many years. According to the new pharmaceutical law issued in December 2019, paper labeling was abolished from the commercial pack with a 2-year transition period, and the latest labeling must be referred from the PMDA website in a basic way. It was decided to utilize the existing code in the outer carton, (a GS1 barcode), as the machine-readable code for e-labeling. A free mobile application to scan the GS1 barcode was co-developed by GS1 Japan, The Federation of Pharmaceutical Manufacturers' Associations of Japan (FPMAJ), and The Japan Federation of Medical Devices Association (JFMDA) and was released as

of April 1, 2021. Also, the MHLW announced in August 2016 the mandatory labeling of GS1 DataBar (primary and secondary package) and GS1-128 (outer carton) for prescription medicines, and this was enforced from April 2021, preventing medical accidents due to mix-ups and improving traceability in medical practice.

In Singapore, since e-labeling adoption is on a voluntary basis, companies that are planning to implement e-labeling are required to submit their proposals to the HSA using an online notification form. Applicants may also include their e-labeling proposals in the submission dossiers for new drug applications.

2.2.4. Communication

It is equally important that the e-label accessibility format to be adopted by a particular market be consulted with relevant stakeholders and end-users. Public consultations, pilot studies, surveys, information campaigns and e-labeling guidelines may be utilized to achieved this.

In Taiwan, the e-labeling pilot plan of the Taiwan FDA released in 2022 adopted use of a QR code instead of the GS1 barcode. This was to address concerns raised during the adoption phase of the Medicine Scan APP[14]. In Singapore, the e-labeling guidelines require that appropriate instructions for users on how to access e-labels should be provided by the applicants. Discussions for pilot studies are ongoing for Malaysia, Thailand, Philippines, Indonesia and India.

2.2.5. Expectation

It is ideal that there should be a single, reader-friendly accessibility code format printed on the pharmaceutical product packaging, that links directly to the electronic product information upon scanning by a suitable device, and that this code format may also be utilized to contain other information that may be required in a particular market such as in the case of serialization. However, given the benefits and risks presented for the various formats used in Asia, it is recommended to adopt a stepwise approach in the implementation of accessibility formats to allow for adoption of e-labeling while considering the varying levels of capacity of markets in the region[7]. For instance, the e-label could be made accessible first to users via a QR code with URL, which can then be changed in the future to a GS1 barcode upon market readiness to technological requirements. For those markets utilizing the GS1 barcodes for supply chain purposes, these codes may already be leveraged to adapt to e-labeling purposes. Through this, a single code may serve both purpose of providing access to product information while ensuring the integrity of the pharmaceutical supply chain.

2.3. Paperless

2.3.1. Goal

2.3.1.1. Paperless refers to the removal of paper product information (PI) from commercial pack and replacing it with electronic PI as part of the e-labeling regulation.

The COVID-19 pandemic highlighted the need for an agile pharmaceutical supply chain, which will ensure the continuous availability of lifesaving medicines. Flexibility to mitigate supply disruptions amidst the imposition of various movement restrictions and border closures is needed. It is at this time when regulatory consideration on paper labeling materials were introduced which paved way for some Asian countries such as Malaysia, Philippines, Thailand and Korea to also look into e-labeling.

Without the need to print on paper the labeling information, supply chains were able to deliver every drug — not only lifesaving medicines, but also COVID-19 vaccines and medicines — at a much shorter lead time. By eliminating printed paper PI from physical products, information is provided in a timely manner as e-labeling. From a supply-chain and environmental perspective, removing paper PI from the commercial pack brings benefits to a broader stakeholders, which is not limited to the pharmaceutical industry.

In the Asian region, Japan and Singapore have regulations on e-labeling, with the former fully paperless and the latter implemented on a voluntary basis.

It is the goal of this position paper to advocate for the implementation of e-labeling and remove the requirement to print labeling information.

2.3.2. Methods

With the advancement of digital technology in healthcare, the implementation of electronic labeling or e-labeling can replace the conventional paper leaflet for pharmaceutical products. In this position paper, we will discuss three areas for consideration to transition in removing paper PI from the commercial pack: 1) implementation timelines, 2) operation, and 3) regulatory aspects.

2.3.2.1. From implementation aspect

From an implementation timeline perspective, we will need to ensure that there is a sufficient grace period for e-labeling implementation. The implementation of pilot projects allows healthcare professionals (HCPs) and patients to embrace the e-labeling concept and practice gradually. There are two options for e-PI and paper insert management during the grace period. One option is the paper PI may co-exist together with e-labeling during the interim period to allow HCPs transition from paper PI to e-labeling (e.g., Singapore and Japan). During the pilot phase, regulators and the pharmaceutical industry will have the opportunity to understand the HCP and patients' needs to improve for the full implementation of e-PI without a paper insert.

In December 2019, an amendment of the Act on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices (known as the Pharmaceuticals and Medical Devices Act or PMD Act) was stipulated and was enforced from August 2021 to have a smoother transition to e-labeling in Japan. In principle, paper package inserts that are to be enclosed with products are abolished in principle from August 2021. But as part of a transitional measure for Drugs, etc. that requires information disclosure that were manufactured and sold between the 2-year transition period from 1st of August 2021 to 31st of July 2023, products can still include their paper package inserts in which "information on precautions, etc." is printed. However, inclusion of paper package inserts should be avoided after 31st of July 2023. Thus, full implementation of E-labeling (including GS1 barcode) will be expected from 1st of August 2023. This was communicated in various forms such as international conferences, release of regulatory guidance and notification and even through conducting seminar or a meeting with various stakeholders such as HCPs and pharmaceutical trade organization.

