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Review Article: Comparison of International Regulations for Written Medicine Information (WMI) on Prescription Medicines

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Declaration of Conflicting Interests

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Comparison of International Regulations for Written Medicine Information (WMI) on Prescription Medicines

ABSTRACT: This paper presents a review of the literature, including government legislations, policies, guidelines and recommendations available in the European Union, the United States of America and Australia pertaining to the availability, development and distribution of written medicine information (WMI) for prescription medicines. The online databases searched were Embase, International Pharmaceutical Abstracts, Medline and PubMed, together with Google as the Internet search engine. The design and content of WMI documents have similarities and differences across all the 3 geographical regions. All the 3 regions have legislations in place to evaluate and regulate WMI documents for health care professionals (HCPs) and to some degree, for patients; however, the degree of regulation varies between the 3 regions. The regulations around the content and information design of WMI impacts how well the WMI performs and consequently influences patients' knowledge and medication-taking behavior. Legislation in certain areas could be seen as more beneficial and can be implemented across the 3 regions. Furthermore, the required legislation on the evaluation of the content of WMIs can be seen in some areas to be more stringent and comprehensive, which when taken onboard across the 3 regions can be valuable when creating WMIs for both patients and HCPs.

KEYWORDS: summary of product characteristics, package leaflet, package insert, consumer medication information, consumer medicine information, product information

BACKGROUND

The intended use of written medicine information (WMI) is first and foremost to increase patient and HCPs' understanding of the therapeutic nature of the prescription medicine, in particular,

about the medicine's safety, efficacy and use. It is understood from the published literature that the information content of a well-informed, structured, formatted and styled WMI for prescription medicines allows patients and HCPs to utilize the medicine information to achieve the desirable therapeutic outcomes.[1-3] In order to achieve appropriate use of all therapeutic products, suitable legislations, regulations and guidelines must be in place to provide the pharmaceutical sponsors the guidance and recommendations needed when developing appropriate WMIs.

Patients' understanding of how to use their prescribed medicines is dependent on the way they interpret information given to them verbally and/or in written format.[4] The way that patients perceive and use WMI is impacted by the quality and usability of WMI as well as their own health literacy and existing knowledge about their condition and medicine.

In the European Union, the United States of America and Australia, the established regulations and standards on WMI for prescription medicines varies for each government health agency. The potential benefits of determining the similarities and differences between the government health agencies in regards to their government legislations, guidelines, and policies around WMI for prescription medicines would provide a greater and more in-depth understanding of how WMI can be regulated and prepared in order to optimize their quality content and potential therapeutic outcomes. The overall aim of the literature review was therefore, to identify the legislations, policies and guidelines for the development, availability and distribution, and use of WMI documents in the European Union (EU), the United States of America (USA) and Australia (AUS), which are intended to promote the quality use of medicines by consumers of prescription medicines.

METHODS

This paper presents a narrative review of the literature published in peer reviewed journals, non-peer reviewed journals, and the grey literature on websites (government, non-government and private), pertaining to the last 25 years (1992 to 2017, inclusive).

The review focused on literature about WMI intended for patients using prescription medicines, as well as WMI used by health care professionals (HCPs), such as pharmacists, physicians and other prescribers, who provide information to their patients. The articles attained for written medicine information were limited to those on government legislations, policies, regulations, guidelines as well as recommendations regarding development (design and content), availability and distribution of written medicine information for prescription medicines.

The research articles have been obtained from the following English language regions and countries: the EU, the United States and Australia.

The databases used were Embase, International Pharmaceutical Abstracts, Medline and PubMed, together with Google as the Internet search engine. The keywords used for the database and Google searches are illustrated in Table 1 and were categorized in 3 different concepts, namely health agencies, WMI, and regulations.

A total of 62 references were identified that met the review inclusion criteria.

This article does not contain any studies with human or animal subjects performed by any of the authors.

RESULTS

REGULATIONS FOR WRITTEN MEDICINE INFORMATION IN DIFFERENT INTERNATIONAL REGIONS

This section describes the current government legislations, policies, guidelines and recommendations available in the European Union, the United States of America and Australia pertaining to the availability, development and distribution of WMI for prescription medicines.

