Introduction to MedDRA Labeling Grouping (MLG): A standardized approach to grouping adverse reactions in product safety labels

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Report of the CIOMS MLG Expert Working Group

Geneva 2024

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ISBN: 978-929036105-3

Suggested citation: Introduction to MedDRA Labeling Grouping (MLG): a standardized approach to grouping adverse reactions in product safety labels. Report of the CIOMS MLG Expert Working Group. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 2024. doi:10.56759/hmku5307. Licence: CC BY-NC-SA 4.0

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This publication is freely available on the CIOMS website at: https://doi.org/10.56759/hmku5307

Note on style: This publication uses the World Health Organization's WHO style guide, 2nd Edition, 2013 (WHO/KMS/WHP/13.1) wherever possible for spelling, punctuation, terminology and formatting. The WHO style guide combines British and American English conventions. The names of MLGs are in American spelling.

ACKNOWLEDGEMENTS

The Council for International Organizations of Medical Sciences (CIOMS) gratefully acknowledges the contributions of the members of the CIOMS Expert Working Group (EWG) on MedDRA Labeling Grouping (MLG) for dedicating their time and providing their expertise to finalize this publication.

Moreover, CIOMS recognizes the contribution of all members of the CIOMS MLG EWG during the earlier stages, as well as the generous support of the regulatory authorities, pharmaceutical companies, and other organizations and institutions which provided the expertise and resources that resulted in this publication.

CIOMS thanks especially those members who chaired the meetings for their capable leadership, and the rapporteurs for their dedication and professional contributions.

The editorial group, comprising Drs Ilona Grosse-Michaelis, Radhika Rao, Scott Proestel, Silvia Bader-Weder, Brian Dillman, Catherine Penfornis, Ms Lynn Macdonald, and Mr Aniello Santoro, merit special mention and thanks. CIOMS expresses special appreciation to Drs Ilona Grosse-Michaelis and Radhika Rao as chief editors of the final report.
Special credit should be given to Dr William Gregory for his ideas, profound subject knowledge and dedication in setting up this EWG.
CIOMS also thanks Ms Monika Zweygarth for help with the presentation and layout of the report.

The work has involved a number of meetings organized by the CIOMS Secretariat, and contributions from regulatory agencies and pharmaceutical companies are especially acknowledged.

Lembit Rägo, MD, PhD
Secretary-General, CIOMS

Geneva, Switzerland, March 2024

DEDICATION:
Dr JUDITH K JONES

This report is dedicated to Dr Judith K Jones, MD, PhD, in honor of her valuable contributions to CIOMS Working Groups. Judith was a member of the longest-standing CIOMS Working Group, which was active from 2003 to 2019 to develop standardised queries to search for adverse drug reactions in different databases using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Judith was also a member of the follow-on group on MedDRA Labeling Groupings and a speaker on this topic at the DIA 2019 Global Annual Meeting. She was a frequent, authoritative speaker in many other scientific venues and served on several influential drug safety advisory committees.

A medical doctor and clinical pharmacologist, Judith received her formal education at Baylor College of Medicine, followed by clinical training, a fellowship in clinical pharmacology, and a PhD in developmental pharmacology at the University of California at San Francisco. She then transitioned to public service as Director of the Division of Drug and Biological Experience at the U.S. FDA (now the Office of Safety & Epidemiology) from 1978-1985. She subsequently founded and served as President and CEO of The Degge Group, Ltd., which she built into a premier drug safety service provider. In 2017 the company joined the PharmaLex Group, a full-service biopharmaceutical contract research organization. In the same year she also received the prestigious Honorary Lifetime Fellowship award of the International Society for Pharmacoepidemiology (ISPE) for her lifetime achievements in pharmacoepidemiology and for her pioneering role in the Society. She was also a frequent contributor to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), the American Society for Clinical Pharmacology and Therapeutics (ASCPT), the Drug Information Association (DIA), the United States Adopted Names (USAN) Council, and many others.

Judith K. Jones passed away peacefully on 4 August 2020 after months of battling lung cancer. She is survived by her husband, William C. Rogers, of Clifton, Virginia, a sister, Tobi Jones, of Woodland, California, and a sister, Patricia Huff, of Brunswick, Georgia. Her obituary was published in the Washington Post on 10 August 2020.

DEDICATION:
Dr BRIAN S DILLMAN

Image from: Franciscan Health

This report is dedicated to our co-author and dear colleague, Dr Brian S Dillman, MD, in honor of his outstanding contributions to the CIOMS MLG Expert Working Group. Brian S Dillman died at age 49, on 19 May 2022, after being struck by a vehicle near his family's home in Indianapolis, United States.

Brian was a member of the CIOMS Working Group on MedDRA Labeling Groupings (MLG), to which he contributed his experience as Clinical Research Physician at Eli Lilly's Global Patient Safety organization. Having joined the company in 2009, he continued to work as an emergency room physician on a part time basis.

The CIOMS Working Group is devastated about Brian's tragic and untimely death. Brian was a kind and respected team member as well as a wonderful person and working with him over the past three years has been the group's great honor and pleasure. He was friendly and compassionate and had the great ability to listen to people and find compromises. He always saw the best in others, and his good nature brought people together.

Brian is survived by his wife, their daughter, a sister, and his parents. Brian's obituary is found on his online memorial site.

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INITIALISMS

This list of initialisms and the glossary provided in Appendix 1 contain key terms used in this report.

ADR/AR/UE	adverse drug reaction / adverse reaction; synonym: undesirable effect
AE	adverse event
CCDS	company core data sheet
CIOMS	Council for International Organizations of Medical Sciences
EMA	European Medicines Agency
EPAR	European public assessment report
EU	European Union
EWG	Expert Working Group
FDA	Food and Drug Administration (United States)
HCP	healthcare professional/provider
HLGT	High Level Group Term
HLT	High Level Term
IB	investigator's brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (formerly: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) Sometimes referred to as "International Council for Harmonisation"
ICSR	individual case safety report
ISS	integrated summary of safety
IWG	Implementation Working Group
LLT	Lowest Level Term
MAH	marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
MLE	MedDRA Labelling Entity (former naming idea for MLG)
MLG	MedDRA Labeling Grouping
MMC	MedDRA Management Committee
MSSO	MedDRA Maintenance and Support Services Organization
NEC	not elsewhere classified (in MedDRA)
PBRER	periodic benefit−risk evaluation report

PI	product information
PL	package leaflet (also called “patient information leaflet”, PIL)
PSL	product safety label/labeling
PSUR	periodic safety update report
PT	Preferred Term
SmPC	summary of product characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
U.S.	United States

PREFACE

The Council for International Organizations of Medical Sciences (CIOMS) Working Groups (WGs) within the area of drug safety have evolved over the years. A broad range of challenging drug safety topics have been addressed by these WGs, which comprised expert senior scientists from regulatory authorities, the biopharmaceutical industry and academia. These experts have developed consensus guidelines and pragmatic recommendations in important public health areas.

One of the CIOMS initiatives was the creation of an expert group to develop Standardised Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs) that were ultimately adopted by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) for inclusion in MedDRA. SMQ development by an expert group continued from 2002 to 2018, initially as a WG and later as a smaller core group and implementation working group (IWG). The SMQ IWG held its 14th Meeting on 11-12 September 2018 in Geneva. While SMQs were designed for safety signal detection toward the end of its existence, participants discussed the concept of MedDRA Labeling Groupings (MLGs) for use in product safety labels (PSL). It was noted that term groupings were being developed and used independently in several jurisdictions; however, no standards or principles existed to facilitate consistency and harmonization in the process. A concept paper and a more concise one-pager regarding the development and use of MLGs were developed and submitted to the MedDRA Management Committee (MMC) for consideration; further investigation into the topic of MLGs was recommended to inform any future decisions regarding MLGs.

Given its long-standing contributions towards the design of SMQs, CIOMS convened an Expert Working Group (EWG) with involvement of multiple major stakeholders to produce a consensus document on principles and points to consider in the development of MLGs. The MLG EWG identified current approaches in grouping of MedDRA Preferred Terms (PTs) in PSLs, and in this document proposes a consensus approach. It is envisaged that the use of these consensus recommendations would be voluntary and applied to PSLs in a manner that is consistent with existing regulatory frameworks.

DISCLAIMERS AND CLARIFICATIONS

The Medical Dictionary for Regulatory Activities (MedDRA®) trademark is registered by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The term "MedDRA" is used without the trademark sign ® throughout this report (except in this paragraph).

MedDRA terminology is updated twice yearly (MedDRA versions .0 and .1); therefore, always check the MedDRA version number particularly for the examples. The respective MedDRA version information will change over time as new MedDRA versions are issued. Accordingly, the respective MedDRA documentation is regularly updated to inform customers about changes. The supporting documents are found on the MedDRA website,[1] but only those relating to recent MedDRA versions are shown. MedDRA users who wish to view the documentation for older versions should request this from the MedDRA Maintenance and Support Services Organization (MSSO).[2]

Throughout this report, unless indicated otherwise, the MedDRA versions used are MedDRA versions 24.0 and 24.1.

Throughout this report, unless indicated otherwise, the term "drug" is meant to include all medicines (e.g., drugs, vaccines, biotechnology products) for prevention, prophylaxis or treatment of a disease or medical condition, and possibly for use in diagnosis.

Throughout this report, unless indicated otherwise, the short term "EWG" refers to the Council for International Organization of Medical Sciences (CIOMS) Medical Dictionary for Regulatory Activities Labeling Grouping (MLG) Expert Working Group (EWG).

Members of the CIOMS MLG EWG have contributed their views and technical expertise to the content of this report, and these do not necessarily represent the views of their respective organizations.

Important topics are repeated in different chapters, allowing readers to focus on specific chapters only.

[1] https://www.meddra.org/how-to-use/support-documentation/english, accessed 7 November 2022

[2] Details are found at https://www.meddra.org/contact.

DECLARATIONS OF INTEREST BY CIOMS EXPERTS

The Council for International Organizations of Medical Sciences (CIOMS), as indicated in Article 2 of its Statutes,[3] aims to "promote public health through international collaboration and coordination including, but not limited to, medical products safety and ethical principles governing the conduct of biomedical research involving human subjects". In that capacity it brings together representatives of health authorities, non-governmental organizations, the private sector, academia, medical research, religion, philosophy, and law, as well as lay persons. To assure the technical integrity and impartiality of CIOMS's work, it is necessary to avoid situations in which other interests might affect the outcome of that work.

Each expert is therefore asked to declare any interests that could constitute a real, potential, or apparent conflict of interest within the last five years, with respect to his/her involvement in the meeting or work, between commercial entities and the participant personally, and commercial entities and the administrative unit with which the participant has an employment relationship. "Commercial entity" refers to any company, association (e.g., trade association), organization or any other entity of any nature whatsoever, with commercial interests.