Gradual implementation might however lead to a slower full implementation. During the grace period, new technology might emerge and it could be a threat to e-labeling platform. Thus, there is a need to consider an appropriate grace period or steps/timeline according to the market concerned.

In Australia, a third-party website (the Pharmacy Guild) hosts e-labeling for many years now, with just-in-time printing available at the Pharmacy. On the other hand, paper leaflets may also be removed during the pilot phase. In Belgium and Luxembourg, the paper label version was not provided during the pilot phase for limited number of products used in hospital setting. A survey was conducted, and the results showed that the e-label provides adequate information to the HCPs and the absence of paper leaflets in the packaging has not generated any inconvenience in their daily practice[7].

2.3.2.2. From operational aspect

In addition, the operation aspect should also be taken into consideration including the cost, resources, and efficiency to implement both paper leaflet and e-labeling concurrently or removal of the paper leaflet. The paper package insert version may be different compared to the e-PI. Additional resources are required to conduct the checking and communicate the differences to HCPs and patients to avoid confusion. On the other hand, from a product quality perspective, the paper package insert may serve as a "cushion" for the medicine in the carton box. Hence, it is essential to conduct an impact assessment before removing the paper leaflet. Removing the paper leaflet may require packaging redesigning.

As mentioned above, redesigning of packaging is required in some cases, and securing the latest e-labeling provision is required at the time of eliminating printed PI. For packaging redesign, it needs time therefore gradual implementation discussed above can work to be prepared.

2.3.2.3. From regulatory aspect

As one of the markets implementing e-labeling, Japanese regulation[8] can be an example. Here is a summary of regulatory requirements in Japan.

1) e-labeling (to eliminate printed package insert) has been enforced from the 1st of August 2021 with 2 years grace period each.
2) Detail operation is regulated by government notice as well as PMD law.
3) 100% e-labeling for prescription products is available at the PMDA website shown in HTML with a link to XML and PDF format.
4) PIL is not for all prescription products but for designated products. Available in PDF format.
5) GS1 code is required to be printed in the product package to access product information.
6) Establishment of an organization/ system to provide package insert information is required.

From a regulatory aspect, regulations need to be considered to establish e-labeling implementation for eliminating printed package insert, relating to 1) availability of electronic file format (e.g., PDF) of e-labeling; 2) scope of e-labeling (Rx/OTC, HCP/Patients, etc.); 3) detail procedure of publishing e-labeling; 4) detail procedure of managing revision of e-labeling; 5) managing and securing access to the latest e-labeling by a symbol and place to publish e-labeling, at an early stage of e-labeling implementation.

In addition, to be prepared for e-labeling implementation, the infrastructure and technologies including the mobile devices, its applications, data transfer, methods of “managing and securing access to the latest e-labeling” should be discussed periodically and regulations should be revised accordingly.

On the other hand, when regulations are presented in a detailed manner, paperless implementation could take time to prepare. Considering the availability of technologies and emerging risks in the internet such as cyber security, steps and required regulations to realize “paperless” needs to be adjusted from market to market.

2.3.3. Tools

It is recommended that surveys be conducted to assess the status of readiness and the best approaches for implementation in the transition towards paperless. This may cover surveys on HCP, enterprises such as pharmaceutical companies/printing vendors/IT system vendors, and patients. A survey on HCPs can be used to evaluate access, use, and reading of e-PI. A survey on pharmaceutical companies can evaluate readiness and challenges. Surveys before and after a pilot phase can help towards improving the approaches and final implementation plans e.g., from questions received after the implementation of a pilot e-labeling project in the survey on participating enterprises.

For eliminating paper PI, it should be implemented along with the ideas discussed in the other sections than Paperless.

2.3.4. Communication

Before implementing paperless PI, it is recommended to communicate to all stakeholders on the proposed implementation plan and seek feedback to ensure a smooth roll-out. This may be in the form of public consultations through appropriate platforms.

Educational materials or publicity materials for awareness of this change to paperless PI may be helpful in the adoption of paperless PI.

It is important to consider that appropriate communication channels are available for stakeholders to obtain the product information needed in situations where there are disruptions or access issues to the paperless PI.

2.3.5. Expectation

2.3.5.1. Benefits -- Enhance patient safety by efficiently sharing of safety and efficacy updates of e-labeling in a paperless manner

The use of e-labeling will facilitate the safe use of drugs better than the traditional paper PI. It is known that the traditional paper PI will take several months to print, insert and transmit to the patient and HCP. But when e-labeling is implemented, it will just need several days, even less than 24 hours to transmit the approved and/or updated PI information to the patient and healthcare professionals. In addition, e-labeling can ensure all patients and HCPs have access to the current and consolidated PI information approved by HA avoiding confusion caused by inserting different versions of outdated paper PI approved at different timeframe.

2.3.5.2. Advance environmental sustainability (reduce paper wastage) -- saving resources and promoting environmental protection

According to statistics, approximately 90 billion sheets of paper labeling of drugs are wasted in America every year, some of which are even not used[15]. Similarly, in Japan, it is estimated that about 10 billion paper PIs and in Asian region approximately 40 billion paper PIs can be reduced if the paper PI is replaced with e-labeling[1]. The application of electronic labeling can reduce waste and consumption of a large amount of paper that are used by pharmaceutical companies to manufacture drugs in revising and updating product labeling, including recalling drugs after launch. E-labeling can not only reduce production costs of enterprises, but also greatly save natural resources and protect the environment.

