D R A F T WHITE PAPER

Regulators Work Toward Harmonizing Safe Medication Container Labeling and Packaging

INTRODUCTION

The complexity of the medication management system continually introduces factors that can compromise its safety and that of patients at large.[1] Globally, it is estimated that 64 million disability-adjusted life years are lost yearly due to unsafe care.[2] The presentation of the primary and secondary packaging of drugs is a determining factor in how they are identified and used.[3] Aspects such as unclear, ambiguous medicine label information and similarities in appearance can lead to selection errors and inappropriate use including wrong drug, formulation, dose, or route of administration errors.[4,5,6] With the world becoming a global village, addressing the differences in global product labeling and packaging becomes vitally important. A study of international generic drugs highlighted the non-equivalence in the labeling and packaging standards for these products.[7] Such differences create potential for medication errors to occur. In 1998, more than one third (33%) of medication errors reported to United States Pharmacopeia's (USP) voluntary error reporting program involved product labeling or packaging.[8] In 2001, Kenagy and Stein[9] estimated that medication errors related to labeling and packaging injure or kill about 10,000 patients yearly.

Medication errors affect millions of patients around the world, sometimes leading to death or serious harm. Globally, the cost associated with medication errors has been estimated at $42 billion USD annually[10]. Each year in the U.S., serious preventable medication errors occur in 3.8 million inpatient admissions and 3.3 million outpatient visits.[11,12] Recently, the National Health Services (NHS) in England estimated that 237 million of medication errors occur at some point in the medication use process per year.[13] A landmark study published in 2000 estimated that as many as 98,000 people die each year in the US from medical errors occurring in hospitals. Medication errors is a significant public health concern that accounts for an estimated 7,000 deaths annually in the US[14] and contributes to 1,708 deaths in England.[13]

In 2011, the Network for Excellence in Health Innovation reported that outpatient and inpatient preventable medication errors cost approximately $20 billion each year.[15] The NHS in England places the estimated cost of avoidable adverse drug reactions at £98.5 million per year, consuming 181,626 bed-days.[13] A recent study in the European Union (EU) showed a steady increase in the number and proportion of Individual Case Safety Reports (ICSRs) of medication errors in the EudraVigilance database between 2002 and 2015, to a peak of 5% of all ICSRs in the database.[16]

Though the true incidence is unknown, preventable medication errors significantly increase healthcare cost. Problems associated with medications are common.[17] While multiple interventions addressing the frequency and impact of medication errors have been developed, their implementation varies.[17] To achieve a reduction of overall harm related to medication errors, harmonization at the global level is necessary. Many of the product labeling, packaging and naming issues are common across the countries.

BACKGROUND

An analysis of medication errors related to labeling and packaging indicated that look-alike labeling and packaging; use of dangerous or misleading abbreviations; lack of clarity with expression of strength; lack

of prominence of non-proprietary name (generic name); legibility and readability of information; contributed to medication errors.[18] A lack of consistent drug container labeling and packaging across the globe can contribute to errors especially because some countries rely solely on imported drugs, others also import drugs to address drug shortages in their country. To advance global harmonization of container labeling and packaging standards and reduce overall harm associated with medication errors, the International Medication Safety Network (IMSN) and the US Food and Drug Administration (FDA) held a summit for regulators on drug container labeling and packaging safety in June 2018 (https://www.intmedsafe.net/global-regulators-and-safety-advocates-meet-about-drug-container-labelling-and-packaging/). Goals of the summit included the creation of a minimum set of best practices for pharmaceutical container labeling and packaging aimed at reducing medication errors and the implementation of support for safety technologies such as label barcodes to be used with scanning equipment to reduce medication errors.

The summit was held at the FDA White Oak (Silver Spring) campus in MD, and convened a group of regulators, FDA staff, IMSN members, and invited international speakers. The meeting was co-chaired by FDA's Lubna Merchant, Deputy Director of the Office of Medication Error Prevention and Risk Management and Acting Director of the Division of Medication Error Prevention and Analysis, and Michael Cohen, chair of IMSN and president of the Institute for Safe Medication Practices (ISMP).