[3] Available on the CIOMS website at: https://cioms.ch/wp-content/uploads/2021/09/CIOMS-Statutes_2021_English.pdf

EXECUTIVE SUMMARY

Chapter 1. Background and problem statement

Medical product safety label (PSL) information needs to be clear, consistent, and understandable to the healthcare community. The Medical Dictionary for Regulatory Activities (MedDRA) of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (formerly International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) is used in product safety labeling to describe adverse drug reactions. Due to the high granularity of MedDRA, Preferred Terms (PTs) relevant to an adverse reaction (AR) may be located in different locations of the MedDRA terminology and may warrant to be grouped for communication of that AR in a PSL since they represent the same clinical concept. MedDRA does not currently provide groupings of adverse reaction terms conveying the same medical concept that are intended for use in PSLs. When different adverse reaction terms that convey the same clinical concept are used as separate individual terms in PSLs, the result can obscure the safety information that is being provided. Therefore, there is a need to combine adverse reaction terms that describe the same concepts.

To fulfil this need, some institutions have developed their own groupings, but in the absence of agreed conventions, this has inevitably led to considerable variability in approaches.

The Council for International Organization of Medical Sciences (CIOMS) Expert Working Group (EWG) was established to develop international consensus principles for a new type of groupings, termed MedDRA Labeling Groupings (MLGs). The group's membership is shown in Appendix 2.

In a possible follow-up phase, an EWG would develop actual MLGs for international use. If a decision is taken to pursue this second phase project, the established ICH process would be engaged to seek endorsement.

Chapter 2. MLG concept and principles

MLGs are groupings of near-synonymous MedDRA PTs that convey substantially similar clinical concepts. They are different from the existing Standardised MedDRA Queries (SMQs), which are groupings of adverse reactions used for safety signal detection (see Appendix 3 for a comparison). The objective of MLGs is to support accurate and consistent presentation of adverse reactions within product safety labels (PSLs). MLGs can help to achieve harmonization in this regard. This would be a significant advance over the current situation of different institutions either taking different approaches when creating their own groupings (examples are shown in Appendix 4) or not creating groupings at all when presenting safety information in PSLs. It is expected that MLGs, when used appropriately, would enhance the communication of the true safety profile of medicinal products in product safety labeling, thus benefiting healthcare professionals (HCP).

The current primary MLG application is in product safety labeling. While MLGs may have limited potential applications beyond product safety labeling— such as for signal detection and other

evaluation of clinical study safety data—these applications are not currently the objective or remit of the CIOMS MLG EWG.

The EWG agreed on the following principles:

Principles for the development and use of MLGs

1. MedDRA PTs that convey **substantially similar clinical concepts** should be combined into MLGs when presented in product safety labeling.
2. The process of grouping of PTs into MLGs should not result in the loss of **clinically meaningful safety information.**
3. The use of MLGs, while recommended, should be **voluntary.**
4. The content of MLGs, when used publicly, should be specified in order to ensure **transparency**.
5. The use of MLGs is intended to foster international harmonization in a manner **consistent with existing regulatory frameworks**.
6. MLGs should be made **easily accessible** and widely available to ensure transparency and **consistency**.

Chapter 3. Methodology of developing MLGs

Based on a feasibility exercise that created five MLG examples (Appendix 5), the EWG identified some of the determinations that will be important for MLG developer(s) to address. Acknowledging that there is subjectivity inherent in creating any grouping of PTs, the EWG considers that an open and deliberate process guided by the MLG principles will be a significant advance over the current situation of different institutions taking different approaches.

The feasibility exercise provided the basis for a proposed methodology for creating MLGs. Taking into account the current practices of groupings by different institutions the CIOMS MLG EWG aimed to achieve a consensus approach. To achieve the desired consistency in PT groupings internationally, the EWG proposed a set of conventions that provide specific and practical rules for MLG development. The group also identified the main design features of MLGs and proposed steps for MLG creation.

Chapter 4. Practical considerations

A number of practical issues must be addressed in order to achieve successful implementation of MLGs. These include MLG ownership and their maintenance in line with evolving versions of MedDRA. This report also discusses the application of MLGs in ways that are consistent with current regulatory labeling requirements in different jurisdictions. This initiative should not result in any alteration of current global labeling regulations or reporting requirements. The group furthermore considered to what extent it would be possible to use and document MLGs in product safety labeling of new and existing products. Beyond MLGs, the group acknowledged that it may also be appropriate, depending on the circumstances of a development program, to create non-MLG custom

groupings of MedDRA terms. These may include terms that, although less similar than those in MLGs, may need to be grouped in a label to fulfill some product-specific needs.

Chapter 5. Conclusions

The CIOMS MLG EWG has accomplished the intended objective of the first phase, i.e., creation of the MLG definition, MLG scope and applications, the MLGs principles. In addition, the CIOMS MLG EWG also identified a stepwise methodology and MLG conventions to support the creation of MLG examples.

MLG development, maintenance and implementation will require significant and ongoing resources. The CIOMS MLG EWG therefore recommends that an existing organization with representation from various stakeholder groups should help coordinate MLG ownership and maintenance.

Implementing MLGs consistently across products and jurisdictions will be a challenge, especially given that their use is voluntary. Nevertheless, the EWG believes that MLGs will foster consistency across product safety labels and provide the most utility if they were available as pre-codified groupings.

In 2018 the CIOMS MLG EWG submitted its proposals to the MedDRA Management Committee, which responded with a number of questions and points for clarification. Those have been carefully reviewed and addressed while preparing this report.

While the implementation of MLGs poses some significant challenges, we believe that they are surmountable and have provided some suggested approaches and considerations in this report.

CHAPTER 1.

BACKGROUND AND PROBLEM STATEMENT

Driven by public health considerations, business needs and regulatory guidance, many sponsors—such as pharmaceutical companies—and drug regulatory authorities have begun to develop individual approaches to clustering similar adverse reaction (AR) terms in product safety labels (PSLs). However, this has been done in a non-harmonized manner in the absence of agreed-upon conventions. In order to improve safety communication to patients and healthcare providers (HCPs), there is a need to harmonize the approach to grouping highly similar ARs in product safety labeling.

Given its long-standing contribution towards the development of Standardised Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs), the Council for International Organization of Medical Sciences (CIOMS) convened a dedicated Expert Working Group (EWG) with representation mainly from regulators and industry, with the mandate of investigating the feasibility of developing a harmonized approach to grouping nearly synonymous medical concepts when presenting ARs in PSL. Based on the requirement of usage of MedDRA, these medical concepts in ARs are typically Preferred Terms (PTs) but could also be other terms as MedDRA is not always required in PSLs.

The CIOMS EWG developed this report to propose principles and recommendations that could underpin the creation and utilization in PSLs of harmonized MedDRA Labeling Groupings (MLGs). It is envisaged that the use of the recommendations proposed herewith will be voluntary and applied in compliance with existing regulatory frameworks.

1.1 Use of MedDRA terminology in product safety labeling

Medical product safety label (PSL) information needs to be clear, consistent, and understandable to the healthcare community. Large amounts of safety evidence from product development programs must be distilled in a clear and pragmatic way within the product information (PI), consistent with existing regulations. Flexibility is allowed as to how adverse reactions (ARs) are described in the product safety labeling, with consideration given to the fact that the presentation of safety data may be subject to variable degrees of complexity.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), which brings together national regulatory authorities and the pharmaceutical industry to discuss scientific and technical aspects of drug registration, facilitates and recommends the use of Medical Dictionary for Regulatory Activities (MedDRA) through all phases of a medicine's life cycle, from clinical trials to post-marketing surveillance.[1] MedDRA is a standardized medical terminology developed to facilitate sharing of regulatory information internationally for human medical products.

The use of MedDRA by all pharmacovigilance stakeholders is required in the European Union for the "classification, retrieval, presentation, risk-benefit evaluation and assessment, electronic exchange and communication of pharmacovigilance and medical product information",[2] and is also required by the United States (U.S.) Food and Drug Administration (FDA) for clinical trial safety reporting by all commercial pharmaceutical sponsors.[3]

1.2 Grouping MedDRA terms

ARs can be represented in labeling as either individual or grouped terms.[4,5,6] As described in the U.S. FDA. Guidance for Industry, Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products: "There should ordinarily be a common classification scheme across all studies in the safety database. Events that are reported under different terms in the database, but that represent the same phenomenon (e.g., sedation, somnolence, drowsiness) should ordinarily be grouped together as a single adverse reaction to avoid diluting or obscuring the true effect."[4] Similar descriptions are noted in European Union (EU) summary of product characteristics guidance (SmPC) [5] and in the Health Canada guidance on Product Monograph [6] with focus on the use of MedDRA terminology for AR representation.

Due to the high granularity of MedDRA, which has more than 25,000 PTs in version 24.1,[7] several distinct Preferred Terms (PTs) may be available in different sections of the terminology to represent highly similar clinical concepts. MedDRA provides different groupings of PTs, both within the hierarchy, in the form of the existing superordinate levels, e.g., High Level Terms (HLTs) or outside the hierarchy, in the form of Standardised MedDRA queries (SMQs). However, as illustrated below, neither of them is adequate to clearly communicate safety information to the healthcare community within product safety labels.

1.2.1 MedDRA hierarchy

The MedDRA hierarchy is typically not useful for grouping AR terms for communication in product safety labels, as PTs relevant to one AR may be located in

more than one HLT, while one HLT may also contain PTs outside of the scope of that specific AR.

Example: Why the HLT e.g. *Gastrointestinal and abdominal pains (excl oral and throat)* may not be adequate to communicate AR of Abdominal pain in the product safety label

PTs describing the AR Abdominal pain are in at least two HLTs:
(1) HLT *Gastrointestinal and abdominal pains (excl oral and throat)*, e.g., PT *Abdominal pain*, and
(2) HLT *Gastrointestinal signs and symptoms NEC*, e.g., PT *Abdominal discomfort*.

However, not all PTs from these two HLTs would be included in an MLG for the AR abdominal pain. The following PTs would likely not be considered appropriate to represent the concept abdominal pain:
(1) PTs *Oesophageal pain* and *Visceral pain* within the HLT *Gastrointestinal and abdominal pains (excl oral and throat),* and
(2) PTs *Mastication disorder* and *Hiccups* within the HLT *Gastrointestinal signs and symptoms NEC*.

AR=adverse reaction; HLT=High Level Term; NEC=Not elsewhere classified; PT=Preferred Term

1.2.2 Differences between SMQs and MLGs

Purpose of SMQs

Combining the AR terms in medically meaningful ways greatly facilitates the interpretation of data displays in study reports, Integrated Summaries of Safety (ISS), and benefit-risk assessments. These data are subsequently distilled for communication of ARs to healthcare providers in product safety labels. SMQs are comprised of MedDRA PTs that focus on certain medical conditions. They are used for searching, analyzing and presenting MedDRA-coded data during safety data analyses. The value of SMQs in aggregating related PTs into clinically relevant concepts has been shown.[8]

Some institutions have developed their own MLG-like custom PT groupings and report benefiting from them, but an internationally agreed-upon set of MLGs does not exist at the time of publication of this report.

SMQs versus MLGs

Due to their heterogeneous nature, one SMQ may contain a combination of MedDRA PTs related to a medical concept including signs and symptoms, diagnosis, and diagnostic and therapeutic measurements. Hence when an SMQ is utilized for data retrieval, the output is more sensitive, although less specific than an MLG. In contrast, an MLG by nature is homogenous and intended to contain MedDRA PTs that are near-synonymous to an individual medical concept such as signs or symptoms only or diagnosis only, or diagnostic measurements only, or therapeutic measurements only. Therefore, an MLG may be too specific and little sensitive for the purposes of data retrieval, and would generally be expected to be contained in an SMQ for the

same concept, but not always, due to the requirement of different inclusion/exclusion criteria of the medical concepts of both groupings. However, SMQs would typically be expected to contain many more PTs given their use for safety signal detection and lower requirement for similarity.