2.3.5.3. Improved supply management (redressing of paper PI not required), reducing resources

Instead of spending millions of resources updating artwork, printing, and working out the logistics for distributing the labels in paper, implementing e-labeling will save on cost and resources.

Meanwhile, e-labeling can ensure that updated information was communicated in a timely manner. Providing up-to-date PI will also increase compliance by decreasing risks of recalls due to errors in paper PI.

2.3.5.4. Faster access to drugs

In addition, e-labeling will also shorten the lead time for paper PI printing and packaging to make the patient have faster access to drugs. Especially the importance was illustrated during the COVID-19 pandemic outbreak where e-labeling provided more flexibility and brought a positive impact on the availability of up-to-date approved drug information. Delays were also avoided even when there is border closure due to Covid-19.

2.3.5.5. Implementation process of e-labeling in paperless

In order to ultimately realize e-labeling in paperless, it is suggested to stipulate at the legislative level that e-labeling in paperless be the only form to deliver product information. To promote the implementation, there can be pilot projects (such as selecting varieties of drugs and/or enterprises/ or regions), setting transition periods, stepwise implementation, and then national implementation. It may allow the co-existence of paper PI and e-labeling during the pilot or transition period, and then implement the e-labeling for the whole country or region/market after the accumulation of experience. The duration of the transition period should be considered depending on the readiness of the market and the enterprises concerned and voluntary implementation should also be allowed during this period. Flexibilities during the pilot or transition period may foster smoother adoption in the early stage.

2.4. Common electronic standards

2.4.1. Goal

In current digital era, there are myriads of electronic file formats and electronic standards adopted in different countries. As regulatory agencies adopted digital format and standard at different timelines, the file format and electronic standard vary among countries. Some of the markets in Asia have published labeling in PDF on their health authority websites, but not structured product labeling except for Japan. In Taiwan, TFDA is establishing a machine-readable, structured format, such as XML, for drug e-labeling. In Singapore, HSA issued Guidance on e-labeling in 2021. In the guidance, e-labeling refers to product information, including the package insert (PI) and patient information leaflet (PIL), which is distributed via electronic means, such as through a machine-readable code or an URL on the product carton which links to a secure online system. As an advantage of e-labeling, digitalized information can be handled electronically and flow to other digital health systems, such as electronic health records and e-prescribing systems, facilitating efficient information flow. A common electronic standard for ePI should be adopted in the creation, submission, and review process to allow searching, reuse, and potential integration with other digital health platforms i.e., interoperability. In contrast, a

lack of standardization may pose as a stumbling block to a successful implementation of e-labeling in the market. This section aims to provide an account on the currently available standards for the following purposes:

1) To increase the awareness of different common electronic standards that have been adopted, so as to encourage the adoption of these standards;
2) To serve as a common resource for APAC markets to understand the pros and cons of various electronic standards; and
3) To aid the decision making for APAC markets on the adoption of a common electronic standard in consideration of potential future interoperability with wider digital health platforms and harmonization among countries.

2.4.2. Methods

In order to achieve the benefit and expectation in Patients, Healthcare Professionals, and Industry described in the Introduction section, APAC e-labeling EWG conducted the research in a two-step process. The first step introduces the existing electronic standards which could be identified within the timeline of the research to give a basis for the later analysis. Then, the second step presents the analysis of the pros and cons for each electronic standard by adopting the 4A approach (Acceptability, Affordability, Accessibility, and Awareness) which is generally used to view the product or service offering from the perspective of a user. However, given the limited public information on the regulators' perspectives when adopting the electronic standards, the research instead focuses on the APAC's perspective which could be used as a reference for any regulator when considering the adoption of e-labeling in their respective country in the future.

The section is presented in a way which is easy to understand for all the readers, including those who have no prior knowledge of e-labeling and/or electronic standards. Within the limited timeframe, the research may not cover all the electronic standards that are currently in use.

The details of each methodology are described in the following sub-sections.

2.4.2.1. Identification of existing electronic standards

The term "electronic standard" in terms of e-labeling generally references two types: file format (e.g., Microsoft Word file, PDF, etc.) and structured contents format (HL7 V3, HL7 FHIR, etc.). Digitalization of labeling generally standardize the file format first and then the structured contents format, as the US, EU, and Japan has walked through. This position paper focuses more on the electronic standards for the structured content as it aims to present the most recent position of APAC to the electronic standard for e-labeling. Hereinafter, the term "electronic standard" stands for the ones for structured contents.

2.4.2.2. Analysis of pros and cons for existing electronic standards

Given the limited information on the views and considerations of the regulators when adopting the electronic standards, and given the limited timeframe of this paper, the analysis of pros and cons for the existing electronic standards is conducted from the perspective of the APAC. Specifically, the analysis presents what are considered as pros or cons by the APAC if a regulator is considering the adoption of such a standard.

Depending on the local legislation framework and the development of digital transformation status of the local healthcare system in each market, the electronic standards must ensure that the main goal of the e-labeling purpose is to allow all healthcare professionals and patients access to up-to-date labeling information at the soonest possible.

Our analysis is based on the key evaluation indicators called 4As (Acceptability, Affordability, Accessibility, and Awareness) which is developed by Jagdish Sheth and Dr. Rajendra Sisodia and commonly used in Marketing. The use of the 4As in this analysis mainly follows the principles and concepts of the original model, with some minor adjustment to fit with the context of e-labeling. One of the adjustments is to incorporate 'interoperability'. This paper refers to the definition of Healthcare Information and Management Systems Society (HIMSS) which describes 'interoperability' as the extent to which systems and devices can exchange data and interpret that shared data. In simple terms, it is the ability to ensure efficient information flow between the two systems so that they can exchange data and subsequently present that data such that it can be understood by a user.