Summit participants included the Brazilian Health Regulatory Agency (ANVISA), Mexico Federal Commission for the Protection against Sanitary Risks (COFEPRIS), European Medicines Agency (EMA), Health Canada, Portugal National Authority of Medicines and Health Products (INFARMED), Netherlands Medicines Evaluation Board (MEB), United Kingdom Medicines & Healthcare products Regulatory Agency (MHRA), Saudi Food and Drug Authority (SFDA), FDA, WHO, IMSN members (ISMP, ISMP Canada, ISMP Spain, United Arab Emirates, Danish Patient Safety Authority, and Canadian Patient Safety Institute) and Global Standards One (GS1).

Recognizing the importance of pharmaceutical industry' involvement when addressing safer drug container labeling and packaging, the proceedings from the June 2018 meeting were discussed during a follow-up meeting (as part of IMSN 13th Annual meeting) held in October 2018 (Cascais, Portugal). Participants included, representatives of pharmaceutical companies (Abbvie, USA; Baxter, Portugal; BMS, USA; Eli Lilly, UK; Hikma, USA; Janssen/J&J, Netherlands; Novartis, USA; Pfizer, USA; UCB, USA), medicine agencies (FDA, USA; ANVISA, Brazil; MHRA,UK; Norway Medicine Agency), WHO (via teleconference), IMSN members (ISMP, ISMP Canada, ISMP Spain, ISMP Brasil, Prescrire, Hong Kong health authority, Portuguese Association of Hospital Pharmacists (APFH), United Arab Emirates, and Health Quality and Safety Commission New Zealand [HQSC]). Also, in attendance were pharmacovigilance centers: Centre anti poison et de pharmacovigilance du Maroc, FDA, French network of regional pharmacovigilance, MHRA, New Zealand Pharmacovigilance Center, Norway Medicine Agency, Portuguese Pharmacovigilance, and Drug Commission of the German Medical Association), and others (Organizacion de Farmaceuticos Ibero Latinoamericanos, Brand Institute, and Med-ERRs).

Meeting participants strongly advocate for the global acceptance of ten drug container labeling and packaging recommendations brought forth in this document. These recommendations are intended for container labels and carton labeling for drug and therapeutic biological products, although they may also be relevant for other products. While many safe drug container labeling and packaging practices were discussed, the purpose of this paper is to limit the discussion of the recommendations that the summit participants agreed upon.

RECOMMENDATIONS

Immediate and outer container labels

1. *For small volume injectable products, the product strength should include the amount per mL and the total quantity per volume.*

A product's strength or concentration is critically important information. Healthcare professionals rely on the amount of ingredient (strength) in a drug to properly treat patients.[19] Strength expression is an essential piece of information on product labels, unclear expression of strength can lead to incorrect selection and use of products.[20] Volume mismatch of product in the container with the expression of strength (i.e., the strength expression on the label states the amount of product per milliliter, but the vial contains more than 1 mL) has introduced confusion leading to medication errors.[21] Such errors have been reported for decades. For example, a nurse and medical resident inadvertently administered 30,000 units of heparin instead of 3,000 units. Both practitioners thought a 10 mL vial of heparin held a total of 1,000 units when, in fact, each vial contained 10,000 units (1,000 units/mL). This mistake led to the death of the patient after development of an intracranial hemorrhage and brain stem herniation.[21]

Many regulators already demand for products to be labeled with both the per mL and the per container quantity.[3,20,22,23,24,25] While EMA and MHRA require the per container quantity to be prominently displayed on the label, the FDA and Health Canada explicitly recommend the product strength to be expressed as total quantity per total volume followed in close proximity by the concentration per mL in parenthesis. There may be some exceptions (noted below) to expressing strength per total volume. In certain cases, the primary and prominent expression of the total drug content per container would not be effective in preventing medication errors, for example;

- Containers with less than 1 mL total volume, only the amount per volume provided (e.g., 3 mg / 0.5 mL) should be listed.[20,25]
- Unit dose ready-to-use formats such as prefilled syringes, only the amount per volume provided should be listed (e.g., 6 mg / 1.2 mL, 4 mg / 0.8 mL). The per ml amount can be provided in the prescribing information.[20]

This position is also supported by IMSN[4], Pharmaceutical Management Agency (PHARMAC)[26], and United States Pharmacopoeia (USP)[27]. Prominently labeling products with both the total quantity per total volume and amount per mL can help avoid confusion and reduce the risk of medication errors.