SMQs can contain narrow scope searches (i.e., terms more likely to be associated with a condition) and broad scope searches (i.e., terms that are less specific for the condition of interest which are included to increase the sensitivity of the search strategy). However, even the narrow searches of SMQs can include less closely related terms than what is needed to describe a specific AR in the product safety label, and are therefore not amenable for MLGs.

Parallels can be drawn between SMQs and the proposed MLGs. Both are based on MedDRA terminology and are combinations of MedDRA PTs, although with different aims. Both are intended as tools to promote harmonization and simplification by use of a standardized approach and are developed based on need. However, MLGs are not intended to be used for safety signal detection or to alter the approach to safety data analyses. The proposed approach of grouping near-synonymous MedDRA PTs is intended to achieve a clinically meaningful representation of adverse reactions in the PSL for healthcare providers.

SMQs are used for safety signal detection in MedDRA-coded adverse event (AE) data sets, while MLGs would be used to communicate the ARs in product safety labeling.

The CIOMS MLG Expert Working Group (EWG) believes that SMQs and MLGs would serve different primary purposes, the former for signal detection and the latter for labeling. MLGs would have merit on their own as tools for improving safety communication in PSL.

A comparison of SMQ and MLG is shown in Table 1 (abbreviated version).
A more detailed comparison with an example of a draft MLG is given in Appendix 3.

Table 1. Comparison of SMQ and MLG

Characteristics	Standardised MedDRA Queries (SMQ)	MedDRA Labeling Groupings (MLG)
Purpose	Safety signal detection in MedDRA-coded adverse events data	Safety communication in product safety label
Status	International MedDRA Preferred Term (PT) groupings exist	To be established*
Content	Consist of MedDRA PTs that reflect a range or different aspects of a medical concept (heterogeneous concept)	Consist of MedDRA PTs that are nearly synonymous (homogeneous concept)

*An internationally agreed set of MLGs does not exist at the moment. Some institutions have developed their own MLG-like custom PT groupings and report benefiting from them.

1.2.3 Origins of the MLG concept

The need to group terms to provide clarity in medicine labels has been identified for some time and is reflected within regulatory guidance.

Subsequent initiatives that brought together national regulatory authorities and the pharmaceutical industry achieved greater harmonization worldwide. The use of MedDRA through all phases of a medicine's life cycle, from clinical trials to post-marketing surveillance by all pharmacovigilance stakeholders is required or recommended by most regulatory authorities.

The need to combine similar PTs was previously discussed by MedDRA's expert forum called the "Blue-Ribbon Panel"[9] in March 2005,[10] and subsequently at the ICH MedDRA Management Board Meeting in May 2005.[11] Of note, at that time these PT groupings were referred to as MedDRA Labelling Entities (MLE). It was concluded that the development of PT groupings for product safety labeling was not considered a priority.[11]

The ICH MedDRA *Data Retrieval and Presentation: Points to Consider* document [12] also discusses the presentation of data within the hierarchical structure of MedDRA terminology when presenting estimates of the occurrence of an AR. On the other hand, MLGs mainly do not fit into the hierarchical MedDRA structures, and therefore might have to be presented separately.

The issue is also addressed in regulatory guidance texts,[4,5,6] which generally state that ARs that are reported under different terms but represent the same phenomenon should ordinarily be grouped together as a single AR (see Section 4.3 Regulatory labeling requirements for details). Similarly, ARs that represent a syndrome complex should ordinarily be grouped together under an appropriate heading.[4]

The activity of the MLG EWG places itself within this context, as an attempt to provide a response to the need to group nearly synonymous MedDRA PTs representing an adverse reaction for communication within the product safety label of medicinal products. To fulfill this, principles for a consistent and harmonized approach have been developed by the group.

Finally, previous documents (2018, 2022) created by the CIOMS MLG EWG highlight the importance of combining nearly synonymous PTs in medical PSLs through the use of principles that promote a consistent and harmonized approach.[13,14,15] During the past few years, the CIOMS EWG refined the principles described in earlier documents and updated principles and recommendations which are presented in the current report.

1.3 Problem statement

In the absence of specific guidance to combine similar AR terms in product safety labels, several organizations have independently created their own groups of medically related terms for communication of ARs in product safety labels (custom groupings), which has inevitably resulted in different approaches (see Appendix 4). The same clinical entity may be described through different groupings of MedDRA terms by different organizations and, in other cases, via individual PTs with no grouping at all. The current usage of the MedDRA PT groupings in the product safety label by different institutions across the world is not standardized. Hence the true intent of transparently conveying the safety of the product to the healthcare provider is not always achieved. This may derive from a variety of factors, such as lack of knowledge or resources for creation of appropriate groupings, as well as the absence of an agreed-upon and well-established methodology. This heterogeneity in approach may adversely impact the presentation of safety information to the healthcare provider, including the possibility to perform a comparative appraisal between different products in identical patient populations, and may result in obscuring or diluting the safety information. A standardized approach towards the creation of groupings of clinically related PTs for the safety label is proposed as a way to counteract these risks.

1.4 The CIOMS Expert Working Group on MLGs

Establishment of the EWG

The output of the CIOMS SMQ Implementation Working Group (IWG) [16] illustrates the value of SMQs.

But SMQs are not designed for AR presentation in the PSL. Hence in 2018 a concept paper [13] and a more concise one-pager [14] on principles for grouping similar MedDRA Terms for unique medical concepts, named MLGs, were submitted to the ICH MedDRA Management Committee (MMC) for consideration, and CIOMS received the Committee's support for further exploration.

In order to foster harmonization, CIOMS formed in 2019 the EWG with the mandate to explore the feasibility of establishing internationally agreed-upon principles and guidance to facilitate the creation of MLGs.

A list of EWG membership, meetings and activities is shown in Appendix 2.

Goal

The goal of the CIOMS MLG EWG was to develop international consensus principles and recommendations for voluntary consideration, to achieve consistent grouping of MedDRA PTs into a new type of grouping, i.e., MLGs. The primary objective of those new entities is to simplify the product information and enhance the communication to healthcare providers of safety information via the product safety label. Planned CIOMS MLG EWG deliverables included the creation of a few MLG draft examples.

Initial phase

As a first step, the CIOMS MLG EWG developed non-binding consensus principles and guidance for creating MLGs. The group focused on how to create groupings of terms in labeling that would build upon the existing MedDRA hierarchy, ICH recommendations for data displays, experience with SMQs, and current regulatory safety labeling requirements to expand principles for pragmatic and sustained communication of important medical concepts over time. It was initially envisaged that CIOMS recommendations would be generally applicable to ARs in all forms of product safety labels. The deliverable for this first phase was set to be a consensus report focused on principles and practices for non-binding use of MLGs. A small set of draft examples of MLGs has been constructed for illustrative purposes (Appendix 5). As envisioned by this CIOMS initiative, consensus was achieved by the CIOMS MLG EWG on the principles.

Possible follow-up phase

The CIOMS initiative envisioned that the first phase, i.e., development of principles and guidelines for application of non-binding MLGs, would inform possibilities for a future second phase, i.e., development and feasibility of proposed creation of a broader set of MLGs according to the agreed MLG principles. In the future it may be envisioned to further assess the feasibility, implications, and value of developing specific MLGs for broad stakeholder evaluation. If a decision is taken to pursue development of actual MLGs, an extended work plan would be developed. At the appropriate time, the established ICH process will be engaged to seek endorsement of this future second phase of the project.

1.5 Purpose and content of this report

The aim of this report is to inform stakeholders involved in medical product development and in the development of safety sections of labeling about the purpose and appropriate creation of MLGs. The report summarizes the information compiled and considered by the EWG and provides consensus recommendations and principles for MLGs. It explores the current environment and practice of grouping PTs for labeling purposes, and the feasibility of developing MLGs for global use. Future considerations for MLG development and maintenance were also explored and are summarized for consideration.

Target audience

The primary target audience for this report includes regulatory authorities, scientific institutions, pharmaceutical companies and other organizations or individuals responsible or involved in the regulatory process of communicating ARs in product safety labels.

It is anticipated that MLGs will serve mainly as a means of improving communication of safety information to health care professionals via product safety labeling. The EWG's intention, as described in this report, is to work within existing regulatory frameworks and reporting requirements, and this initiative is not intended to have any impact on those requirements.

CHAPTER 2.

MLG CONCEPT AND PRINCIPLES

Medical Dictionary for Regulatory Activities (MedDRA) Labeling Groupings (MLGs) are groupings of near-synonymous MedDRA Preferred Terms (PTs) that convey substantially similar clinical concepts for presentation of information on adverse reactions in product safety labeling. Based on its long-standing experience with MedDRA and with grouping of MedDRA terms, the Council for International Organization of Medical Sciences (CIOMS) Expert Working Group (EWG) proposed a concept, identified the scope and potential benefits and limitations of MLGs. The EWG also agreed on a set of guiding principles underpinning the creation and use of MLGs.

2.1 Definition

Medical Dictionary for Regulatory Activities (MedDRA) Labeling Groupings (MLGs) are groupings of near-synonymous MedDRA Preferred Terms (PTs) that convey substantially similar clinical concepts. This grouping is performed to communicate information on an adverse reaction (AR) in a manner that is expected to give the most accurate and understandable description in product safety labeling (PSL).

MLGs are conceived as groupings comprised of near-synonymous PTs for a single medical concept. Also due to similar etiology and homogeneity of the PTs, the scope of the MLG medical concept is quite narrow.

An MLG can represent a medical diagnosis or describe specific clinical signs and symptoms, but will generally not group all potential signs and symptoms under a medical diagnosis unless the PTs for these categories are near-synonymous (for example, MLG *Hyperkalemia* is described below).

An MLG contains a group of MedDRA PTs, and each PT includes all associated Lowest Level Terms (LLTs). MLGs are product-agnostic when created with standardized principles that use a medical concept definition and group PTs that fit to the medical concept.

For more details please see Box 2 in Section 3.2.1, also please see Section 3.2.3 Steps in creating MLGs.

Example: MLG *Hyperkalemia*

MLG concept/name: *Hyperkalemia*

PTs considered for inclusion in MLG *Hyperkalemia*:
- PT *Blood potassium increased* (System Organ Class (SOC) *Investigations*)
- PT *Hyperkalaemia* (SOC *Metabolism and nutrition disorders*).

PT examples not included in MLG *Hyperkalemia:*
- PT *Blood potassium abnormal*
- PT *Pseudohyperkalaemia*

Discussion:
(1) The two included PTs belong to two different MedDRA SOCs but are seen as describing the same medical concept. As these are near-synonymous PTs, even though they are representing signs, symptoms and diagnosis, they are grouped together.
(2) PTs that indicate nonspecific laboratory results such as "abnormal" may be included in an MLG only if the lab abnormality is clinically meaningful in only one direction, e.g., PT *Blood potassium increased.* On the other hand, PT *Blood potassium abnormal* is clinically meaningful in both directions of laboratory abnormality and hence is not included under MLG *Hyperkalemia.*
(3) The PT *Pseudohyperkalaemia* represents a false elevation in potassium that reflects a different medical concept than Hyperkalemia. Therefore, it is not included in the MLG *Hyperkalemia*.