Nowadays, there are so many complex systems being networked together, therefore, the concept of interoperability should be on the minds of the people working in all types of organizations, with healthcare, and in particular e-labeling being no exception. Interoperability is significantly important when thinking about e-labeling as it affects the time, cost, and productivity aspects of the adoption of e-labeling, which ultimately have an impact on the health outcomes for individuals and populations.

The details of the 4As model in the context of e-labeling are as below.

- Acceptability
  - Is it expected to meet local requirements in APAC markets?
  - Is it interoperable (inter-national, inter-system, and such)?
  - Is there any barrier (technical/political/resources/infrastructure/regulation) in the APAC markets to adopt it?

- Affordability
  - How much does it cost to adopt the standard? (to develop, implement and/or operate, etc.)

- Accessibility

- Is it available to APAC markets?
- What expertise is needed to understand it? Is the expertise available in APAC markets?
- Is there any challenge to use the standard?

- Awareness
  - Is it broadly acknowledged in the world? How has it been evaluated?
  - Has it been implemented in any markets? Is it planned to be implemented in any markets?

2.4.3. Communication

2.4.3.1. Identification of existing electronic standards

The Internet research identified 4 implementations of electronic standard for labeling documents as shown in the Table 2-2.

Table 2-2: Electronic Standards

Market	Implementation (Current or Planned)	Electronic Standard
Canada	XML PM (Product Monograph in XML format)	HL7 Structured Product Labeling
EU	ePI (electronic Product Information)	HL7 Fast Healthcare Interoperability Resources
Japan	PMDA XML PI [a]	PMDA-custom XML Schema
USA	SPL (Structured Product Labeling)	HL7 Structured Product Labeling

[a] No official English name is available. For convenience, it is called "PMDA XML PI" in this paper.

2.4.3.1.1 HL7 SPL

HL7 SPL (Structured Product Labeling) is a subset of the HL7 Version 3 (HL7v3). While the HL7v3 covers a broad area of messaging, including but not limited to eCTD v4, product information, etc., the HL7 SPL focuses on product labeling. The development of SPL was started with members of the HL7 Regulated Clinical Research Information Management Technical Committee. It was first released in early 2005[16] and its development was strongly driven by the US government and medical information users.

HL7 SPL was developed to address some challenges with the previous standard(s), increase worldwide awareness and adoption of the standard, and support exchange of labeling content to meet the needs of health authorities. Therefore, SPL has been implemented with Extensible Markup Language (XML) format that is both human and machine-readable.

HL7 SPL consists of two main components: 1) labeling content and 2) the data structures from the Common Product Model (CPM). The latter and the XML schema encoding them have been in use

since the early 2000s, and particularly since 2009 for registering (i.e., listing) all drug products legally marketed in the US.

The latest release of HL7 SPL is Release 8 in 2017[17]. The HL7 SPL is currently adopted by the US FDA and Health Canada.

– In February 2004, the US FDA announced its plans to adopt SPL as its standard for electronic submission of labeling content, as identified in the Draft Guidance "Providing Regulatory Submissions in Electronic Format – Content of Labeling." One year later, the US FDA published the first guidance for the industry on using SPL standard for submission of labeling content. In addition to the use of SPL, the US FDA and the National Institutes of Health (NIH) together developed an SPL image standard, which is called SPLIMAGE for image files of oral solid dosage forms that are submitted with SPL documents.
– In April 2019, Health Canada informed about its intent to transition product monograph templates to a structured format based on XML format[18]. SPL was officially put in use from June 2020 with a phased approach and is in Phase II today with voluntary application of XML product monographs.

2.4.3.1.2 HL7 FHIR

As the digitization of healthcare information has progressed and the need for interoperability has simultaneously grown, the HL7 (Health Level Seven International, a non-profit ANSI-accredited standards development organization) has taken the major role of developing interoperability standards in the field of healthcare. Since the late 1980s, the HL7 has developed standards including HL7 Version 2, HL7v3, and CDA, and in the 2010s, the HL7 built a new standard FHIR (Fast Healthcare Interoperability Resources) by combining the best features of the previous standards and leveraging the web service technology, focusing tightly on implementability[19].

The FHIR became a normative standard in October 2019[20], and HL7 has actively monitored its implementations in order to continue improvements of the specification to be responsive to their needs. As of June 2022, the FHIR has not yet been implemented in e-labeling field in any of the major markets; however, numerous FHIR related projects are underway.

In US, the SPL is the current standard behind a range of information processed by US FDA and public information systems. The US FDA mentioned in the CDER Data Standards Program 2021 Annual Assessment, "As HL7 is transitioning to a more advanced FHIR standard, FDA is performing its due diligence by conducting an assessment of the FHIR capability to support the full range of current functions and, potentially, new use cases in a more efficient, robust, and sustainable way."[21] In May 2022, the US FDA mentioned in their Data Standard Program Action Plan[18] that they are examining the FHIR as an alternative to SPL. The FDA's SPL to FHIR Implementation Guide project is still in development but a draft is available online as of February 2022.

In 2021, an International Electronic Medicinal Product Information (ePI) project started as one of HL7 Vulcan[i] projects in collaboration with Gravitate Health[ii]. The International ePI project is working for defining a common structure for product information that supports cross-border exchange of data for patients and develop international HL7 FHIR ePI standard. This ePI has successfully developed an Implementation Guide for FHIR ePI prototypes. In February 2022, the EMA released a news that the European Medicines Regulatory Network adapted the FHIR as a common standard for the electronic product information (ePI) on medicines in EU[22].