UNITED STATES OF AMERICA

In January 2006 under the US Food and Drugs Act of 1906, the US Food and Drug Administration (FDA) disclosed a set of revised labeling guidelines on the format of the package insert (formally named prescribing information). The newly designed package insert is considered to be a WMI that draws the HCPs' attention to the medicine information that is most important before the medicine is used.[5] Prior to delivering the revised labeling guidelines, the FDA had gone through an extensive evaluation from December 2000 in regard to the value of the medicine information for patients and HCPs in order to establish how format and content of the medicine information can be improved.[5,6] The FDA utilized the comments from public meetings, focus groups, national physician surveys and written comments from a diverse group of stakeholders (citizen petition) to create the revised adopted labeling format.[5,6] Also in November 2005, the agency initiated a request to ask all pharmaceutical sponsors to provide package inserts to the FDA in the revised labeling format. This initiative provided HCPs the ability to obtain easily accessible medicine information in the package insert, approved by the FDA for all prescription medicines approved in the US.[5] The whole purpose of the revised labeling guidance was to minimize the risk associated with using medicines and to decrease the number of medicine errors. The revised-designed package insert was intended to

be able to deliver information in a reader friendly format that can attract HCPs' attention to the most significant part of the medicine information before a medicine is prescribed.[5,7]

According to the revised US labeling guidelines,[7-18] the content of the package insert consists of several components as indicated in Table 2. This revised format provided the requirements for the medicine information for recently approved and new medicines' package insert, and includes the specific graphical obligations and the rearrangement of important information, which allows HCPs to locate information quickly.[7-18] Those important changes include: a new area named "highlights", a table of contents, patient counseling information, year of first approval, a toll free telephone number and online adverse event reporting for any suspected side effects.[7-18] The revised design of the package insert also provides the HCP easy access to critical information about the medicine's benefits and its safety to communicate with their patients. The revised guidelines for package insert were considered beneficial in providing HCPs with the information and tools to maximize the treatment regimen for patients during consultations and to improve clinical diagnoses made by physicians in a more patient focused and medicine personalized manner.[5]

The "highlights" section is a summary section, prominently displayed at the beginning of the first page, and aims to raise awareness and access to the most important information regarding risks and benefits, allowing HCPs to quickly locate the information they want. The highlights deliver a clear and succinct summary about particular parts including: dosage and administration, indication and usage, dosage forms and strengths, contraindications, warnings and precautions, adverse reactions and most importantly the Boxed Warning. The "highlights" section also leads the HCP to a specific area of the full prescribing information by referencing certain sections from the table of contents.[7,8] Furthermore, the pharmaceutical sponsor is required to include a list of all recent variations in the last 12 months for any amend-

ments that were made to the package insert, in order for the HCPs to gain instant access to any recent updated information about the medicine before writing a prescription.[7]

A table of contents section was designed for simple reference to the comprehensive efficacy and safety information, to again improve usability of the document. Another section that delivers information on patient counseling information provides greater weight to the importance of communication between HCPs and patients, particularly patients who are having the medicine for the first time. This section was created as an aid to HCPs in advising their patients about the medicine's usage and potential adverse effects and other potential risks.[7-18]

When a medicine approval has been obtained from the FDA, the approval information appears at the beginning of the package insert.[7] This section also contains the toll free telephone numbers for reporting any suspected adverse reactions to either the pharmaceutical sponsor or the FDA and a web link to the FDA safety information and adverse event reporting program.[19,20]

In order to gain market approval for a new medicinal product from the FDA, the regulatory affairs, medical and marketing personnel from the pharmaceutical sponsor must follow the guidance set out above when creating the package insert and submit it together with the new drug application to be evaluated by the Center for Drug Evaluation and Research (CDER) within the FDA. As the package insert is approved or updated, it is used to provide the relevant medicine information for the DailyMed, which is considered as a web-based medicine information database that delivers the most current package insert to all HCPs and consumers (free of charge).[21]

The revised labeling guidelines also include guidance on Consumer Medication Information (US-CMI) that targets patients; the purpose of this guidance was to aid organizations (e.g. pharmacies, health care associations, and private vendors) in creating WMI for patients.[8] The

content of the US-CMI consists of several components as indicated in Table 2. In the US, the US-CMI is considered as a WMI document developed by organizations but not by the pharmaceutical sponsor and it is not evaluated by the FDA.[8] Although this guidance is not legally enforceable by the FDA for the organizations when developing US-CMIs, the FDA advises that the creators of US-CMI utilize this US-CMI guidance document to ensure that their US-CMI is helpful and valuable to patients.[8]

Furthermore, there is FDA guidance on Medication Guides. The Medication Guide is a type of WMI that is required by law to be given together with certain prescribed/biological medicines.[22,23] According to the guidance, Medication Guides need to be generated by the pharmaceutical sponsor under several circumstances, such as the medicine is one which the Medication Guide could assist in preventing serious adverse effects, or when knowledge of a serious adverse effect can impact treatment decision making or medication taking.[22,23] The content of the Medication Guide consists of several components as indicated in table 2. A study was conducted to examine the readability, suitability, and comprehensibility of the Medication Guides, which showed that this particular WMI is of lesser value to patients because the Guides are hard and complicated to understand, especially for those patients with limited reading ability.[24] The regulatory affairs, medical and marketing personnel from the pharmaceutical sponsor must follow the Medication Guide guidance when creating the Medication Guide and seek approval from the FDA before it is available directly for HCPs or indirectly for patients via the HCPs.