2. *Use of metric units in the strength expression for products.*

The strength expression on product labels should appear in metric units of measure such as mL, mg, mcg or g, rather than non-metric units. Apothecary or household measurements such as teaspoon, drams, grains or ratios (e.g., 1:1000) should not be used. There is a need for healthcare practitioners to understand how to measure the correct dose of a medication. Unit conversion

errors are common. Fatal medication errors have occurred when healthcare providers or patients are converting from one unit of measure to another.[25] Conversion and calculating errors can be prevented via the use of a standard unit thereby reducing the need for conversion.[28] Wheeler et al[29] reported an increased number of errors when the concentration of **EPINEPH**rine was expressed as a ratio (1:1,000) compared with metric units (1 mg/ml).

Many error cases have been published related to the ratio expression of medication strength including the death of a teenage boy being treated for priapism. The physician misunderstood the ratio expression of **EPINEPH**rine 1:1,000 and inadvertently administered 4 mL of undiluted **EPINEPH**rine 1:1,000 (4 mg) instead of 4 mL of 1:1,000,000 (a dose normally prepared by diluting 1 mg of **EPINEPH**rine 1:1,000 in a liter of normal saline).[30]

In an effort to improve patient safety, on May 1, 2016, USP eliminated ratio expression for single entity drug labels such as **EPINEPH**rine, neostigmine, and isoprotenol.[31]
Drug regulators recognize that a product's strength or concentration is critically important information for the end user. Since the purpose of expressing strength in the name of a product is to give the most relevant information regarding the content of the product in view of its use[23], it is therefore important to express the dose strength of health products in appropriate metric unit system.[20] To allow for safe transition to metric-only labelling, the strength on container labels should be expressed in both metric unit as well as the formal unit in parenthesis during the transition period.[32] The use of metric units to express the dose of drug products have been supported by IMSN,[4] FDA,[25] Health Canada,[20] Australian Therapeutic Goods (TGA),[33] FIP[34], and others.

Although, there was consensus on the use of metric units, it is important to note that there may be a few exceptions to the use of metric units for strength expression. For example, units of measure other than metric may be acceptable in certain situations, such as expressing the potency for certain biological products or percentage strength for topical preparations. It is important to consider older expressions of strength for which there has been a historical practice and understanding among users without evidence of medications errors. Changes to expressions of strength in these few cases may be problematic if the strength has been expressed in a non-metric unit without evidence of medication errors.

Also, strengths and concentrations should consistently be expressed in units of measure that are congruent with those used in the dosing instructions.[20,25]

3. *Eliminate potentially error-prone abbreviations and dose designations on immediate and outer container labels.*

Communication failures in healthcare contribute to errors. In fact, this accounted for more than 20% of sentinel events in 2014.[35] Certain abbreviations used to communicate medication orders can lead to communication lapses.[36] Concerns about error-prone abbreviations and dose designations led The Joint Commission (TJC) to introduce the “Do Not Use” list of abbreviations as part of its National Patient Safety Goals in 2004.[37] In addition to TJC, ISMP, ISMP Canada, the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP), Accreditation Canada, and the Health Quality of Alberta advocate for the prohibition of dangerous abbreviations and dose designations.[38]

Despite this advocacy, several instances of medication errors related to the use of abbreviations have been reported. In a study to determine patient harm related to the use of abbreviations, the use of "U" for units accounted for 13.1% of errors.[36] The use of the abbreviation "U" contributes to errors when misread as zero (0), often leading to 10-fold or greater overdose.[39,40] Such errors can be particularly dangerous when insulin units are involved, but other drugs are also measured in units and just as prone to serious overdose errors. Another abbreviation of units that has been reported is the use of "IU" for international units, which has been mistaken as intravenous (IV)[36,40,41,42] For example, in preparing a dose of "Vitamin E 100 IU," a nurse misinterpreted "IU" as "IV" and drew up the content of the oil-based capsule into a syringe for IV administration. Fortunately, the mistake was noticed before administration to the patient.[43]

The use of trailing zeros (e.g., 1.0) is another concerning dose designation. In a study that evaluated the use of dangerous abbreviations and dose designations, errors related to trailing zeros increased between January 2005 and 2009.[38] If decimal places or commas are not seen, it can lead to a 10-fold overdose or underdose.[20]

The use of naked decimal points (e.g., .5) should also be avoided. Fatal errors have been published regarding naked decimal points, such as the tragic death of a 9-month-old baby who received 10 mg of IV morphine within two hours. The physician had prescribed ".5 mg" of IV morphine but the order was inadvertently transcribed as 5 mg of IV morphine.[44]

To improve the safety of drug labels globally, it is crucial to avoid error prone abbreviations and dose designations. Many regulators and organizations already recommend against the use of trailing zeros, "U" for units e.g., Health Canada,[20] FDA,[25] Australian commission on Safety and Quality in Heathcare,[41] FIP,[34] HQSC,[41] and "IU" for international units on drug labels e.g., Health Products Regulatory Authority,[22] PHARMAC[26] Australian commission on Safety and Quality in Healthcare.[41]

There may be instances where it is not be feasible to avoid use of these abbreviations especially for multilingual labels given the limited space on labels. However, whenever feasible, these abbreviations should be avoided.