In UK, NHS released a note in October 2021 about a new information standard of medications and allergy/intolerance information sharing between NHS and social care organizations to support reduce medicines related errors and improve patient safety. The standard is also expected to enable healthcare professionals to obtain medicines information in a quicker and more efficient manner, and coming into effect on March 2023, it has been based on FHIR[22].

In addition, the Vulcan also keeps investigating whether FHIR ePI can be produced for the US and Japanese label while the HL7 FHIR ePI implementation guide is developed as an international core.

As mentioned above, HL7 FHIR is being considered as a next-generation standard for e-labeling in multiple major markets.

2.4.3.1.3 PMDA-custom XML Schema

PMDA XML PI with PMDA-custom XML schema as Japan e-labeling has officially started in Japan since April 2019. In Japan, digitization of package insert and its utilization have been considered since the Internet became commercially available. It is required that pharmaceutical companies provide e-labeling information that can be handled directly by a computer in addition to PDF which is soft copies of package inserts on paper. This has been continued since 1999. PMDA XML PI has replaced the e-labeling information in Standard Generalized Markup Language (SGML) format traditionally used in Japan.

The PMDA-custom XML schema has the following features:

- Designed to align with the heading structure of the labeling (for HCPs) for Japan.
- The amount of information in PMDA XML PI is the same as that in PDF.
- Effective as part of review of labeling by PMDA
- Provided a dedicated tool for creating the PMDA XML PI.
- Japanese and English can be handled in the same scheme.

[i] The HL7 Vulcan is one of the HL7 Accelerator projects for diverse and multiple stakeholders to develop an effective solution for exchanging healthcare information efficiently in HL7 FHIR format together.

[ii] The Gravitate Health is a public-private partnership with 39 members from Europe and the US, funded by the Innovative Medicines Initiative (IMI).

- Focuses on describing and appearance of e-labeling and has limited functionality but can handle rich text.

The PMDA-custom XML schema is specialized for regulated e-labeling structure in Japan and thus has less flexibility to import labeling information from other markets.

There is no API intended for use by third party applications that use package insert information as seen in other electronic standards. However, PMDA servers that store e-labeling information provide a server-based Web application in which the package inserts can be searched and viewed, and comparison points between old and new ones can be shown. However, information on the operation of the server system will not be disclosed.

It is unknown whether e-labeling information has been used for purposes other than use cases to view package inserts.

2.4.3.2. Analysis of pros and cons for existing electronic standards

The pros and cons of each standard are summarized in Table 2-3. The details are described in the subsections.

The acceptability of HL7 SPL and FHIR are relatively high from technical perspective as they are both designed to be interoperable, comparing with the PMDA-custom XML Schema. Since the US FDA is currently examining migration from SPL to FHIR, the expectation is that FHIR is higher in acceptability: however, the potential users/implementers should be aware that FHIR has not yet been implemented in practical use in any country/region for e-labeling and that it has not confirmed that FHIR is practically acceptable and feasible for e-labeling in APAC markets. It is encouraged for APAC markets to collaboratively and/or independently assess the feasibility of HL7 FHIR in the markets.

Regarding the affordability, theoretically speaking, the total and long-term cost to implement and operate interoperable standard will be lower than that for non-interoperable standard, as the nature of the interoperability across systems would lead to commoditization of the function handling the standardized data. It is encouraged for the APAC markets to nurture HL7 FHIR experts in APAC markets so that adoption of the standard would be widely generalized in the country/region at a reasonable cost.

The HL7 standards are highly accessible than PMDA-custom XML Schema because the HL7 is an open, international standard development organization: the standards and relevant information are all available in English on their website. Since one of the motivations to develop FHIR was the complexity of HL7 Version 3 standard (the standard the SPL is based on), the FHIR can be considered to have higher accessibility than SPL, but the technical, business, and regulatory feasibilities should be assessed by the country/region adopting it. It is indispensable to nurture FHIR experts in APAC markets.

The SPL and FHIR are well known in international healthcare standardization communities while the PMDA-custom XML Schema is only recognized in Japan. The awareness of the HL7 standards for the use in e-labeling in APAC markets has been emerged recently and growing gradually.

Overall, it is expected that FHIR is to be a better solution than other 2 standards in 4A indicators. However, the fact that FHIR has not yet been implemented for e-labeling in any region/country should be carefully considered when evaluating the value and feasibility of the standard in APAC markets.

Table 2-3: Pros and Cons of Electronic Standards

		Acceptability in APAC	Affordability in APAC	Accessibility in APAC	Worldwide Awareness
HL7 SPL	**Pros**	• Interoperable • A history of over 15 years of use in healthcare messaging with lessons learned and best practices • Familiar: the US and Canada have adopted • Flexible: allow putting additional constraints or requirements on the labeling content submissions, if required	• –	• Standard is freely accessible • Written in English • Lots of available resources for reference	• Adopted by the US and Canada in labeling field
	Cons	• No backward compatible	• Initial cost might be high if previously adopted HL7v2 • Maintenance cost may increase since resources are shifting to focus on developing FHIR.	• Transition to FHIR • Training required for users familiar with traditional tools (MS Word, PDF, etc)	• Less awareness outside North America