There is currently a proposed future direction on the "One-Document Solution" which was initiated in 2008 by a diverse group of stakeholders from health care associations, national communities and alliances.[6] The proposal was in the form of a citizen petition submitted to the FDA.[6] The citizen petition requested actions to be taken by the FDA in order to address

the issue of several different types of WMI (PI, US-CMI & Medication Guides) and other documentation (highlights of the PI and brief summary of the PI) that are given to the patients by the pharmacist.[6] Patients may be receiving several WMIs consisting of information that may be conflicting or redundant.[6] In most cases, all the different types of WMI can be incomprehensible and overly-complex for patients possibly because they are generated from different sources and written by different authors.[6] In the citizen petition, the FDA was encouraged and advised to develop a single WMI documentation or "One-Document Solution" in order for the patient to have a single document that is well designed, useful and user friendly.[6] The FDA is supportive and committed to this approach and to develop solutions to avoid overwhelming patients with the WMI received.[25] Therefore at present a new WMI framework is in progress by the FDA to offer patients with quality WMI that will encourage the safe use of medicines. The purpose of this new WMI framework is to introduce a new Patient Medication Information (PMI) whereby pharmaceutical sponsors would submit an abbreviated one-page document in order to deliver patient-oriented and easy to understand information that highlights the most important medicine information in a single, standardized PMI document for each medicine.[26,27]

EUROPEAN UNION

In 1992, the European Union (EU) delivered a directive that was the first initiative toward the provision of patient information included as package leaflets for all prescription and pharmacist-only medicines.[28-30] The pharmaceutical companies and the public community were in agreement and welcomed the idea of WMI that is comprehensive and understandable for the patients.[31,32]

Within the EU, the legislation published by the European Commission (EC) for the pharmaceutical sector is supported by a series of guidelines that have been published in volumes of

"The rules governing medicinal products in the European Union".[33] Volume 2c focuses on a list of regulatory guidelines related to procedural and regulatory requirements such as the summary of product characteristics (SmPC) for HCPs and the package leaflets (PLs) for patients.[34] The European Medicines Agency (EMA) is the organization which adopts all pharmaceutical guidelines published by the European Commission. Under the guidelines, EMA also has Quality Review Documents (QRD) published by the working group on QRD which provides support and recommendations to the EMA's scientific committees and to the pharmaceutical sponsors on WMI. An example is the "Quality Review of Documents (QRD) human product information annotated template." This template provides standard wording and statements that must be used where applicable. This was put in place by the EMA to assist pharmaceutical sponsors to ensure that the creation of their SmPC and PL are of the highest expected quality when they submit their applications to the agency for new medicines or updates to current marketing authorisations.[35] There are also other guidelines for WMI published by the Committee for Human Medicinal Products (CHMP) whose members are nominated by the European Union Member States in consultation with the EMA's Medicine Board which provide some expert guidance on WMI.[36,37] All the pharmaceutical companies are required to follow the legislation and guidelines set out when preparing their WMI. For a new prescription medicine to get approved in the EU, the pharmaceutical sponsors must also follow the legislation and guidelines set out for WMI, namely, the annexes within the Quality Review Document guideline, when creating both the SmPC and the PL. If the information in the WMI has not been created appropriately, then the risk of having a new medicine application rejected is high.[38] Both the SmPC and the PL have fundamental information for HCPs and patients, respectively, on the safe and effective use of prescription products.[38]

The SmPC must be updated regularly throughout the medicine's lifecycle as new safety and efficacy post-marketing data emerge. SmPC is also an essential document used for the crea-

tion of PL.[39] In September 2009, the EC published a revision 2 of the guideline on the SmPC.[38] The primary aim of the guideline is to provide appropriate directions for the sponsor when creating SmPC and PL, in order to ensure the information in the WMIs are accurate, up-to-date and can be easily interpreted by the health care professionals and the patients. The content of the SmPC and the PL consists of several components as indicated in Table 3. The guideline provides recommendations on the principles of written information in the SmPC, such as the sponsors must keep the integrity of every section of the documentation by only providing information which is related to each individual section heading. This is due to the fact that there may be some safety concerns that need to be addressed in more than one section of the SmPC, therefore the sponsor in this situation can cross reference the individual statement relating to safety concerns in other sections of the SmPC where it contains more relevant information for the HCPs. Ultimately, this makes it easier to obtain relevant information for the safe, appropriate and effective use of medicines.[38] The guideline is just one of the obligations that the sponsor must follow and fulfill when getting a new medicine application approved by the EMA. However, in order for the sponsor to fulfill its entire obligation with the EMA and register the medicine onto the market, the new medicine application must be submitted to the EMA on the basis of several other components such as data/information for methods/control of medicine manufacturing, nonclinical (animal) and clinical (human) studies.[4] Furthermore, throughout the product life cycle, the EMA has a group of scientific evaluators who check the competency of WMI (SmPC and PL). If the WMI does not pass the validation of the evaluator, then the EMA has the authority to issue a market cease of the medicinal product.