MLG=MedDRA Labeling Grouping; PT=Preferred Term; SOC=System Organ Class

2.2 Objective of MLGs

MLGs are intended to be used in product safety label for communication of safety information to health care providers. The objective of MLGs is to provide an accurate and consistent presentation of adverse reactions within product safety labels.

2.3 MLG benefits and limitations

2.3.1 Benefits

MLGs comprised of PTs that describe the same or substantially similar medical or clinical concept can achieve consistency in AR representation in the product safety labels. This harmonized presentation of safety information across products, particularly products in the same therapeutic class, will be beneficial.

The current usage of custom MedDRA PT groupings in the product safety label by different institutions across the world is not standardized, and this could result in

diluting or obscuring the true effect (see also Section 1.3 Problem statement). It is postulated that one of the benefits of MLG would be to avoid diluting or obscuring the true effect which is acknowledged in relevant regulatory guidances as an important objective while presenting the safety information.[4,5,6]

The clear communication of medical product safety information is acknowledged in relevant regulatory guidance as an important objective.[5] The Council for International Organization of Medical Sciences (CIOMS) MLG Expert Working Group (EWG) believes that when used appropriately, MLGs will enhance the communication of the true safety profile of medicinal products, thus benefiting healthcare professionals.[15]

2.3.2 Limitations

Not all medical concepts may be amenable for MLG creation, either because a certain AR is represented most appropriately by only a single PT or because it may need to be described through ways other than MLGs.

If the grouping of PTs is based on data of a specific product only, this product-specific grouping may not be applicable to other products and hence cannot be considered an MLG.

Also, by the nature of MedDRA terminology, there may not be PTs available for grouping in the current MedDRA versions for all the medical concepts.

Example: *Hypersensitivity*

Some medical concepts may encompass various clinical entities, and those in turn may have very different manifestations and seriousness. One such example is the umbrella medical concept of Hypersensitivity reactions that includes various types of exaggerated or inappropriate immunological responses to stimuli, ranging from Urticaria to Anaphylactic reaction. If an MLG were to be created for Hypersensitivity, in line with the concept definition, it would possibly include only the near synonym PT *Drug hypersensitivity*, but not for instance PT *Urticaria* or PT *Anaphylactic reaction*, since those represent specific types of hypersensitivity reactions with different severity.

MLG=MedDRA Labeling Grouping; PT=Preferred Term

The CIOMS MLG EWG acknowledges that lack of consistency across labels can be a challenge, particularly given that the use of MLGs would be voluntary. The aim of having a set of principles to guide the creation of MLGs is to foster a consistent approach. The CIOMS MLG EWG believes that MLGs would foster consistency across PSLs and provide the most utility if they were available as pre-codified groupings available to all MedDRA users.

2.4 Scope of MLG application

This section reviews the intended applications of MLGs in the AR representation and also other potential applications of MLGs.

The intended scope of MLGs is the PSL. However, the EWG acknowledges that there are other documents, such as e.g. the company core data sheet (CCDS), package leaflet (PL) and investigator's brochure (IB), where MLGs may also be useful. The CIOMS MLG EWG recommends that the existing regulatory framework should be followed.

2.4.1 MLG application

As stated above, the main objective of MLGs is to enhance communication of ARs in product safety labeling. Accordingly, the focus of the EWG was the use of MLGs in commercial labels. But the EWG believes that MLGs could also be used in other institutional safety information, such as the CCDS, if they are utilized to provide clinically meaningful safety information.

All the PTs in an MLG should exist in the MedDRA version of the data that the MLG is being applied to,[12] (i.e., not necessarily the most current version should be used).

Product safety labels are legal documents negotiated between sponsors and regulators. The CIOMS MLG EWG envisages that MLGs should be for voluntary use (see Section 2.5 Principles, Principle 3), and should only serve as a pool of PTs to be considered by the marketing authorisation holder (MAH) when intending to present observed ARs in the product safety label. This means that MAHs would always remain free to select, within a given MLG, only the PTs reported for that product so far (please see Option 1 below).

MLGs could be utilized to represent ARs in a label in several display options. The MLG example *Abdominal pain* is described in the illustration below for different options of presentation. There are two proposed options for illustration of MLG in the PSL.

The first option is to include in the footnotes only those terms within an MLG for which adverse events (AE) have been reported with the product. Please see the MLG *Abdominal pain* illustration, option 1, below.

The second option is to include in the footnotes all terms that were grouped, stating which ones were reported. Please see the MLG *Abdominal pain* illustration, option 2, below.

In the future, when MLGs may be internationally available, MLG *Abdominal pain* with internationally defined content, when used in the adverse drug reaction (ADR) table could be identified as "MLG". This promotes transparency of the content of the respective MLG. On the other hand, the label is utilized by many stakeholders with no

prior MedDRA knowledge or experience and hence may not understand the MLG principles or the groupings that an MLG represents.

The EWG acknowledges that as more MLG examples are internationally available, there could be other options of MLG presentations promoted in the PSL.

Please see below illustration of section 4.8 of the European Union (EU) summary of product characteristics (SmPC) for Product X shown in **Figure 1** below**.** Also please see Figure 2 in Section 4.4.2 Specifying the content of MLGs for two different options of MLG content displays.

Figure 1. Illustration of a part of section 4.8 of SmPC for product X

Frequency	Adverse reactions
SOC *Gastrointestinal disorder*	
Very common	*Nausea*
Common	*Abdominal pain* *

*Options of presenting an example MLG are illustrated below:

Option 1
Footnotes include only terms for which adverse events were reported

Abdominal pain* includes the **reported *terms Abdominal pain, Abdominal pain upper* and ***Gastrointestinal pain***.

Option 2
Footnotes include all terms that were grouped, stating which ones were reported

Abdominal pain* includes terms *Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Epigastric discomfort,* and *Gastrointestinal pain*. Only the terms ***Abdominal pain, Abdominal pain upper* and ***Gastrointestinal pain*** **have been reported**.

2.4.2 Unexplored potential applications

CCDS, investigator's brochures, package leaflets

The CIOMS MLG EWG has considered downstream impacts of possible application of MLGs in other safety documents with product-related information, such as PLs and IB. Wherever MedDRA PTs are utilized to describe clinically meaningful safety information, grouping the MedDRA PTs could be helpful. At this stage, the CIOMS MLG EWG has not explored the possible applications of MLGs in the CCDS, PLs, and IB. If MLGs are used in safety documents in addition to the safety section of the PSL, consistent AR representation in regard to MLG grouping is important.

Safety data from clinical trials

During the review of safety data from clinical trials—e.g., compassionate use, investigations, data from spontaneous reports, etc.—there may be an interest in using MLGs. However, MLGs are not primarily designed for signal detection, and the scope

of PT groupings likely to be utilized for signal detection purposes would generally be broader than that of MLGs (see the example below, and see also Section 1.2.2 Differences between SMQs and MLGs and Appendix 3).

The CIOMS MLG EWG acknowledges that MLGs may have limited potential applications beyond product safety labeling, such as for signal detection and other evaluation of clinical study safety data. However, these applications are not the objective or remit of the CIOMS MLG EWG currently.

Example: PT groupings for signal detection purposes would generally be broader than those for MLGs

A grouping to evaluate for a potential signal of upper respiratory tract infections could include PTs *Upper respiratory tract infection*, *Nasopharyngitis*, *Pharyngitis*, *Pharyngotonsillitis*, *Sinusitis*, *Acute sinusitis*, *Chronic sinusitis*, and potentially other terms. While such a grouping could be well-suited for signal detection, the event terms might be too disparate to be considered for inclusion in a single MLG.

MLG=MedDRA Labeling Grouping; PT=Preferred Term

2.5 Principles

After extensive discussions, the CIOMS MLG EWG gained consensus on six recommended principles for the development and use of MLGs (**Box 1**). Some principles were easier to achieve consensus on than others. The EWG's considerations with regard to each principle are outlined in the remainder of this section.

Box 1. Principles for the development and use of MLGs

1. MedDRA PTs that convey **substantially similar clinical concepts** should be combined into MLGs when presented in product safety labeling.
2. The process of grouping of PTs into MLGs should not result in the loss of **clinically meaningful safety information.**
3. The use of MLGs, while recommended, should be **voluntary.**
4. The content of MLGs, when used publicly, should be specified in order to ensure **transparency**.
5. The use of MLGs is intended to foster international harmonization in a manner **consistent with existing regulatory frameworks**.
6. MLGs should be made **easily accessible** and widely available to ensure transparency and **consistency**.

Principle 1: MedDRA PTs that convey substantially similar clinical concepts should be combined into MLGs when presented in product safety labeling.

Regulatory guidances [4,5,6] recommend grouping ARs that represent highly similar medical concepts in the PSL to avoid diluting or obscuring the true effect (see also Section 1.2.3 Origins of MLGs). MLGs are intended to provide a tool to enhance communication of ARs in PSL. Therefore, only PTs that represent a highly similar medical concept should be grouped in an MLG, i.e., those that relate to the definition of the medical concept of an MLG.

Principle 2: The process of grouping of PTs into MLGs should not result in the loss of clinically meaningful safety information.

The CIOMS MLG EWG attempted to create examples of MLGs. In practice while creating some of these examples, the balance between the benefit of combining similar PTs and minimizing the loss of clinically meaningful safety information was not easily achieved.

Principle 2 initially contained the wording "loss of important safety information" rather than "loss of clinically meaningful safety information". Concern was raised during discussions that "important" was too vague and should be clarified as referring to the "loss of important safety information with regard to specificity, seriousness, severity, outcome, and duration of the AR". However, it was concluded that even the same PT can have a wide range of severities, and the seriousness of PTs is generally based more on the event outcome than an inherent component of the PT. Therefore, the CIOMS MLG EWG ultimately decided to adopt the wording "loss of clinically meaningful safety information" without further specification to allow flexibility to the ultimate developers of MLGs.

Principle 3: The use of MLGs, while recommended, should be voluntary.

The CIOMS MLG EWG believes that MLG use should be voluntary. It was acknowledged that in some regulatory jurisdictions the use of MedDRA PTs in labeling is not mandatory; therefore, their voluntary use would need to be clearly stated for regulatory compliance purposes.

Some institutions/organizations may consider creating institution-specific custom PT groupings based on their needs. These should not be named MLGs. The CIOMS MLG EWG recommends using the MLG principles shown here as much as possible when creating such custom groupings to achieve similar standardization as for MLGs.

As a first step, the CIOMS MLG EWG provides principles for creation of MLGs and also recommends their use for creation of custom groupings.

Principle 4: The content of MLGs, when used publicly, should be specified in order to ensure transparency.

The CIOMS MLG EWG was generally in favor of transparency in the application of MLGs to product safety labeling. However, the concept of "transparency" could be limited to a simple acknowledgment in the product safety label when MLGs have been used, or it could refer to a need to specify all the PTs that have been grouped into an MLG, perhaps as a footnote (see Figure 1 in Section 2.4.1. MLG application for an illustration).