		Acceptability in APAC	Affordability in APAC	Accessibility in APAC	Worldwide Awareness
HL7 FHIR	**Pros**	• Interoperable • APAC requirements (if any) will be met by either core or extended specification. • Strong support of implementation	• Low total and long-term cost when FHIR is adopted	• Freely accessible • Written in English • Based on well-accepted technologies	• High awareness in international healthcare standardization communities • Many major markets have adopted in non-labeling healthcare (e.g., US. EU, Canada, Japan and UK)
	Cons	• Unfamiliar: no APAC market has been participated • No country/region has implemented yet	• Initial cost might be relatively high because APAC domestic vendors have not so familiar with FHIR.	• Might be tough to catch up	• Practical evidence supporting the value in e-labeling field is not yet available
PMDA-custom XML Schema	**Pros**	• Used over 2 years • English labeling is applicable	• –	• Specifications for the Schema is already available	• –
	Cons	• Currently only support for Japan e-labeling • Not designed to be interoperable	• Initial cost might be high due to implement e-labeling management system specific for PMDA-custom XML schema	• Documentations are written in Japanese	• Less awareness outside Japan • No reuse case of e-labeling information was found

2.4.3.2.1 HL7 SPL

Acceptability

The HL7 SPL is considered highly acceptable to APAC from the perspectives of interoperability, compliance with potential requirements from APAC markets, and low barrier for implementation.

The HL7 SPL has been used in the early 2000s in healthcare messaging, adopted by the US (for over 15 years) for labeling content submissions and updates, and Canada (recently) for product monographs. It has been updated several times by HL7 through 8 releases to meet the practical needs during the implementation by the authorities.

The HL7 SPL is open and flexible enough to enable an individual health authority to put additional constraints or requirements on the labeling content submissions. A simple example of its flexibility is that the authority could choose to make data elements which are originally defined as optional in the schema to be mandatory, depending on the local regulations.

As the HL7 SPL was originally developed to define a consistent data model and create a more precise standard, compared to the HL7v2 standard, it was created as a new standard that would not be compatible with older HL7v2 versions. Therefore, the adoption of HL7 SPL is mainly observed for applications without historical use of HL7v2 in communications, or in regions that have high government enforcement of HL7v3 usage.

Affordability

There is the long history of HL7 SPL implementation in the US. This fact leads to an assumption that, comparing to the standard with no history of implementation, it would be relatively easier to find the vendors in the US which are familiar and could support both the authorities and industries with the adoption of the standard in APAC markets.

The approximate total cost needed to implement and operate HL7 SPL depends on each situation. For users who have previously adopted HL7v2-based applications, they will need to deploy and maintain new HL7v3 applications in parallel and implement interfaces between them to adopt HL7v3.

However, the nature of SPL (e.g., its interoperability, ease of implementation, and accredited international standard development organization as a development body, etc.) are generally considered to lower the total and long-term cost, comparing with other standards without these nature.

Accessibility

The SPL is developed by HL7, a volunteer organization consisting of members from industry, government agencies, vendors and others wanting to advance standards in healthcare arena, therefore, all the information about the SPL is easily accessible to anybody on the HL7 websites. The information about the adoption of SPL by the US and Canada is also published, with guidelines, process and training resources. Although they are in English, which might be counted as a barrier for non-English

native speakers: however, taking into account that English is one of the most accessible languages in most of the international community today, it is considered that accessibility of SPL is not detracted by the language.

For users who are familiar with working with other formats, it requires additional training to get familiar with the XML-based environment. While there is no official notice about the discontinuation of SPL, HL7 has developed a new generation of standards, building on the best features of HL7v2, HL7v3, and HL7 CDA, so there is a natural tendency to shift focus from SPL to FHIR moving forward.

Awareness

The HL7 SPL is currently used by thousands of both US and non-US companies to submit their labeling content submissions to the US FDA. The adoption by Health Canada is also in phase two where companies are encouraged to submit product monographs in SPL format.

However, the so-far use of SPL is mainly in English-speaking markets and no practical examples of how to apply it for non-English-speaking ones.

2.4.3.2.2 HL7 FHIR

Acceptability

The HL7 FHIR is deemed highly acceptable to APAC from the perspectives of interoperability, compliance with potential requirements from APAC markets, and low barrier for implementation.

FHIR, as the “I” of its abbreviation stands for, has been designed to be interoperable. It is based on internet standards widely used by industries outside of healthcare, and “The philosophy behind FHIR is to build a base set of resources that, either by themselves or when combined, satisfy the majority of common use cases. FHIR resources aim to define the information contents and structure for the core information set that is shared by most implementations.”[23] These characteristics of FHIR leads the users to be able to share and exchange data in a real-time fashion using widely accepted internet technologies.

Since its release as a draft standard for trial use in 2014, FHIR has been upgraded several times. In October 2019, FHIR R4 became a Normative standard. The potential implementers (e.g., APAC markets) have opportunities to submit their requirements to HL7 anytime they want, and those requirements will be discussed in a release cycle of approximately 18-24 months. The 80/20 rule of FHIR also supports non-early adopters of this standard: the FHIR specification covers 80% of the needs, and knowing the remaining 20% is not covered, FHIR allows extension and customization to meet market-specific requirements.

From technical specification perspective, FHIR is based on well-accepted technologies and standards, and multiple vendors and toolkits for implementation are available. These features of FHIR lead to low barrier for implementation.

Affordability

The approximate cost needed to implement and operate FHIR depends on the situations and is not expected to be officially estimated or published. However, the nature of FHIR (e.g., its interoperability, implementability, and accredited international standard development organization as a development body, etc.) are considered to lower the total and long-term cost, comparing with other standards.