4. *Prominently display cautionary statements on outer and immediate container labels of neuromuscular blockers, potassium chloride concentrate injection, methotrexate, and other selected error-prone medications.*

Some medications have an increased risk of causing significant patient harm (especially when used inappropriately), which should be highlighted on the label. Fatal errors with high-alert medications, such as neuromuscular blockers (e.g., suxamethonium [succinylcholine], rocuronium, vecuronium), methotrexate, and potassium chloride concentrate injection have been averted due to a prominent display of cautionary statements. For example, a nurse inadvertently selected succinylcholine instead of heparin. While walking to the patient's bedside, she noticed white lettering on the red cap that read "WARNING: PARALYZING AGENT", which prompted her to verify the vial thereby preventing a medication error. She indicated that the prominently displayed cautionary statement enabled her to identify this near miss.[45] When first noticed, even when the product is not in active use, such as when seen while in storage, these brief warning statements also serve to educate users about medication properties of which they may not be aware.

Designing warnings is a complicated task that should be based on human factors and practice considerations.[46] Warning or cautionary statements convey critical information about the product to the user, to facilitate correct product use and to prevent an error that may result in serious harm or death.[47]

Since evidence has demonstrated that the effectiveness of warnings and messages increases with prominence[48], the guidance documents of some countries and organizations state that these warning should be the most prominent information on the label and package [25,26]; be positive and affirmative [4,20,24,25]; brief and explicit [20,47]; and incorporate signal words (e.g., "DANGER" "WARNING", "ALERT").[20]

Examples of warnings approved by some regulators and organizations include:

Vinca alkaloids	"For Intravenous Use Only – Fatal If Given by Other Routes"(IMSN,[4] Health Canada,[20] USP,[47] MHRA[49])
Oral methotrexate	"Check dose and frequency – Methotrexate is usually taken once a week" (IMSN,[4] Health Canada,[20] MHRA[49])
Potassium Chloride concentrate injection	"Must Dilute Before Use" (IMSN,[4] Health Canada,[20] MHRA[49])
Neuromuscular blocking agents	"Warning: Paralyzing Agent" (Health Canada,[20] ISMP Canada,[45] TGA[50])

Some regulators allow for cautionary statements to be included in the product labeling or on the surface of the ferrule or cap overseal of a vial containing an injectable product. [20,25] To globally prevent medication errors related to these vinca alkaloids, oral methotrexate, potassium chloride concentration injection, and neuromuscular blocking agents, cautionary statements/special warnings should be prominently applied to the product label.

Also, these cautionary statements should have a consistent message globally e.g., the message on the warning label for neuromuscular blocking agents in Europe should be the same for neuromuscular blocking agents in Australia, USA, Canada etc.

5. *For the labels on glass ampules, contrasting label backgrounds and appropriate font size and label orientation should be used, to improve readability.*

Glass ampules have been widely used in packaging injectable drugs especially in emerging markets[51] due to the low cost of production.[52] However, poor glass ampule labeling continually contributes to medication errors. Ampules with a clear background have a poor contrast and are difficult to read, especially when the printing is black or another dark color.[53] Overlapping text printed on both sides of an ampule and poor visual contrast between container closure and label information; text and background, has led to wrong drug and dose errors.[25] Abeysekara et al[54] stated that 20.8% of drug errors reported to the Australian incident monitoring program were due to wrong drug ampule selection or a labeling error. Studies have demonstrated that using a contrasting background on ampule labels improves legibility and decreases reading errors.[55,56]