Some EWG members favored the option to display all terms that were grouped, stating which were reported as it would help readers to have a better understanding of what each MLG represents, while others felt that this option might be misleading as it could lead to placing PTs in labels because they exist in an MLG even if they had never occurred in association with the drug.

Concern was also raised that listing PTs of an MLG in a footnote might unnecessarily complicate the label, as the reason the PTs were grouped together in the first place was because of their high degree of similarity due to the defined medical concept.

The CIOMS MLG EWG believes that the presentation of MLG content is more geared towards providing clinically meaningful information. The EWG ultimately decided that this determination of the MLG presentation option would be best made after the creation of MLGs, as the degree of similarity between PTs in the MLG would be an important factor in the decision.

We believe that healthcare providers should be able to read product safety labels without the need for specialized training on label design. The information should be provided in a manner that is intuitive and clear.

Principle 5: The use of MLGs is intended to foster international harmonization in a manner consistent with existing regulatory frameworks.

The current regulatory guidances for AR presentation [4,5,6] recommend use of PT groupings when feasible to avoid diluting or obscuring the medical concept. It is anticipated that MLGs will serve mainly as a means of improving communication of safety information.

The CIOMS MLG EWG discussed the impact of the use of MLGs in the AR presentation of the product safety label on AE reporting requirements such as for assessment of expectedness of individual case safety reports (ICSRs). The CIOMS MLG EWG's intention is to work within the existing regulatory framework and reporting requirements, and this initiative will not have any impact on those requirements.

Labels will continue to be the result of negotiations between MAHs and regulators.

Principle 6: MLGs should be made easily accessible and widely available to ensure transparency and consistency.

The concept of "easily accessible and widely available" received significant attention by the CIOMS MLG EWG during the development of the principles. One question raised was whether this concept simply referred to publication of the principles, or whether the expectation would be that whoever ultimately developed the MLGs should ensure their broad dissemination. Concern was also raised as to whether such a principle might be beyond the scope of the CIOMS MLG EWG and more appropriately left to MLG developer(s).

Ultimately, a majority of the CIOMS MLG EWG believed that as these are intended to be guiding principles, aspirational statements would be appropriate regarding accessibility and availability. It was also noted that having the MLGs "easily accessible and widely available" was consistent with the principle of harmonization, which can only be achieved if the MLGs are readily accessible.

CHAPTER 3.

METHODOLOGY OF DEVELOPING MLGs

The Council for International Organization of Medical Sciences (CIOMS) Medical Dictionary for Regulatory Activities (MedDRA) Labeling Grouping (MLG) Expert Working Group (EWG) conducted a feasibility exercise by creating some examples of MLGs. This enabled the development of a methodology with conventions to help achieve consistency in MLG creation. The necessary steps were identified. The EWG postulates that providing a centrally pre-codified option of MLGs, as opposed to multiple institutions creating groupings (MLGs/custom groupings) using various standards, would maximize the utility of MLGs.

3.1 CIOMS MLG EWG experience with MLG examples

The Council for International Organization of Medical Sciences (CIOMS) Medical Dictionary for Regulatory Activities (MedDRA) Labeling Grouping (MLG) Expert Working Group (EWG) performed a feasibility exercise that created five MLG examples (Appendix 5). One of these is briefly described below, illustrating some of the determinations that will be important for MLG developer(s) to address.

Example: MLG *Abdominal pain*

Abdominal pain is a medical concept commonly reported in product safety labels (PSL). Multiple Preferred Terms (PTs) indicate a similar concept, such as PTs *Abdominal pain*, *Abdominal pain lower*, *Abdominal pain upper*, *Abdominal discomfort*, *Epigastric discomfort*, *Gastrointestinal pain*, and *Abdominal tenderness*. Based on the MLG principles, these additional PTs might be grouped into a single MLG called *Abdominal pain*.

But other PTs, such as *Rebound tenderness* and *Abdominal rigidity*, might not be grouped in such an MLG as they might be considered to represent events with greater severity. Similarly, a PT such as *Hepatic pain* or another organ pain might be considered more specific than the concept of abdominal pain and therefore not included in the MLG *Abdominal pain*.

(Continued)

(Example, continued)

Additionally, it should also be noted that abdominal pain can be poorly localized by patients, and the location of pain can change over time. Therefore, describing the location of the abdominal pain reported could potentially be less important than informing the healthcare provider about abdominal pain itself.
MLG=MedDRA Labeling Grouping

This is but one of many sets of determinations that will be important for MLG developer(s) to address.

Even though MLG definition is based on the medical definition of the medical/clinical adverse event (AE), there are different schools of thought behind this approach. Therefore, there is subjectivity in determining which PTs are appropriate for any given MLG. For example, the medical concept for an MLG *Headache* (see Appendix 5) can certainly be debated, leading to different conclusions. The intention is that the groupings contain only events which are near-synonymous (see the example of the MLG *Hyperkalemia* in Appendix 5).

Generally, the EWG found that is difficult to avoid subjectivity in the creation of a grouping. This is true whether the grouping is a Standardised MedDRA Query (SMQ) or an MLG. The CIOMS MLG EWG believes having a shared set of MLGs created centrally by a broad stakeholders' base and available to all MedDRA users would help to mitigate the subjectivity inherent if individual entities created MLGs. The EWG postulates that providing a pre-codified option of MLGs, as opposed to multiple entities creating MLGs using various standards, would maximize the utility of MLGs.

However, despite the benefits of having a common set of MLGs, it is beyond the CIOMS MLG EWG's remit to dictate that creation of MLGs will occur in a centralized fashion only. If needed, custom groupings can be created by individual stakeholders. Please note the name MLG should be utilized only when the PT groupings are created in a centralized fashion for international availability.

While creating such MLGs is not likely to be easy, the CIOMS MLG EWG considers that an open and deliberate process guided by the MLG principles will be a significant advance over the current situation of different institutions taking different approaches in product safety labeling when either creating their own PT groupings—or not creating PT groupings at all. For additional MLG examples and explanations see Appendix 5.

3.2 Methodology of creating MLGs

The CIOMS MLG EWG's exercise of creating MLG examples served to delineate the methodology for creating MLGs. Currently, different stakeholders have implemented various practices for grouping PTs in product safety labels (see Appendix 4). The CIOMS MLG EWG reviewed some of these practices to inform its efforts to achieve a

consensus approach. Based on this review, the CIOMS MLG EWG concluded that in order to achieve the desired consistency in PT groupings internationally, a set of conventions should be used during MLG and custom groupings creation.

3.2.1 MLG conventions

While the MLG principles listed in Section 2.5 Principles represent the values that provide the foundation for creating and using MLGs (such as transparency and consistency), the MLG conventions provide more specific and practical rules that should be followed during MLG creation. They are shown in **Box 2**.

Box 2. MLG conventions

1. MLGs are based on MedDRA terminology and are comprised of **MedDRA PTs**.
2. The medical **concept** of the MLG should be clearly defined.
   MLGs represent defined clinical conditions like diagnoses or specific clinical signs or symptoms or test results.
   If an MLG represents a diagnosis, PT content usually does not reflect signs or symptoms of the AR.
   Typically, an MLG does not include complications of an AR.
3. PTs that specify or imply different **etiologies** should not be combined in the same MLG (e.g., should not combine "hemolytic anemia" with "anemia").
4. PTs included should be **age-agnostic**.
   Specific age groups should not be included (e.g., "neonatal").
5. PTs that indicate different **clinical importance** should not be grouped together, e.g.
   PT *Abdominal pain* / PT *Abdominal rigidity,*
   PT *Migraine* / PT *Headache,*
   PT *Renal impairment* / PT *Renal failure,*
   PT *Haematoma* / PT *Subarachnoid haemorrhage,*
   PT *Angina pectoris* / PT *Myocardial infarction.*
6. The clinical concept reflected by the PTs should not be different from the **concept implied by the MLG name**.
7. PTs that indicate nonspecific laboratory results such as "abnormal" may be included in an MLG only if the **lab abnormality is clinically meaningful in only one direction**, e.g., PT *Blood glucose abnormal* should not be included in the MLG *Hyperglycemia* because both increase and decrease of blood glucose are clinically meaningful. However, PT *Blood creatinine abnormal* could be included in an MLG *Renal insufficiency* because decreased blood creatinine is generally not clinically meaningful.
8. MLGs, when created, should be in the most **current MedDRA version**.
9. The MedDRA version of the MLG and the **MedDRA version of the respective data** should always be identical.

AR=adverse reaction; MedDRA=Medical Dictionary for Regulatory Activities; MLG=MedDRA Labeling Grouping; PT=Preferred Term

3.2.2 MLG design features

MLGs should be designed to provide precise information about a medical event or condition, while being user friendly and promoting transparency. Three critical elements are needed for this purpose: the MLG name, its content, and documentation of how it was created (**Box 3**).

Box 3. Overview of MLG design features

MLG name: An easy identifier (e.g., MLG *Headache*).

MLG content: A list of MedDRA PTs conveying the specific clinical representations of the AR. The content guarantees the correct standardized conversion and usage of the MedDRA PTs for the respective medical event.

Documentation of MLG creation: Additional information to provide full transparency: Clearly stated inclusion and exclusion criteria (e.g., in the MLG *Headache*, exclusion of PTs *Drug withdrawal headache*, *Exertional headache*, *Basilar migraine*, *Familial hemiplegic migraine*). This allows the end user of the product safety label to get the full picture of PTs being chosen for inclusion or exclusion, as there are many borderline PTs available where the argumentation could go into one or the other direction.

AR=adverse reaction; MedDRA=Medical Dictionary for Regulatory Activities; MLG=MedDRA Labeling Grouping; PT=Preferred Term

Some examples of MLGs proposed by the Expert Working Group are shown in Appendix 5.

3.2.3 Steps in creating MLGs

The CIOMS MLG EWG recommends the following steps in creating MLGs.

A: Define the medical concept of an AR/MLG

MLG creation is initiated based on the medical concept that is to be presented in the product safety label. Once the medical concept is clearly identified and named, then it is important to define the medical concept in detail, so that it provides guidance in making decisions for inclusion or exclusion of each relevant PT.

- An MLG can represent a medical diagnosis or describe specific clinical signs or symptoms or test results.

Example: MLG *Abdominal pain*

Abdominal pain is a medical concept commonly reported in product safety labels. Multiple PTs indicate a similar concept, such as PTs *Abdominal pain*, *Abdominal pain lower*, *Abdominal pain upper*, *Abdominal discomfort*, *Epigastric discomfort*, *Gastrointestinal pain*, and *Abdominal tenderness*. Based on the MLG principles, these additional PTs might be grouped into a single MLG called *Abdominal pain*.

MLG=MedDRA Labeling Grouping; PT=Preferred Term

- An MLG will not group all potential signs and symptoms under a medical diagnosis as this would be too heterogeneous. For example, a grouping to evaluate for a potential signal of upper respiratory tract infections could include PTs *Acute sinusitis*, *Chronic sinusitis*, *Nasopharyngitis*, *Pharyngitis*, *Pharyngotonsillitis*, *Sinusitis* and *Upper respiratory tract infection*. For an MLG, however, the event terms are too disparate to be considered for inclusion. Further MLGs of individual signs and symptoms of upper respiratory tract infections might be necessary.