The advantage of interoperability works when the standard is widely adopted across varied business fields, and the same principle applies to the cost. For example, if the data in clinical researches, electronic health records, and labeling are standardized, data mapping across IT systems would be easily conducted when exchanging the data, which eventually lowers cost for system deployment. Also, since FHIR is an open, international standard accessible to anybody and developed based on well-accepted internet standards, it should avoid the vendor lock-in from happening, which supports fair cost for implementation, operation, and maintenance of the IT systems.

Accessibility

Since the HL7 is an open, international standard development organization, the released FHIR standards are technically accessible to anybody. If a party submits their requirements to HL7 and wants to participate to the discussion in the development phase, the HL7 membership (annual charge) is needed[24]. All the discussion and documents are in English, which might be counted as a barrier for non-English native speakers: however, taking into account that English is one of the most accessible languages in most of the international community today, it is considered that accessibility of FHIR is not detracted by the language.

A certain level of technical expertise is needed to understand FHIR; however, it is still considered fairly accessible to everybody because it is based on widely accepted internet standard and is not specific to any party.

Awareness

HL7 FHIR for e-labeling is not well known in APAC markets today, but it is well-recognized in international healthcare standardization/harmonization communities. For example, the ICH has been monitoring the FHIR development and maturity progress since 2016[25] and finalized the white paper on HL7 FHIR for ICH implications in 2019[26]. The CDISC published version 1.0 of the FHIR to CDISC Joint Mapping Implementation Guide in 2021.

In labeling business field, no regulator in APAC markets has officially mentioned about FHIR, but as mentioned in 2.4.3.1, the US FDA and EMA are planning to use FHIR as a potential standard for their next generation labeling or ePI. In Japan, although PMDA custom XML Schema has been implemented as e-labeling standard, FHIR has been well known by the MHLW as it adopted FHIR as the standard for 3 documents (patient referral document, discharge summary, and medical examination

report) and 6 prescription information (diagnosis, allergy, infectious disease, drug contraindications, test, and medication)[27] in March 2022.

2.4.3.2.3 PMDA-custom XML Schema

Acceptability

PMDA Custom XML Schema is designed specifically for Japanese e-labeling and regulations, it is difficult to support e labeling in other APAC countries due to current difficulties with interoperability.

The operation/management method of e-labeling in Japan largely depends on the server system of PMDA, but the system configuration and operation method of the server are not disclosed. Even if other APAC countries use PMDA custom XML schema, it is necessary to separately consider the operation/management method of e-labeling with server systems, which is one of the factors that make it difficult to introduce it.

Affordability

In Japan, PMDA already provides necessary systems and tools, and pharmaceutical companies is possible to operate only with operation costs of PMDA XML PI e-labeling preparation. In APAC countries/regions other than Japan, cost and human resources are necessary to establish the same system and operation as PMDA even the current specifications can be utilized.

Accessibility

PMDA custom XML schema uses XML, which is the technical standard, and the specifications have been published, so the technical hurdle is relatively low to describe e-labeling in XML. But the specifications are written only in Japanese, and to understand the specifications, knowledge of the composition of Japanese package inserts is essential. For use PMDA custom XML scheme in countries other than Japan, the local label information must be able to be mapped to the Japanese label information to import.

Awareness

The PMDA Custom XML scheme seems to be known only in Japan and not in other countries/regions, due to public relation or awareness activities for using the PMDA custom XML scheme for e-labeling have been conducted only in Japan. The widespread use of the PMDA Custom XML scheme in countries/regions other than Japan has not been considered.

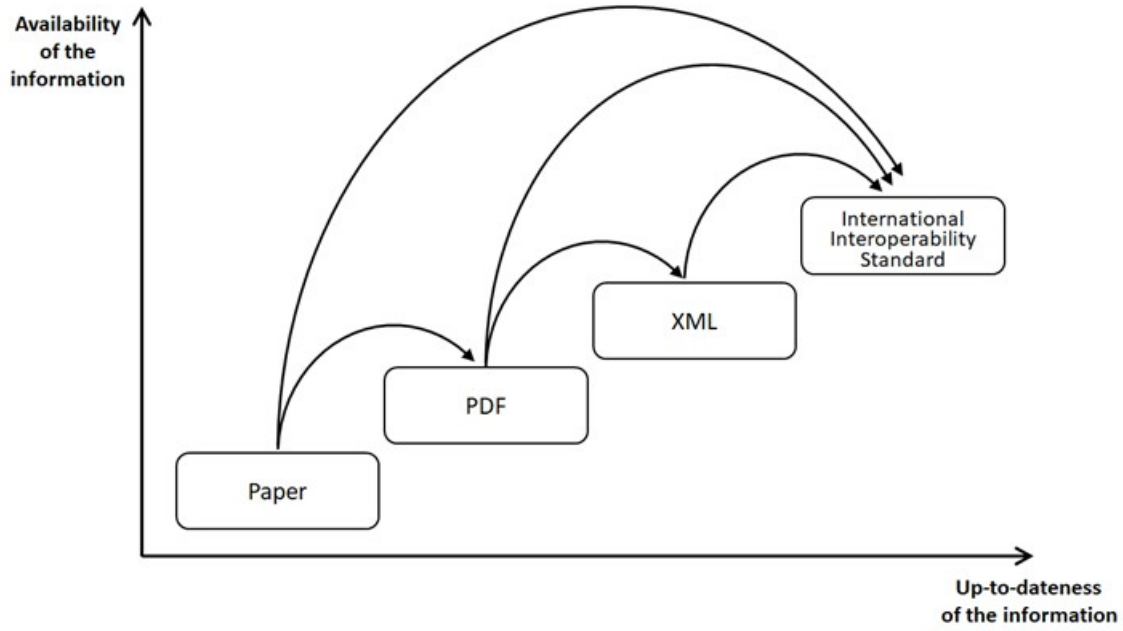
2.4.4. Expectation

2.4.4.1. Benefits

In the process of implementing e-labeling in different regions around the globe, different countries adopt different electronic standards according to the degree to which they implement e-labeling progress, generally standardize the file format first and then the structured contents format, as the US,