There is also a published guideline that includes testing the readability of a package leaflet.[4] Article 63(2) of Directive 2001/83/EC requires the package leaflet to be written and designed to be clear and understandable, enabling the patients to act appropriately when following the

WMI, and where necessary, with the help of the health care professionals. The package must be clearly legible in the official language or languages of the Member State(s) in which the medicinal product is placed on the market.[40] Also, Article 59(3) of Directive 2001/83/EC requires that the PL be easy to use, clear, and legible.[40] Therefore, one of the ways to fulfill Article 63(2) and 59(3) is to perform "user testing" on the PL. User testing is an iterative process in regard to the goal of testing the usability and identifying whether the medicine information document is able to deliver messages that are understandable and can be acted upon by the intended reader.[41,42] Essentially, user testing provides information on the problematic areas that exist in WMI and which need to be rectified based on the findings of the testing. For example, a group of individuals from the target group for the medicine are chosen and questions given to them individually to respond in relation to the PL, the questions are set out to mainly examine two aspects of usability: user ability to locate the information and once the information is found, their interpretation and understanding of the information. In addition, the testing process includes a qualitative phase, where the participants are asked open questions about what they did and did not like about the PL. Where problems are found, good practice in information writing and design are applied, to remedy the problems – the revised PL should then be tested again. The data/information gathered from the user testing would need to be included in the new medicine application, as this is also one of the obligations that the sponsor must fulfill when getting the application approved by the EMA.[4,41,42]

A linguistic review of WMI for all member state languages is examined post adoption of positive voting (preliminary approval of the new drug application) by the CHMP members in order to safeguard the consistency of the WMI in all countries within the EU. The reason for this linguistic review is because only one set of English WMIs are prepared and submitted for evaluation which are then translated to the different member state languages after approval. Every language translation will be subjected to linguistic review by the respective member

states and comments on the translation will be provided to the pharmaceutical sponsor. The EMA also conducts a checking procedure to see if all the member states' comments have been implemented by the pharmaceutical sponsor for the WMI used in both labelling and packaging for the all medicines. The purpose of this procedure is to improve the quality of printed materials (SmPC and PL) that the healthcare professionals and the patients receive with a medicine.[43,44]

Also, in the "Product information: Reference documents and guidelines," there are other supplementary guidelines and reference documents on the quality of product information that include appropriate use of abbreviations, terminology, style, and the translation of standard terms into different member state languages.[45] The reference documents include nonstandard abbreviations to be included in the SmPC,[46] stylistic matters,[47] use of terms,[48] style of final text layout,[49] package leaflet requirements for the pediatric or incapacitated patient,[50] recommendations on the expression of strength,[51] excipients in the package leaflet and label.[52]

As the SmPC and PL are approved or updated, they will then be used to provide the relevant medicine information for the electronic Medicine Compendium within EU, which is considered as a web-based medicine information database that delivers the most current SmPC and PL to all the patients and the consumers.[53]

Lastly, there is a report published in 2016 by the Dutch Health Research Institute (NIVEL) and the University of Leeds where there were findings that the EU guidance on PL should allow more flexibility in the information recommended in the QRD template as well as reformulating the guidelines on good information design. There should also be more involvement from patients by making "user testing" more iterative, and more attention should be paid when translating tested leaflets for the different member states in order to ensure that the

language introduced in layman terms from the result of testing in one language is not lost during translation.[54-56] The findings of these reports are likely to shape PL in the future.[55,56]

AUSTRALIA

In Australia, the legislation for WMI is covered by the Therapeutic Goods Act 1989 (the Act), which also ensures that the medicines supplied in Australia have appropriate efficacy, safety and quality standards. The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and adopts all pharmaceutical guidelines released by the Therapeutic Goods Act 1989.[57] Guidance 8 of Product Information and a "Form For Providing Product Information"[57,58] provide the list of regulatory requirements for product information intended for use by HCPs.[57,58] All regulatory, medical and marketing personnel from the pharmaceutical companies are required to follow the legislation and guidelines set out when preparing their PI. In order for a new prescription medicine to get approval in Australia, it is a requirement under Guidance 8 to submit the PI to the TGA for evaluation and approval before the medicine can be placed on the Australian Register of Therapeutic Goods (ARTG).[57]

In Australia, the Consumer Medicine Information is a WMI document aimed for the use of patients. There is currently no appropriate legislated guidance for Consumer Medicine Information (AUS-CMI). Although schedule 12 and 13 (Sub regulation 9A[1]) do exist, they only contain simple description of what a AUS-CMI should include. The only guidance (not legislated) that can be obtained currently is the Usability Guidelines for Consumer Medicine Information from the Australian Self-Medication Industry (ASMI), which was last updated in 2006, and which may not be regularly used by the Pharmaceutical Sponsors in Australia whose role is to create the AUS-CMI. The Usability Guidelines are not a formal TGA guidance document. However, the TGA encourages their use by the pharmaceutical sponsors

when developing their AUS-CMI. Furthermore, the AUS-CMI is only required for TGA evaluation when the pharmaceutical sponsor submits their initial new chemical entity/new biological entity or new indication application. The TGA evaluation of the AUS-CMI is to examine whether information written in layman terms in the AUS-CMI aligns with the clinical evidence provided in the PI in relation to the safe use and side effects of the medicine. Once the application has been approved, the TGA does not require the sponsor to submit any subsequent AUS-CMI however only the subsequent PI is required for evaluation, if any changes are made.