B: Select a name for the MLG

- The name of the MLG should reflect the medical concept as precisely as possible (see Step A above).
- The name of an MLG should provide an accurate characterization of an undesirable effect. This MLG name can be phrased in a descriptive language, or can represent a MedDRA term, i.e., a High Level Group Term (HLGT), High Level Term (HLT) or PT.[13]

C: Document selection criteria and version history

During the selection of the PTs that match the named medical concept, it is important to document the reasons or rationale for inclusion of a PT into the MLG. This rationale can be captured as “Inclusion criteria”.

Similarly, the rationale for excluding a particular PT from the named medical concept of MLG, i.e., “Exclusion criteria”, needs to be captured.

- A compilation of specific inclusion and exclusion criteria should be maintained and followed to ensure consistency in MLG creation.
- The PTs included in an MLG should be represented in the most current version of MedDRA. With each versioning of MedDRA (two per year), MLGs should be checked and may need to be updated in case the included PTs have become non-current or new PTs might be of interest. As good practice, the updates with each versioning or any interim changes should be captured in the version history described in the documentation accompanying the MLG.

D: Select PTs that are (near) synonymous with the medical concept

Near-synonymous PTs that match the medical concept of the MLG are selected based on the following considerations:

- The PTs selected for the content of an MLG represent the AR.
- PTs representing specific AR information for similar medical concepts are linked to the same MLG (e.g., MLG *Abdominal pain*, see a proposed example in Appendix 5)
- MLGs represent defined medical concepts of a diagnosis of a clinical condition, or its specific clinical signs or symptoms, or the test results for that clinical condition (see Step A above). Additionally, for some ARs, similar PTs describing either the clinical diagnosis or the laboratory results such as PTs *Hyperkalaemia* and *Blood potassium increased*, can be grouped together in an MLG.
- If an MLG represents a diagnosis, PT content usually does not reflect signs or symptoms or test results of the AR.
    - Example: MLG of *Pancreatitis* does not include the PTs representing signs or symptoms of pancreatitis such as PT *Nausea*, PT *Amylase increased* etc.
- Typically, an MLG does not include complications of an AR.

The number of PTs linked to one MLG ranges from two to many.

Due to the homogeneity of the near-synonymous PTs in a MLG, it is anticipated that one PT will be linked to one MLG only. This will also be helpful for frequency calculations.

The above conventions and steps for MLG creation are proposed as a general guidance. The CIOMS MLG EWG recommends that the future creators of MLGs should revisit the definition of medical concepts to ensure that the state-of-the-art MLG medical concept definition and the PT content in the MLG are appropriately communicating the safety information in product safety labeling.

CHAPTER 4.

PRACTICAL CONSIDERATIONS

A number of practical issues must be addressed in order to achieve successful implementation of Medical Dictionary for Regulatory Activities (MedDRA) Labeling Groupings (MLGs). These include determining whether MLGs should be owned and maintained by multiple entities or a single authority, deciding how to update MLGs as both MedDRA and medical practice evolve, and determining how to characterize MLGs in product safety labeling. For instance, when representing an adverse reaction in a label of a drug, should all Preferred Terms (PTs) in an MLG be stated in the label itself, or only the ones that were determined to be caused by that drug? And if the individual PTs are placed in the label, would providing them as a footnote in a table be sufficient? In addition, as custom PT groupings are already being created by stakeholders, the continued creation and use of such groupings should be considered. This chapter will discuss the practical implications associated with the development and use of MLGs in greater detail.

The main purposes of drug safety labeling are to provide information to healthcare providers and patients regarding the adverse reactions that have been identified with a product and information regarding how to mitigate those reactions. Therefore, to the extent that the individual terms within an MLG qualify as nearly synonymous, placing those terms in the label was viewed by some Expert Working Group (EWG) members as adding little meaning or insight into the safety of the product, and therefore might only clutter the label and potentially impede understanding. Other EWG members felt that specifying these nearly synonymous terms in the label would provide an appropriate level of transparency regarding the exact composition of the groupings being used.

4.1 MLG ownership

One of the primary questions that needs to be addressed when considering Medical Dictionary for Regulatory Activities (MedDRA) Labeling Grouping (MLG) implementation is who should be primarily responsible for MLG ownership, i.e., creation, dissemination, and maintenance of MLGs.

As one of the key goals of MLGs is to achieve consistency in how Preferred Terms (PTs) are combined in product safety labeling, it is likely preferable to have a single entity maintain MLG ownership. Alternatively, if MLGs were owned and maintained by different organizations, the group feels that they would inevitably be subject to variability, hence defeating the primary objective of this initiative, e.g., to promote

consistency in the representation of an adverse drug reaction (ADR) within the label of different drugs.

Considering that many stakeholders have an interest in medical product safety labeling, it would be appropriate to include in the entity that owns and maintains MLGs, as a minimum, representatives from pharmaceutical industry and regulatory authorities. Time-limited periods of service could be provided by stakeholder representatives in support of the MLG ownership role. This would help to ensure familiarity with MLGs across a wide range of groups, encourage input from multiple stakeholders, and help to prevent the MLG work from becoming an excessive drain on resources for any one group.

Lastly, the use of an existing group with expertise in the interpretation and communication of adverse reactions generally, and MedDRA terminology in particular, would likely be more efficient than creating an entirely new organization. Examples of such organizations include the MedDRA Maintenance and Support Services Organization (MSSO) or potentially another component of the International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), or the World Health Organization (WHO).

Whichever group ultimately owns or coordinates ownership of MLGs, an additional critical aspect of ownership would be the development of a charter to clearly indicate the mission and procedures to be used by the organization, which would provide transparency and help to minimize drift from the original mission.

4.2 MLG maintenance

MedDRA versioning

As MLGs will be based on MedDRA PTs, they should reflect any changes in MedDRA. MLG maintenance would therefore require ongoing alignment with MedDRA versioning. MedDRA is revised twice a year with e.g. addition or deletion of terms as medical knowledge grows, resulting in the need for changes to existing terms or improvements in the structure of MedDRA.

When MLGs would be used for presentation of adverse drug reactions in product safety labeling (PSL), the impact of MedDRA changes on the PTs in PSL with each MedDRA versioning would need to be assessed.

In addition, changes to MLGs could be triggered by requests submitted by MLG users. The governance for MLG maintenance would be linked to ownership.

Standardized set of MLGs

The Council for International Organization of Medical Sciences (CIOMS) MLG Expert Working Group (EWG) has published an open-access article formulating principles that are useful both for MLGs as a pre-codified option to all MedDRA users and for custom PT groupings created by individual marketing authorisation holders (MAHs).[15] The CIOMS MLG EWG believes that MLGs would have the most utility and consistency if they were available as a pre-codified option to all MedDRA users.

This would be more efficient than having MAHs create and maintain their own listings and would promote consistency across safety labels. The regular maintenance of a global standardized set of MLGs available to all MedDRA users would take considerable resources, which would need to be identified. However, the EWG believes that the benefits would be worth the effort.

4.3 Regulatory labeling requirements

The consensus recommendations provided in this report are voluntary and would need to be applied to product safety labels in a manner that is consistent with existing regulatory frameworks. Labeling requirements are described in specific guidance documents.[4,5,6] These regulatory guidance texts all present very similar wording that "Reactions that are reported under different terms but represent the same phenomenon (e.g., sedation, somnolence, drowsiness) should ordinarily be grouped together as a single adverse reaction to avoid diluting or obscuring the true effect."[5] Details for jurisdictions of Europe, the United States and Canada are outlined below for reference. For labeling purposes, it is generally recommended that adverse reactions (ARs) are represented as either individual or grouped terms.[4,5,6]

Europe

The European Union (EU) Guideline on summary of product characteristics (SmPC) [5] provides advice on the principles of presenting information in the Section 4.8 Undesirable effects:

> "This section should include all adverse reactions from clinical trials, post-authorisation safety studies and spontaneous reporting for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event (AE) is at least a reasonable possibility, based for example on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual case reports."[5]

The guideline provides examples of a pragmatic approach to the location of terms in order to make the identification of adverse reactions simpler and clinically appropriate for the reader:

> "Within each MedDRA SOC, adverse reactions should be classified according to their frequency of occurrence. Prior to estimating frequency of occurrence of adverse events from systematic studies (clinical trials or other sources), appropriate levels of the MedDRA hierarchy should be used in order to group together clinically related conditions in a meaningful way. For example, if 'postural dizziness', 'exertional dizziness' and 'unspecified dizziness' were each reported by 2% of patients, this might reasonably be represented in the SmPC as 'Dizziness' occurring in 6% of patients (assuming that only one report of dizziness applied to each patient). It may also be appropriate to use ad hoc groupings of terms, or to adapt MedDRA group terms if the

established MedDRA group terms are not completely suitable, e.g. reports of adverse reactions represented as 'Diarrhoea', 'Diarrhoea aggravated', 'Loose stools', 'Stools watery', 'Intestinal hypermotility' or other might all reasonably be represented as the single term 'Diarrhoea' in the interest of making the SmPC relevant and comprehensible to patients. The total number of those cases should be used to estimate the frequency of diarrhoea."[5]

United States

In the Food and Drug Administration (FDA) Guidance, Section on General Principles for Presenting Adverse Reactions Data in a Table or List, similar instructions are provided for classifying AR:[4]

> "Adverse reactions should be classified using meaningful and specific terms that best communicate the nature and significance of the reaction. There should ordinarily be a common classification scheme across all studies in the safety database. Events that are reported under different terms in the database, but that represent the same phenomenon (e.g., sedation, somnolence, drowsiness) should ordinarily be grouped together as a single adverse reaction to avoid diluting or obscuring the true effect. Similarly, adverse events reported in more than one body system that appear to represent a common pathophysiologic event should be grouped together to better characterize the reaction."

Canada

The Health Canada Guidance on Product Monograph [6] recommends as well that AR representing the same phenomenon or disease pathophysiology in more than one MedDRA body system should be grouped together:

> "MedDRA (www.meddra.org) should be used as the preferred terminology to describe adverse reactions. This will be at the Preferred Term (PT) Level, although there may be instances where the use of a Lowest Level Term (LLT) or a High-Level Term (HLT) may be appropriate. Indicate the version of MedDRA used for the data described.
>
> Adverse reactions that are reported under different terms in the database, but that represent the same phenomenon (e.g., sedation, somnolence, drowsiness) or disease pathophysiology in more than one body system (e.g., congestive heart failure, nocturnal dyspnea, angina, pedal edema) should be grouped together as a single adverse reaction to avoid diluting or obscuring the true effect."

The development of these documents by regulatory authorities usually includes the pharmaceutical industry and other stakeholder input in a public consultation process.

EWG recommendation

The CIOMS EWG agreed that the MLG initiative should not result in any alteration of labeling regulations or global reporting requirements.[15]

4.4 Labeling considerations

4.4.1 Implementation of MLGs in product safety labels

The report of CIOMS Working Groups III and IV "Guidelines for preparing Core Clinical-Safety Information on Drugs",[17] issued in 1999, already discussed the need of improving the drug safety information.