Besides contrasting background, font size and label orientation also affect the legibility of ampule labels. In 2004, ASTM International published guidelines on the labeling of ampules which were

accepted by the American Society of Anesthesiologist (ASA).[57] The ASTM International guidelines indicate that ampule label should have maximum contrast between the text and the background provided by high contrast color combinations as specified in ASTM International standard, which also minimize the impact of color blindness.[55,57] Standards also include recommendations for font size, extra space for separation around the drug name, and use of additional emphasis for the initial syllable, or a distinctive syllable between similar drug names.[57] These recommendations are also supported by the International Organization for Standardization (ISO) and ISMP.[57,58]

Also, some regulators recommend the use of color contrast that affords adequate legibility of text,[20,23,25] the orientation of text to the field of view so that it is not limited by physical aspects of the small container (e.g., curvature),[20,26] and the avoidance of high gloss, metallic, or reflective packaging.[23] ISMP also recommends that ampule labeling should be oriented so that the label is right side up when the neck of the ampule is held in the right hand using by thumb and forefinger, thus favoring the over 80 % of human beings who are right-handed. A similar recommendation is made for prefilled labeled syringes that are held in the right hand by the syringe plunger. [59]

Despite reported medication errors and published standards, some manufacturers still use ceramic prints on clear glass, without a contrasting background. In view of patient safety, the labels on drug ampules should always have a contrasting background and appropriate readability features including font size and orientation. Harmonization of ampule label requirements will decrease medication errors globally.

6. Prominently display international nonproprietary names (INN) on labels/packages.

Initiated in 1950, WHO published the first list of International Nonproprietary Names (INN) for pharmaceutical substances intended for use in pharmacopoeias, labeling, product information, product promotional materials, drug regulations, and as the basis for product names (such as generic names).[60] Most national nomenclature systems such as the British Approved Names (BAN), Dénominations Communes Françaises (DCF), Japanese Adopted Names (JAN), United States and TGA use names identical to INN (nonproprietary or generic drug name).[60,61]

The nonproprietary drug name (generic name) is a distinctive characteristic of a drug and should be prominently displayed alongside other pertinent information like strength, dosage form, etc. Though many countries have adopted the use of INNs, the prominence of these nonproprietary drug names on drug labels varies. Not prominently displaying the generic names of medications on their label may lead to medication errors including unintentional overdose.[62] A Norwegian study indicated that standardized and prominent placement of substance name and dose with a band of high-contrast color support recognition of the active substance in medications. This simple modification helps users realize that two different packages can contain the same active substance, thus reducing the risk of inadvertent medication overdose. [63]

For safety reasons, many organizations and regulators advocate for the prominent display of the nonproprietary drug name on drug labels (e.g., MEB,[3] IMSN,[4] TGA,[64] European commission,[65] Finnish Medicines Agency Administrative Regulation [FMEA],[66] New Zealand medicine and Medical device safety Authority [MEDSAFE]).[67] Though this might be difficult for multi-component drugs, it is recommended to list all active ingredients on the drug package.[22]

Packaging

7. *Physically link or integrate "special" diluents for "specific drugs" with their powder component.*

Some manufacturers package diluents commonly used for reconstitution, such as sodium chloride injection 0.9% or sterile water for injection along with powdered medications as a convenience to users. However, in other cases, there may be special diluents that are needed for reconstitution od certain drugs and these special diluents are co-packaged with the drug product.[68] When medications are co-packaged with manufacturer-supplied diluents, there is risk for medication errors[69] Drug products packaged with a special diluent are often separated from the diluent during product storage resulting in the administration of only the diluent or incorrect reconstitution of the product with the wrong diluent or an incorrect amount of diluent.[69,70] Cousins et al[71] reported that wrong diluent was used in 1%, 49%, and 18% of hospital cases in the UK, Germany, and France respectively.

Incorrect reconstitution may cause reduction in drug solubility, which can lead to powder particulates being administered to the patient.[68,71] For vaccines, it can result in inadequate protection of the patient against disease. It can also lead to product instability, precipitation[68,71] and contamination. Though these products usually come with information concerning the diluent,[68] errors related to these products are continually being reported.

Packaging these products in a container closure system that allows for the drug and diluent to be physically linked or integrated will help reduce these errors.