The PI requirements provided in the "Form for Providing Product Information" in relation to prescription medicines states specific headings in the order given such as, Name of the medicine, Description, Pharmacology, Clinical trials, Indications, Contraindications, Precautions, Interactions with other medicines, Adverse effects, Dosage and administration, Over dosage, Presentation and storage conditions, name and address of the sponsor, Poison Schedule of the medicine, Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG) and Date of most recent amendment (table 4).[58]

As the PI and AUS-CMI is approved or updated, it will then be uploaded onto the GuildLink, which is considered as a web-based medicine information database that delivers the most current PI and AUS-CMI to all the health care professionals, patients, and on the TGA website for people to get free access to the WMI documents.[59]

RESULTS SUMMARY

In summary, the European Union (EU) has a stronger structured legislation and guidelines in place (Table 3) in regard to the legislated Quality Reference Document (QRD) Guidance providing guidance for both the Summary of Product Characteristic and the Package Leaflet. Both the SmPC and the PL are evaluated by the Committee for Human Medicinal Product

(CHMP) and regulated by the European Medicines Agency (EMA). Also, user testing on WMI in the EU provides information on the problematic areas that exist in WMI and that need to be rectified based on the findings of the testing.

The United States of America has a moderate structured legislation/guideline in place (Table 3). The legislated guidance is designed for the Package Insert and the Medication Guides, and both are evaluated by the Center for Drug Evaluation and Research (CDER) and regulated by the Food and Drug Administration (FDA). Although the Consumer Medication Information (US-CMI) has a labeling guidance, it is not legislated for availability for all the prescription medicines, and the US-CMI are not evaluated by the FDA.

Australia appears to have a weaker structured legislation/guideline in place (Table 4). The legislated Guidance 8 and the Form for providing product information are only designed for the Product Information (PI), with both being simple and providing less structured guidance compared to the EU and the US. It is only the PI which is evaluated by the Office of Medicine Authorization (OMA) and regulated by the Therapeutic Goods Administration (TGA) throughout the product life-cycle. In Australia, there are very limited legislated and well-structured guidance for AUS-CMI, and there is limited evidence on the active use of guidelines such as the usability guidelines for AUS-CMI by pharmaceutical manufacturers / sponsors. The AUS-CMI will only need to be evaluated by the TGA during the initial drug evaluation stage or the new indication application, as the purpose is to examine whether information written in layman terms in the AUS-CMI aligns with the clinical evidence provided in the PI in relation to the safe use and side effects of the medicine. Post-approval evaluation of the AUS-CMI is not required.

In all 3 geographic regions, the EU, US and Australia, there are two separate WMI documents, one targeting HCPs and the others, patients. The design and content for WMI docu-

ments are similar across all the 3 regions; however, the degree of detail varies. All the 3 regions have legislations in place to evaluate and regulate WMI documents for HCPs; however, degree of regulation varies.

Discussion

Similarities Between the Different Regions

This study has identified the legislations, policies and guidelines on the availability of WMI for the patients and the health care professionals in 3 different geographical regions: the European Union, the United States of America and Australia. A number of similarities were observed between these regions.

All the 3 geographical regions have two separate WMI targeting HCPs and patients. The WMI that targets HCPs contains specialized information (including clinical trials information) about the medicinal products and is written at a level intended for HCPs. The information is intended to be understood by the HCPs and to assist them in making clinical decisions on whether the medicine is suitable for use in their patients. On the other hand, the information in the WMI that targets the patients is intended to be in layman terms in order to be easily read and understood by an audience without medical qualification. This WMI should be designed in a way that the patient can easily understand the nature, purpose and instructions for use about the medicine prescribed by their HCPs.