As part of general principles of good safety information governing the overall content of company core safety information, the CIOMS Working Group III stated that "the terms used should be specific and medically informative" and "the use of modifiers or adjectives should be avoided unless they add useful important information."

The presentation and granularity of ARs listed in labels may differ depending on the age of the product. Differences might be due to the standardized medical terminology used at the time of product marketing authorisation submission, especially for older products, and also to the MedDRA version and regulatory guidance in place at the time of subsequent addition of ARs.

The use of MLGs in labeling is more amenable to new product safety labels. Their use in existing product safety labels raises the question if grouping of ARs in MLGs would potentially be applicable to new ARs added to the product safety information only or extended to the ARs already listed. This option might require specific supporting documentation to be provided in the submission of such a change by a pharmaceutical company to regulatory authorities. So, for existing product safety label updates, it should be discussed on a case-by-case basis.

Opportunities for updates

The EU Guideline on SmPC [5] states that the content of the Undesirable effects section should be justified in the Clinical Overview of the marketing authorisation application based upon a best-evidence assessment of all observed adverse events and all facts relevant to the assessment of causality, severity, and frequency. This section should be regularly reviewed and, if necessary, updated with the aim to ensure appropriate information to health care professionals on the safety profile of the product. In addition, the whole section could be revised at the renewal of the marketing authorisation, where the safety profile of most products is likely to be well established, and thereafter at each subsequent periodic safety update report (PSUR).[18] Therefore, opportunities exist for an update of the presentation of the safety information using MLG in the product safety labeling.

CIOMS MLG EWG recommen-dation

The CIOMS MLG EWG discussed how to present adverse reaction frequency information in labels when they are updated with new safety data to which MLGs have been applied. The group agreed that this would be done on a case-by-case basis, focusing on new information added to the product safety label and in line with

the applicable regulatory framework. The CIOMS MLG EWG does not anticipate the need to routinely apply MLGs to all of the existing safety information already contained in product safety labels.

4.4.2 Specifying the content of MLGs

The EWG's discussions on principles of using MLGs in product safety labels involved critical issues such as labeling transparency, regulatory standards, and informativeness (see Section 2.5 Principles). Some members prioritized transparency, and therefore felt that all terms within the MLG should be specified so that the reader fully understands what the MLG is intended to represent, while others prioritized effective communication and thought that only terms within the MLG that qualified as ARs should be listed, as routinely providing all terms could result in unnecessarily cluttered labels and undermine the goal of MLGs, i.e., improving the communication of safety issues. There was also concern that routinely listing in a label all terms within an MLG could result in adding terms to the label that did not qualify as ARs, and therefore would not be consistent with national regulatory standards for AR labeling. Some members also noted that the requirement for PTs to be near-synonymous (e.g., *Abdominal pain* and *Abdominal discomfort*) in order to be included in an MLG would likely mean that their inclusion in labeling would not add useful additional information.

Two options for presenting the content of MLGs for an AR in the adverse reactions section of the product safety label are illustrated below.

In Option 1, only those terms within an MLG are shown for which adverse events have been reported with the product.

In Option 2, all terms included in the MLG are displayed, and stating which ones were reported. (See also Appendix 5 for examples of MLGs for *Hyperkalemia* and *Abdominal pain.*)

In either case, the label should clearly indicate when an AR is represented in a label through an MLG and the incidence rate for that AR has been calculated as a composite of the incidence rates of the various PTs that belong to that MLG. This is important to avoid inappropriate comparisons with other drugs where the incidence rate for the same ADR may have been calculated based on a single PT.

Figure 2. Specifying the content of MLGs: Example of two options

Option 1
Footnotes include only terms for which adverse events were reported

Summary of product characteristics (SmPC)
Product X

4.8 Frequency and Adverse reactions:

SOC *Metabolism and nutrition disorders*

Common: *Hyperkalemia*

SOC *Gastrointestinal disorders*

Very common: *Nausea*
Common: *Abdominal pain***

** *Abdominal pain* includes the **reported terms *Abdominal pain*, *Abdominal pain upper*** and ***Gastrointestinal pain***.

Option 2
Footnotes include all terms that were grouped, stating which ones were reported

Summary of product characteristics (SmPC)
Product X

4.8 Frequency and Adverse reactions:

SOC *Metabolism and nutrition disorders*

Common: *Hyperkalemia**

SOC *Gastrointestinal disorders*

Very common: *Nausea*
Common: *Abdominal pain***

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* *Hyperkalemia* includes the terms *Blood potassium increased* and *Hyperkalaemia.* Only the term ***Hyperkalaemia*** was reported.

** *Abdominal pain* includes terms *Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Epigastric discomfort,* and *Gastrointestinal pain.* Only the terms ***Abdominal pain***, ***Abdominal pain upper*** and ***Gastrointestinal pain*** **have been reported.**

CIOMS MLG EWG conclusion

Ultimately, the EWG agreed on the importance of thoughtfully weighing the issues of transparency and readability and felt that the final decision on how to apply the recommended MLG Principle 4 (see Section 2.5 Principles) should be informed by additional experience with MLG creation and implementation.

4.4.3 Custom groupings beyond MLGs

The CIOMS MLG EWG proposes to use a high threshold for similarity when grouping PTs into MLGs. This should result in MLGs that are useful regardless of the circumstances of any particular medical intervention or therapeutic indication. However, the CIOMS MLG EWG also acknowledges that depending on the circumstances of a development program, additional custom groupings of less similar PTs may also be appropriate.

Two examples of custom groupings are shown below.

Example 1

- The PTs *Cardiac failure congestive* and *Pulmonary oedema* would be unlikely to qualify for grouping based on the conventions for MLGs proposed in this report, as either event can occur in the absence of the other. However, trial investigators

might use either term to describe the same heart failure event, so combining them may be needed to appropriately describe a safety concern in a product safety label.

Example 2

- A custom PT grouping that could be useful in many cases, but not meet our proposed standards for MLGs, might contain PTs describing "seizures" and "convulsions". While these terms are often used interchangeably by both lay persons and healthcare professionals, "convulsion" indicates an involuntary shaking motion of the extremities and has a number of causes, such as hypoglycemia and hypoxia. However, a seizure is specifically caused by an abnormal electrical discharge within the brain and may or may not be associated with any convulsive type movements.
  As seizures and convulsions can each occur in the absence of the other, they would not likely be considered of sufficient similarity to group within an MLG. However, in light of the interchangeable use of these terms, unless the investigators were neurologists or there were other special circumstances, these terms would likely be grouped together in product safety labeling.

CIOMS MLG EWG recommen-dation

Similar to MLGs, custom groupings should be clearly described to minimize confusion and maximize transparency. Of note, as stated in MLG Principle 3 (see Section 2.5 Principles), the name "MLG" should be utilized only when the PT groupings meeting the criteria for MLGs are created in a centralized fashion for international availability. The name "MLG" should not be used for custom groupings.

CHAPTER 5.

CONCLUSIONS

The Council for International Organization of Medical Sciences (CIOMS) Medical Dictionary for Regulatory Activities (MedDRA) Labeling Grouping (MLG) Expert Working Group (EWG) believes that MLGs will serve mainly as a means of improving communication of safety information in product safety labeling and has defined MLGs, identified their scope and applications, and recommended principles for their development and use. In addition, the CIOMS MLG EWG also identified a stepwise methodology and MLG conventions to support the creation of MLGs.

Although the creation and maintenance of a centralized repository of MLGs will require significant and ongoing resources. The CIOMS MLG EWG considers that the overall impact on institutions will be less than if individual stakeholders had to create and maintain individual custom groupings. MLGs will need to be communicated, maintained and updated based on changes in MedDRA terminology and medical practice. For this reason, we recommend using an international organization with terminology expertise, which would consist of representatives from various stakeholders as described in Section 4.1 MLG ownership. However, the decision on the future course of action regarding the creation of centralized MLGs is beyond the remit of this CIOMS MLG EWG.

Secondly, the CIOMS MLG EWG acknowledges that the consistent application of MLGs across labels can be a challenge, particularly given that their use would be voluntary. The CIOMS MLG EWG believes that consistency across product safety labels (PSLs) would be promoted if MLGs were centrally created following the proposed set of principles and were made available as pre-codified groupings for all MedDRA users.

While MLGs are not expected to be a panacea for all challenges in producing clear and consistent product safety labeling, they are deemed to have utility where there is a need to present safety information with a variety of near-synonymous Preferred Terms (PTs) conveying a medical concept. The EWG intention is to work within the existing regulatory framework and reporting requirements, on which the CIOMS MLG EWG initiative will have no impact.

Important issues need to be addressed prior to the successful implementation of MLGs, such as MLG ownership and maintenance, determining how to present MLGs in product safety labels, and how to display custom PT groupings created by pharmaceutical companies and other stakeholders. While the implementation of MLGs poses some significant challenges, we believe that they are surmountable and have provided suggested approaches and considerations in this report.

Conclusion

The CIOMS MLG EWG believes that the current primary scope and focus of MLGs is on product safety labeling. The EWG acknowledges that MLGs may have limited potential application beyond product safety labeling, such as for signal detection and other evaluation of clinical study safety data; however, these applications are not currently the objective or remit of the CIOMS MLG EWG.

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APPENDIX 1.

GLOSSARY

This glossary contains key terms used in this report. Most of these terms have been in common use for some time but, despite various international consensus initiatives, certain terms in the glossary do not have universally accepted definitions. The glossary is not intended to be comprehensive but rather is intended to provide relevant terms and associated definitions as used in this report.

Adverse event (AE)

Synonyms: Adverse experience (U.S.), Undesirable event.

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

- ICH Harmonised Guideline. Integrated Addendum to ICH E6(R1): Guideline for good clinical practice. E6(R2). Geneva: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH); 2016. Available at: https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

Adverse reaction (AR)

Synonyms: Adverse drug reaction (ADR), Undesirable effect.

See also: Summary of product characteristics – SmPC section 4.8 titled "Undesirable effects"

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: A noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

- ICH Harmonised Guideline. Integrated Addendum to ICH E6(R1): Guideline for good clinical practice. E6(R2). Geneva: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH); 2016. Available at: https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

Company core data sheet (CCDS)

A document prepared by the marketing authorisation holder (MAH) containing, in addition to safety information, material related to indications, dosing, pharmacology and other information concerning the product.

- ICH Harmonised Tripartite Guideline. Periodic Benefit-Risk Evaluation Report (PBRER). E2C(R2). 17 December 2012. Available at: https://database.ich.org/sites/default/files/E2C_R2_Guideline.pdf

Custom grouping

Custom groupings are groupings of PTs of similar clinical concepts that are created by individual stakeholders when MLGs do not exist or do not meet their need. They are MLG like PT groupings. CIOMS MLG EWG would encourage use of the MLG Principles and MLG Conventions to help guide the creation of custom groupings, as the custom grouping principles are not transparent and are not standardized.

See also: MedDRA Labeling Grouping (MLG)

Healthcare professional (HCP)

Synonym: Health professional.

A person who is qualified and trained to provide healthcare to humans. This includes doctors, physician assistants in some jurisdictions, nurses, dentists, pharmacists, and midwives. For the purposes of reporting suspected adverse reactions, the definition of healthcare professional additionally includes coroners and medically qualified persons otherwise specified by local regulations.