8. *Increase the adoption of ready-to-use/ready-to-administer syringes, premixed IV solutions, unit-dose packaging, and other more efficient, safer packaging.*

Each year, millions of prescriptions are prepared by pharmacists, nurses, and doctors.[72] Compounded products, produced on a small scale, are necessary for patients requiring specialized medication that is not commercially available.[73,74] In 2013, the US Office of the Inspector General, Department of Health and Human Services, published a memorandum indicating that over 90% of hospitals use compounded sterile preparations.[75] However, these drugs may pose additional risks to patients since regulatory oversight is less rigorous than those of commercial drugs.[73,74] Compounded drugs are exempt from good manufacturing practice regulations, are not clinically evaluated for safety or efficacy[73,74] and are not required to adhere to labeling standards,[73] which increases the potential for preparation errors.[73,76] Sub-standard compounding practices can lead to production of contaminated, super-potent, or poor-quality drugs.[77] While the mention of compounding errors might bring to mind the US incident in 2012 involving the New England Compounding Center's meningitis outbreak that affected hundreds of Americans,[74] Flynn et al[76] reported a 9% error rate in the compounding of intravenous admixtures.

While compounding is an essential component of pharmacy practice, it is also common practice for nurses to compound medications[78] especially in countries outside of the United States. Nurses commonly prepare sterile medications for immediate or emergency use, but their focus may be on the appropriateness of the drug for the patient's diagnosis rather than pharmaceutical calculations and aseptic techniques.[79] In fact, an observational study on types and frequency of

errors in the preparation and administration of drugs by nurses indicated the most frequent errors were lack of hand hygiene (70% in preparation phase, 81% in administration phase) and use of aseptic technique (81% in preparation phase, 85% in the administration phase).[80] Sterile compounding by nurses in nursing units or wards; clinics; at the bedside; in procedural areas; and operating rooms with little direct pharmacy oversight has an increased risk of adverse outcomes, including death, that can occur if medications become contaminated or their potency is altered.[78] Unnecessary use of compounded drugs futilely exposes patients to potentially serious health risks[77] and may increase cost. In fact, fungal contamination of medications in one hospital led to the readmission of 545 patients, costing the hospital system 15,000 hours of personnel time and almost 900,000 US dollars.[81]

The purchase of ready-to-use products eliminate the need for compounding thereby reducing the potential for medication errors and product contamination.[82] Ready-to-use products offer the advantages of reducing preparation time, assuring the drug is properly reconstituted, lengthening expiration dates, and ensuring proper labeling.[83] Also, ready-to-use packages such as prefilled syringes are convenient, suitable for home use, and decrease drug waste.[84] With the increased need to incorporate barcode scanning in the medication use process, ready-to-use products can help facilitate the right product selection and administration.

Many organizations advocate for the purchase and use of premixed parenteral solutions, especially for high alert medications such as concentrated electrolytes.[85] When possible, to promote safe medication administration practices, regulators should encourage the use of commercially prepared drugs. For products with standardized dosing, unit-dose packages should be used, whenever possible.[4] Compounded products should not duplicate an approved drug product.[86]

9. *Develop product-specific global safety standards; for example, standard packaging for non-oncologic methotrexate to prevent accidental daily use and overdose.*

Efforts to decrease medication errors should go beyond requiring people to be infallible.[87] An unintentional overdose of medication might be linked to medication package design.[63] When approving drug products, regulators must consider how people will use them. Consider features that make products more or less safe and those that do not require humans to increase vigilance.[19]

Regarding the prevention of accidental daily use and overdose of methotrexate for non-oncologic indications, a product feature that does not depend on human vigilance is standard packaging. The dosing of methotrexate in the treatment of non-oncologic conditions, such as rheumatoid arthritis, psoriasis, and other conditions, is weekly,[88,89]but prescribing and dispensing errors have led to patients receiving daily doses.[90] A 10-year analysis by the National Patient Safety Agency in the United Kingdom identified 26 cases of serious injury and 25 deaths due to unintentional overdoses of methotrexate.[91]

Due to several reports of fatal dosing errors with methotrexate, many countries have implemented safety strategies to intercept this type of error[88,89], but the errors still exist. Organizations such as IMSN[4], ISMP[90], Prescrire[92], and HQSC[93] propose the repackaging of methotrexate in unit-dose blister calendar packs for non-oncologic indications. Since some regulators indicate that the appropriate pack size should be chosen in accordance with the

duration of treatment[94], methotrexate unit-dose packages for non-oncologic indications should only contain a 30-day supply. Some countries print warnings about the need for weekly dosing on the primary display panel (e.g., Spain).[95]

10. Include barcodes on drug packaging to facilitate scanning at the bedside or other locations where medications are dispensed and administered by healthcare practitioners