EU, and Japan have walked through. The electronic standard APAC expect is that the electronic product information is stored in a structured format in a repository, allowing searching, re-use and interoperability with other digital healthcare platforms. The electronic product information is implemented using an internationally recognized data exchange standard such as HL7 FHIR. The recommendation from APAC is to take a stepwise approach (Figure 2-1) whenever feasible, where the markets are encouraged to digitalize product information by migrating them from paper to PDF first, and then to taking a very important next step to migrate them from PDF to XML so the data can be interoperable with other systems to extend the applications and value of digital labeling. When considering the migration to XML, APAC would like to encourage to consider starting first with the international interoperability standard like HL7 standards can be avoided in the future. The feasibility of the standard in the market should be also taken into account when considering adoption of electronic standard in APAC markets.

Figure 2-1: Stepwise Approach



Our analysis has indicated that the HL7 FHIR as an electronic standard for e-labeling has potential to deliver various advantages, such as the standard is open source and any markets can use it to develop their own applications and interoperate with it; in addition, good support for mobile terminal, safe and convenient customization, good support for new technology, compatible with relevant new standards, good support for extensive digital health platform interoperability and coordination between markets. Although this standard is expected to be better than other two standards based on our analysis, HL7

FHIR has not yet been implemented for e-labeling in any market. It should be carefully considered when evaluating the value and feasibility of the standard in APAC markets.

3. Conclusion

Under the COVID-19 pandemic, various e-labeling initiatives have begun worldwide in the healthcare and pharmaceutical fields as part of a wider digital transformation. In the Asian region, most markets have started to discuss e-labeling initiatives, although there are different kinds of e-labeling initiatives and discussions on e-labeling are still at early stage in the majority of markets. Therefore, the APAC e-labeling EWG would like to propose the following as a regional guidance on how to proceed with e-labeling initiatives to promote a more consistent approach in Asia.

1. Availability of the latest labeling on publicly accessible website
   If there is no resource constraint from the HA in a particular market, it is more advisable to use an HA website as the central platform for all e-labeling product information to better maintain the consistency of format. The consistency of format also means better usability, convenience and understanding which is the end goal of e-labeling. However, if a particular HA decides to give flexibility to MAHs to use their company platform or third vendor platform due to HA's limited resources, the guidelines, rules and even the format should be clearly laid out by the HA in order to avoid inconsistencies and variances in the format of product information by the MAH or third parties. The important thing is to ensure that there is a one-stop shop and single source of e-labeling that will help assure the latest and most reliable information for the end-users. HAs from each market should be able to clarify the deadline by when the latest e-labeling information needs to be uploaded by the MAH and available on a publicly accessible website.

2. Accessibility, reader-friendly format
   Although it is ideal that a single, reader-friendly accessibility code format is printed on the packaging of a pharmaceutical product that can fulfill both e-labeling and serialization requirements, a stepwise approach should be considered by adopting markets. This needs to carefully assess the pros and cons of the available code formats and markets' varying levels of capacity, available technology, internet connectivity and end-user's preference, among other factors. For instance, the e-label could be made accessible first to users via a QR code with a URL, which can then be changed in the future to a GS1 barcode upon market readiness. For those markets utilizing GS1 barcodes for supply chain purposes, these codes may already be leveraged to adapt for e-labeling purposes. Through this, a single code may serve both purposes of providing access to product information while ensuring the integrity of the pharmaceutical supply chain.

3. Paperless
   Removing the paper PI and replacing with e-labeling is one of the goals for e-labeling implementation. We acknowledge that removing the paper PI from the commercial pack

provides an advance in environmental sustainability, improved supply management and allows faster availability of medicines to patients. However, careful assessment should be taken into consideration before the paper PI is removed. Sufficient time is required to allow HCPs and patients to adapt to the concept, drug manufacturers to establish the process, and regulators to update the local regulatory requirements and communicate the changes. Allowing co-existence of both paper PI and e-labeling during the pilot or transition period or staggering the implementation to include a specific scope of products through different phases should be considered to allow smooth implementation.

4. Common electronic standards
   While our analysis identified the advantages of the HL7 FHIR data standard and its inherent interoperability, it should also be noted that it has not yet been implemented for e-labeling in any market yet, although EMA has decided to introduce HL7 FHIR for e-labeling and there is an international movement toward HL7FHIR. Thus, HL7 FHIR should be carefully considered when evaluating the value and feasibility of the standard in APAC markets. Regardless of the standard to implement, a stepwise approach should be taken into account when digitalization of product information is considered in a market.

This position paper sets out some key principles and recommendations for how e-labeling initiatives can proceed in the Asian region in a more consistent and collaborative manner. Close collaboration between agencies, HCPs, patients, and industry associations are important to move e-labeling initiatives forward in Asia. Also, it is important to share experiences in Asia with other regions and vice versa. E-labeling is now a global hot topic in regulatory and digital health circles, with rapid progress being made over the last few years.

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