All the 3 regions have regulations and guidance in place for WMI targeting the HCPs such as the EU Summary of Product Characteristics, the US Package Insert and the Australian Product Information. The reason for having the established guidance and regulations is because that WMI for HCPs is the most crucial piece of written medicine information available for HCPs about medicinal products, and which provides all the necessary information about a medicine that HCPs prescribe and provide to their patients. This information needs to be comprehensive, accu-

rate and up to date. Another reason is that this document is also an important piece of information when it comes to creating WMI for patients. The information in patient-specific WMI is based on the information content of WMI for the HCPs. The content for the sections in WMI targeting the HCPs is considered to be similar when comparing all the 3 regions. All require the following information: name of the medicinal product, description, indication, contraindication, dosage and administration, dosage forms and strength, warning and precautions, adverse effects, over dosage, pharmacology, clinical studies, specific population, how supplied, storage and handling and patient counseling information, name of the sponsor and date of revision of the text. All the 3 regions have a similar process by which the WMI for the HCPs has been prepared; the regulatory, medical and marketing personnel from the pharmaceutical company work collaboratively in creating the WMI. They must follow the regulations and the guidance set out by their respective regulatory agencies as described in Tables 2 to 4. However, the degree of detail of the content varies.

Differences between the different regions

All 3 geographic areas have different regulations and guidance in place for WMI that targets patients. In the US, the Consumer Medication Information for patients (Table 1) is developed by organizations but not the pharmaceutical sponsor and it is not evaluated or approved by the FDA. This could possibly be a concern as the pharmaceutical sponsor is the responsible owner of the medicine, and has access to a great deal of information about the medicine, including that on its benefits and adverse reactions. Therefore, one could argue that US-CMI should be written by the pharmaceutical sponsor to ensure that consistent information is provided to the HCPs and the patients. Equally, it could be argued that independent organizations do not have a conflict of in-

terest with marketing or selling a particular product and therefore they can produce unbiased WMI.

Also in the US, there is another type of WMI called the "medication guides" (Table 1) which is designed for those medicines that could possibly pose significant public health and serious concerns and the WMI must therefore be offered to the patient by the prescriber when the prescription is written or filled, in order for the patient to be fully informed about the risks and how to use the medicine to prevent harm. The medication guides are developed by the pharmaceutical sponsor and require FDA evaluation and approval before distribution to the consumers.[60] The reason that there are two different types of WMI (US-CMI and Medication Guide) targeting patients is that the US-CMI is normally placed inside the bag or stapled to the bag for those medicines with a lower risk/safety concern at the pharmacy and is provided to the patients for the purpose of explaining how to use the medicine; on the other hand, the medication guide is required to be physically handed over to the patient. Availability of the US-CMI, Medication Guides and Package Insert, poses the issue of too many different types of WMI. They are produced from different sources and by different authors. The various types of WMI tend to be overly complex, lengthy, not easy to read and sometimes inconsistent with each other.[61] All these WMIs are written to fulfill the legislated liability of what information must be given to the reader and will unavoidably be confusing and duplicative to the patients.[61] However, there is a proposed future direction on the "One-Document Solution." This direction is able to offer one standardized document called the "Patient Medication Information" in lieu of all other WMIs in providing a concise, clear, and abbreviated one-page document for the patients.

In the EU, the Package Leaflet for patients (Table 1) is developed by the pharmaceutical sponsor and it is fully evaluated by the EMA in the initial new medicine application phase as well as during any post-approval changes. Also, in the EU the sponsor needs to conduct user testing of its PLs to ensure that the information is usable and understandable by patients. Currently, user testing is a legislated requirement only in the EU. While USA and Australia may have user testing, it is not a legislated requirement for sponsors to conduct user testing. User testing provides an indication to the evaluators of problematic areas that exist, which need to be rectified by the pharmaceutical sponsor based on the findings of the test. User testing mainly tests two aspects of usability: user ability to locate the information and once the information is found, their ability to interpret the information. In Australia, a study of consumer medicine information found that user testing should be a standard practice, because user testing has its value in finding areas for improvement in language, layout, and comprehensibility. In this study, it was identified that user testing was vital and an important approach in creating documents that were easier to read, understand, and navigate. User testing should be recommended as standard routine practice in maintaining the high quality of the WMIs for patients and HCPs.[62] It should also be recommended to the US FDA and Australian TGA for implementation.

In Australia, the AUS-CMI is only required for TGA evaluation when the pharmaceutical sponsor submits their initial new chemical/biologic entity application or new indication application. Once the medicine has been approved, the TGA does not require the Sponsor to submit any subsequent AUS-CMI (WMI for patients) for evaluation post-approval of the medicine; only the PI (WMI for HCPs) is required for evaluation during both the pre- and post-approval of the medicine. As the AUS-CMI is not evaluated by the TGA post-approval of the medicine, this raises the

concern that the AUS-CMI may contain outdated or possibly incorrect medicine information, especially if changes have been made to the PI. This runs the risk of incorrect information being given to the patient. TGA evaluation of the AUS-CMI throughout its product life cycle can have its benefits such as it allows the TGA to closely examine the changes made to the AUS-CMI by the pharmaceutical sponsor to ensure that the appropriate information written in layman terms in the AUS-CMI aligns with the clinical evidence provided in the revised PI, and creates a sense of responsibility for the pharmaceutical sponsor to diligently update their AUS-CMI accurately to meet TGA's standards. In the EMA, WMIs for patients (Package Leaflet) as well as those for HCPs (SmPC) require evaluation in both pre and post-approval stages of the medicine. Also, there is currently no legislated guidance for the pharmaceutical sponsor to use in creating AUS-CMI for patients in Australia (Table 1). The only guidance (not legislated) that can be obtained is the usability guidelines from the Australian Self-Medication Industry, which is currently not well utilized within the pharmaceutical industry.