The quality of healthcare depends on safe medication preparation and administration. The use of machine-readable coding and scanning have the potential to identify and intercept errors before they reach the patient.[96] Created to reduce drug administration errors and improve patient safety[97], Barcode medication administration (BCMA) has an error rate of about 1 in 10 million compared to keyboard-entry error rates of 1 in 100.[96,97] BCMA reduces medication errors by verifying the right patient, right dose, and right drug, therefore giving a closed feedback loop.[98] Thompson et al[99] stated a 43.5% decrease in reported medication administration errors after the introduction of BCMA and Bonkowski et al[100] noted an 80.7% relative reduction in the number of administration errors after the implementation of BCMA in an emergency department. BCMA systems can also be used in pharmacy stocking and retrieval to prevent dispensing errors and have demonstrated financial benefits related to the cost of harmful medication errors.[101]

Though studies have shown that many types of errors might be avoided with the use of BCMA,[98,102,103] it's use has not been adopted in many hospitals globally. A recent study indicates a 98.7% implementation in at least one inpatient unit but some hospitals still have not adopted its use or are not using it in every unit.[101] One reason BCMA has not been widely adopted at the bedside globally is the lack of manufactural barcode at the unit-dose package level, requiring pharmacies to manually affix organization-generated barcode labels on up to 65% of doses.[96]

In a separate but related issue, an increase in the global prevalence of falsified medications have led to the adoption and enforcement of anti-counterfeiting laws and regulations. Over 40 countries have enacted track and trace laws[104] which requires drugs to have a unique product identifier on each package that follows the drug throughout the distribution chain from manufacturer to patient. The United States (Drug Supply Chain Security Act -DSCSA) and European Union (Falsified Medicine Directive-FMD) have both enacted track and trace systems with the use of the 2D (data matrix) barcode as the information carrier of the unique.[3,105,106,107] The incorporation of a 2D barcode for track and trace is an excellent opportunity to introduce patient safety initiatives such as barcode scanning at the bedside but unfortunately, these barcodes are not required on the primary drug package (unit-dose level).[105,106,107]

Patient safety is best achieved when practically all medications are barcoded at the primary level. Since implementing barcode verification for the preparation, dispensing, and administration of medications reduces the risk of errors,[108] globally, the track and trace laws should be expanded to ensure that all medications sent to the point of care are barcode labeled.

CONCLUSION

In today's society, medications play an important role and their labeling and packaging represents a vital factor in their safe use.[109] Medication errors related to product labeling and packaging are a global patient safety issue, requiring a multi-faceted approach by international drug regulators and

manufacturers. Labelling alone cannot mitigate all risk, any labeling warning or package element added should be seen in the context of the overall strategy to minimize risk. Factors such as patient/caregiver empowerment, healthcare professionals training and system/practice improvements employed in conjunction with labelling changes to promote safer medication use.[110]

As outlined in this paper, there is a need for global harmonization of product container labeling and packaging. While the content of the label and package is determined by drug manufacturers, this information is assessed and approved by drug regulators. Regulatory authorities must enforce product labels and packages designed to minimize medication errors. Harmonizing safer drug labeling and packaging globally will decrease medication errors, decrease regulatory burden on manufacturers that produce drugs for the global market, and increase the efficiency of the drug approval process. Only when countries agree can we begin to advance patient safety globally.

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Country	**Regulatory Agency, IMSN Members or Pharmaceutical Company**	**Contact Persons**	**Date reviewed**
USA	Institute for Safe Medication Practices (ISMP)	Michael R. Cohen	January 29, 2019, May 17,2019
		BarbraKaryne Nchinda Fobi	January 29, 2019, May 17, 2019
		Christina Michalek	February 6, 2019
USA	US Food and Drug Administration (FDA)	Lubna Merchant	February 22, 2019, May 17, 2019
Canada	ISMP Canada	David U	February 26, 2019
France	Prescrire	Etienne Schmitt	March 7, 2019
United Kingdom	Medicines and Healthcare Products Regulatory Agency (MHRA)	Jan MacDonald	April 12, 2019
Canada	Health Canada	Sally Pepper	May 9, 2019
European Union	European Medicines Agency (EMA)	Alexios Skarlatos	May 16, 2019
Norway	Norwegian Medicines Agency (NOMA)	Sigurd Hortemo	June 6, 2019
USA	Bristol-Myers Squibb	Yusuf Oni	June 10, 2019
		Alpa Bhattacharyya	