Conclusions

From this literature review, it can be seen that in the European Union, the United States and Australia there are legislations in place to produce, evaluate and regulate WMI documents for HCPs and to some degree, for patients; however, the degree of regulation varies between the three.
In relation to the availability of the WMI in each of the regions, they all have WMIs in place for both the patients and the HCPs. Both the EU and Australia each have one WMI for patients and one WMI for HCPs; however in the US there are two different WMIs for patients (US-CMI and Medication Guides). In the US the package insert (for HCPs) are evaluated by the FDA in the initial new drug application phase and throughout the life cycle of the medicine. As for the US-

CMI, it is developed by organizations but not the pharmaceutical sponsor; only the Medication Guides are developed by the pharmaceutical sponsor and evaluated by the FDA. In the EU, the PL has to go through user testing during EMA's evaluation phase of the new medicine application as well as throughout the life cycle of the medicine. For the 3 regions, only the EU conducts user testing for all their WMIs. In Australia, the PI and AUS-CMI are evaluated by the TGA during the evaluation phase of the new medicine application, however only the PI needs to be evaluated by the TGA throughout the life cycle of the medicine and not the AUS-CMI.

There are several future directions that can be provided as recommendations to the government health agencies in order to achieve harmonization within the 3 regions. The legislation of the content of WMI for patients and HCPs varies between the 3 regions; however, legislation in certain areas could be seen as more beneficial and can be implemented across the 3 regions. One example is the user testing that has been implemented in the EU. Furthermore, the required legislation on the evaluation of the content of WMIs can be seen in some areas to be more stringent and comprehensive, which if taken onboard across the 3 regions can be valuable when creating WMIs for both patients and HCPs. Therefore, further investigation on the quality standards of different WMI design within the regions is required in order to recommend harmonization within the 3 regions.

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Table 1 - Search Strategy

Search Strategy: List of search terms i.e. Major Concepts using AND alternative terms (synonyms using OR) below				
Concept 1- health agency	**AND**	**Concept 2- written medicine information**	**AND**	**Concept 3- regulations**
FDA[a]		Patient Information Leaflet/ Package Leaflet[d] (EU specific name)		Legislation/legislations
Or EMA[b]		Or Summary of Product Characteristics[e] (EU specific name)		Or policy/policies
Or TGA[c]		Or Package Insert/Prescribing information[f] (US specific name)		Or guideline/guidelines
		Or Consumer Medication Information/Patient information[g] (US specific name)		Or regulation
		Or Medication Guides[h] (US specific name)		Or recommendation
		Or Consumer Medicine Information[i] (Australia-specific name)		Or regulatory requirement/requirements
		Or Product Information [j] (Australia-specific name)		

[a] Food and Drug Administration – United States; [b] European Medicines Agency – European Union; [c] Therapeutic Goods Administration – Australia; [d] Patient Information Leaflet/ Package Leaflet – WMI intended for patients in the EU; [e] Summary of Product Characteristics – WMI intended for HCPs in the EU; [f] Package Insert/Prescribing information – WMI intended for HCPs in the US; [g] Consumer Medication Information/Patient information – WMI intended for patients in the US; [h] Medication Guides – WMI intended for patients in the US to inform about medicines that pose significant public health and serious concerns; [i] Consumer Medicine Information – WMI intended for patient in Australia; [J] Product Information – WMI intended for HCPs in Australia.

Table 2 - WMI regulation in the United States

	Package Insert (PI)	**Patient Information / Consumer Medication Information (US-CMI)**	**Medication Guides**
Target Audience	Health Care Professionals (HCPs) /	Patients	Patients
Legislative Guidance - Design /Format	Labeling Guidance – Content and format of labelling for human prescription drug and biological products	Labeling Guidance – Useful Written Consumer Medication Information (US-CMI)	Guidance – Medication Guides – Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies
Content	*Highlights, *Indication and Usage, *Dosage and Administration, *Dosage Forms and Strengths, *Contraindications, *Warning and Precautions, *Adverse reactions, *Drug interactions, *Use in Specific Populations, *Drug Abuse and Dependence, *Over Dosage, *Description, *Clinical Pharmacology, *Non-Clinical Pharmacology, *Clinical Studies, *Reference, *How Supplied/storage & handling and Patient Counseling Information	*What is the medicine? *What should I know about it? *What should I tell my HCP before taking the medicine? *How is the medicine given? *Can other Medicines Affect what I am taking? *How should I take? *What should I avoid while taking the medicine? *What are the possible side effects of the medicine? *General information about the medicine	*What is the medicine? *What is the most important information about the medicine? *What may cause serious adverse effects? *What are the symptoms associated with the medicine? *Who to call when symptoms occurs? *What is the medicine? *Who should not take the medicine? *How should I take the medicine? *What should I tell my doctor before taking the medicine? *How should I receive the medicine? *What should I avoid while receiving the medicine? *What are the possible side effects of the medicine? *General information about the medicine?
Writer	Collaborative effort by the Regulatory Affairs, Medical & Marketing Personnel within the Pharmaceutical Company	Developed by organizations	Collaborative effort by the Regulatory Affairs, Medical & Marketing Personnel within the Pharmaceutical Company
Evaluators	Center for Drug Evaluation and Research (CDER) at the US Food and Drug Administration (FDA)	Not evaluated by the CDER of FDA. However, it is recommended by the FDA to use US-CMI Guidance document.	Center for Drug Evaluation and Research (CDER) at the US Food and Drug Administration (FDA)
Other guidance (not limited to)	21 FDA Guidelines in total	N/A	Medication Guides – Adding a Toll-Free Number for Reporting Adverse Events

Table 3 - WMI Regulation in the European Union

	Summary of Product Characteristics (SmPC)	**Package Leaflet / Patient Information Leaflet (PL/PIL)**
Target Audience	Health Care Professionals (HCPs)	Patients
Legislative Guidance – Design/Format	• Quality Review of Documents (QRD) – Annex I (SmPC) • Quality Review of Documents (QRD) – Annex III (b) • The rules governing medicinal product in the European Union – Volume 2c (14 guidance in total)	
Content	*Name of the Medicinal Product, *Qualitative and Quantitative *Composition, *Pharmaceutical Form, *Clinical Particulars, *Pharmaceutical Properties, *Pharmaceutical Particulars, *Marketing Authorisation Holder, *Marketing Authorisation Number(s), *Date of First Authorisation/Renewal of the Authorisation, *Date of Revision of the Text, *Dosimetry, *Instructions for Preparation of Radiopharmaceuticals	*What is in this leaflet, *What X is and what is used for, *What you need to know before you X, *How to X, *Possible side effects, *How to store X, *Contents of the pack and other information
Writer	Collaborative effort by the Regulatory Affairs, Medical & Marketing Personnel within the Pharmaceutical Company	Collaborative effort by the Regulatory Affairs, Medical & Marketing Personnel within the Pharmaceutical Company
Evaluators	Rapporteurs & Co-Rapporteurs of the Committees for Medicinal Products (CHMP) in the European Medicine Agency (EMA)	Rapporteurs & Co-Rapporteurs of the Committees for Medicinal Products (CHMP) in the European Medicine Agency (EMA)
Other guidance (not limited to)	• Recommendation on abbreviations, terminology, style and translation of terms • Recommendation on expression of strengths	• Requirements for pediatric or incapacitated patient • Recommendation on abbreviations, terminology, style and translation of terms • Recommendation on expression of strengths • Guideline on the readability of the labeling and package leaflet of medicinal product for human use (User Testing)

Table 4 – WMI Regulation in Australia

	Product Information (PI)	**Consumer Medicine Information (AUS-CMI)**
Target Audience	Health Care Professionals (HCPs)	Patients
Legislative Guidance – Design/Format	• Guidance 8: Product Information • Product Information form under subsection 7D (1) of the Therapeutic Goods Act 1989 (the Act)	• There is no appropriate legislated guidance – Unlike the Australian PI which has guidance
Legislative Schedules	N/A	• Schedule 12 and 13 (sub regulation 9A [1]) – Simple description of the different components that AUS-CMI should include
Content	*Name of the medicine, *Description, *Pharmacology, *Clinical trials, *Indications, *Contraindications, *Precautions, *Interactions with other medicines, *Adverse effect, *Dosage & administration, *Overdosage, *Presentation and storage conditions, *Name and address of the sponsor, *Poison Schedule of the medicine, *Date of first inclusion in the Australian Register of Therapeutic Goods and * Date of most recent amendment	*Identification, *What the product is used for and how it works, *Advice before using the medicinal product, *How to use the medicinal product properly, *Further information, *Unwanted effects, *In case of overdose, *Where to go for further information, *Sponsor and *Date of information.
Writer	Collaborative effort by the Regulatory Affairs, Medical & Marketing Personnel within the Pharmaceutical Company	Collaborative effort by the Regulatory Affairs, Medical & Marketing Personnel within the Pharmaceutical Company
Evaluators	Office of Medicines Authorization (OMA) at the Therapeutic Goods Administration (TGA)	None
Other guidance (not limited to)	N/A	• Writing about medicines for people: Usability guidelines for consumer medicine information – Not a TGA legislative guidance, only TGA recommendation