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High Level Group Term (HLGT)

See: Medical Dictionary for Regulatory Activities (MedDRA) hierarchy – High Level Group Term (HLGT)

High Level Term (HLT)

See: Medical Dictionary for Regulatory Activities (MedDRA) hierarchy – High Level Term (HLT)

Investigator's brochure (IB)

A compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human participants.

- ICH Harmonised Guideline. Integrated Addendum to ICH E6(R1): Guideline for good clinical practice. E6(R2). Geneva: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH); 2016. Available at: https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf.
- Note: Also see Appendix A. Investigator's Brochure, in the draft revised ICH guideline E6(R3) referenced below; the definition itself has remained unchanged from the ICH E6(R2) guideline.

ICH Harmonised Guideline. Good Clinical Practice (GCP). E6(R3). Draft version, endorsed on 19 May 2023. Geneva: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH); 2023. Available at: https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf

Individual case safety report (ICSR)

The complete information provided by a reporter at a certain point in time to describe an event or incident of interest. The report can include information about a case involving one subject or a group of subjects. [27953 Human Pharmaceutical Reporting].

- ICH E2B Implementation Working Group. Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs). E2B(R3). Data Elements and Message Specification. Version 5.02, 10 November 2016. Available at: https://admin.ich.org/sites/default/files/inline-files/E2B%28R3%29_IG_Complete_Package_v1_09.zip, filename: 1_ICH_ICSR_Implementation_Guide_v5_02.pdf
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Integrated summary of safety (ISS)

Integrated summary of safety is a document that is included in the submission of new drug applications in some jurisdictions such as the United States. This document contains detailed integrated analyses of all relevant data from the clinical study reports on the drug.

- U.S. FDA. Guidance for Industry. Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document. April 2009. Available at: https://www.fda.gov/media/75783/download

Labeling

The definition of this term varies by regulatory jurisdiction. In EU legislation the term refers to the information given on the immediate or outer packaging. In other medicinal product legislation, including that of the U.S., labeling may refer more broadly to the approved content of product information (see Product information).

- EU Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 4) EMA/876333/201 (Rev 4, October 2017). Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-annex-i-definitions-rev-4_en.pdf
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Lowest Level Term (LLT)

See: Medical Dictionary for Regulatory Activities (MedDRA) hierarchy – Lowest Level Term (LLT)

Marketing authorisation holder (MAH)

The company or other legal entity that has the authorisation to market a medicine in one, several or all European Union Member States.

- European Medicines Agency, About us, Glossary of regulatory terms: "Marketing authorisation holder". Available at: https://www.ema.europa.eu/en/glossary/marketing-authorisation-holder, last accessed 4 March 2024.

Medical Dictionary for Regulatory Activities (MedDRA) hierarchy

MedDRA terminology is the international medical terminology developed under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The structure of MedDRA is hierarchical. There are five levels to the MedDRA hierarchy, arranged from very specific to very general.

- Lowest Level Terms (LLTs), see Lowest Level Term
- Preferred Terms (PTs), see Preferred Term
- High Level Terms (HLTs), see High Level Term
- High Level Group Terms (HLGTs), see High Level Group Term
- System Organ Classes (SOC), see System Organ Class

- MedDRA hierarchy. Available at: https://www.meddra.org/how-to-use/basics/hierarchy, accessed 10 November 2022.

System Organ Class (SOC)

The highest (i.e., most general) level within the MedDRA term hierarchy. SOCs are groupings of High Level Group Terms (HLGTs) that are related to each other by etiology (e.g., *Infections and infestations*), manifestation site (e.g., *Gastrointestinal disorders*) or purpose (e.g., *Surgical, and medical procedures*). In addition, there is an SOC for issues pertaining to products and one for issues pertaining to social circumstances.

- MedDRA hierarchy. Available at: https://www.meddra.org/how-to-use/basics/hierarchy, accessed 10 November 2022.

High Level Group Term (HLGT)

The second-highest level of the MedDRA hierarchy. HLLGTs are groupings of HLTs that are related to each other by anatomy, pathology, physiology, etiology, or function.

- MedDRA hierarchy. Available at: https://www.meddra.org/how-to-use/basics/hierarchy, accessed 10 November 2022.

High Level Term (HLT)

The third-highest level of the MedDRA hierarchy. HLTs are groupings of PTs that are related to each other by anatomy, pathology, physiology, etiology, or function.

- MedDRA hierarchy. Available at: https://www.meddra.org/how-to-use/basics/hierarchy, accessed 10 November 2022.

Preferred Term (PT)

The second-lowest level in the MedDRA hierarchy. Each PT is a distinct descriptor (single medical concept) for a symptom, sign, disease diagnosis, therapeutic indication, investigation, surgical or medical procedure, and medical social or family history characteristic. Each PT has at least one LLT (itself) as well as synonyms and lexical variants (e.g., abbreviations, different word order).

- MedDRA hierarchy. Available at: https://www.meddra.org/how-to-use/basics/hierarchy, accessed 10 November 2022.

Lowest Level Term (LLT)

The most specific level term in the MedDRA hierarchy. There are more than 80,000 LLTs which parallel how information is communicated. These LLTs reflect how an observation might be reported in practice. This level directly supports assigning MedDRA terms within a user database. Each LLT is linked to only one PT.

- MedDRA hierarchy. Available at: https://www.meddra.org/how-to-use/basics/hierarchy, accessed 10 November 2022.

MedDRA Labelling Entity (MLE)

Former naming idea for MedDRA Labelling Grouping (MLG).

From: MedDRA Management Board meeting dated May 2005 (discussion of the BRP3 recommendations on MedDRA and product labeling, see https://www.meddra.org/blue-ribbon-panels):

- Document "BRP recommendation and MedDRA Board Outcome". Available at: https://admin.meddra.org/sites/default/files/page/documents_insert/brp3.pdf, accessed 21 January 2022.
- Presentation "MedDRA and product labelling: Best practices". Available at: https://admin.meddra.org/sites/default/files/page/documents_insert/8401-200_brp_3_presentation-for_website12apr05.pdf, accessed 21 January 2022

MedDRA Labeling Grouping (MLG)

MLGs are groupings of near-synonymous MedDRA Preferred Terms (PTs) that convey substantially similar clinical concepts.

- Große-Michaelis I, Proestel S, Rao RM, et al. MedDRA Labeling Groupings to Improve Safety Communication in Product Labels. *Ther Innov Regul Sci*. 2023;57(1):1-6. https://doi.org/10.1007/s43441-022-00393-1

Package leaflet (PL), also called "Patient information leaflet"

A leaflet containing information for the user which accompanies the medicinal product.

- EU Guideline on good pharmacovigilance practices (GVP) – Annex I (Rev 4) EMA/876333/2011 Rev 4. 9 October 2017. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-annex-i-definitions-rev-4_en.pdf

Pharmacovigilance

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

- WHO. Pharmacovigilance strategies [webpage]. Available at: https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance/guidance/strategies, accessed 31 January 2024.

Preferred Term (PT)

See: MedDRA hierarchy, Preferred term (PT)

Product information (PI)

Documents proposed by marketing authorisation holders/applicants, amended if required and agreed by regulatory authorities, which provide information to prescribers/healthcare professionals or patients on the appropriate and safe use of a medicinal product. As such the product information constitutes the main tool used for routine risk minimisation. For examples regarding terminology used in different regulatory jurisdictions see Fig. 1.1 in Chapter I of the CIOMS IX report. The EU labeling on the immediate or outer packaging is a part of product information.

Figure 1.1 from CIOMS IX report:
Examples of nomenclature for components of product information

PRODUCT INFORMATION (PI)	
Product information for healthcare professionals* Summary of product characteristics (SmPC, also sometimes SPC) Data sheet Drug data sheet Safety data sheet Package insert Product information	Product information for patients Package leaflet Patient information leaflet Patient product information Patient information Consumer medicines information Patient instructions for use Patient package insert
Labeling on inner and outer packaging	

- Practical Approaches to Risk Minimisation for Medicinal Products. Report of CIOMS Working Group IX. Geneva: Council for International Organizations of Medical Sciences (CIOMS); 2014. Available at: https://cioms.ch/publications/product/practical-approaches-to-risk-minimisation-for-medicinal-products-report-of-cioms-working-group-ix/

Product safety labeling (PSL)

See Labeling and Product information

Signal

Information on a new or known side effect that may be caused by a medicine and is typically generated from more than a single report of a suspected side effect. It is important to note that a signal does not indicate a direct causal relationship between a side effect and a medicine, but is essentially only a hypothesis that, together with data and arguments, justifies the need for further assessment.

- Uppsala Monitoring Centre (UMC). What is a signal? Available at: https://who-umc.org/signal-work/what-is-a-signal/, last accessed 14 March 2024.

Summary of product characteristics (SmPC)

In the European Union, a document describing the properties and the officially approved conditions of use of a medicine. Summaries of product characteristics form the basis of information for healthcare professionals on how to use the medicine safely and effectively.

- European Commission. A guideline on summary of product characteristics (SmPC). September 2009. Available at: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf

SmPC section 4.8 titled "Undesirable effects"

(Extract from the above reference, page 15:)

4.8 Undesirable effects

This section should include all adverse reactions from clinical trials, post-authorisation safety studies and spontaneous reporting for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual case reports. (…)

See also: Adverse reaction (AR), synonym of "Undesirable effect"

Standardised MedDRA Query (SMQ)

See also: MedDRA hierarchy, Preferred Term (PT)

Standardised MedDRA Queries (SMQs) are groupings of MedDRA terms, ordinarily at the Preferred Term (PT) level that relate to a defined medical condition or area of interest. SMQs are intended to aid in the identification and retrieval of potentially relevant individual case safety reports. The included terms may relate to signs, symptoms, diagnoses, syndromes, physical findings, laboratory and other physiologic test data, etc. The only Lowest Level Terms (LLTs) represented in an SMQ are those that link to a PT used in the SMQ; all others are excluded.

- Introductory Guide for Standardised MedDRA Queries (SMQs). Version 24.1. September 2021. Available at: https://admin.meddra.org/sites/default/files/guidance/file/000595_SMQ_intguide_24_1.pdf)

System Organ Class (SOC)

See: MedDRA hierarchy – System Organ Class (SOC)

APPENDIX 2.

CIOMS WORKING GROUP MEMBERSHIP, MEETINGS AND ACTIVITIES

Members, advisors and observers who contributed to the Expert Working Group (EWG) on MedDRA Labeling Groupings (MLG) (2019-2023)

Name	Organization
Silvia BADER-WEDER	Roche
Sonja BRAJOVIC	U.S. Food and Drug Administration (FDA)
Andrea BROWN	Gilead
Brian DILLMAN †	Eli Lilly
Diane FARKAS	Sanofi Aventis
William GREGORY	Pfizer
Ilona GROßE-MICHAELIS	Bayer/ retired
Tomohiko HARA	Pharmaceuticals and Medical Devices Agency (PMDA), Japan
Tomohiro HATTA	Pharmaceuticals and Medical Devices Agency (PMDA), Japan
Judith JONES †	Pharmalex
Kanae KOBAYASHI	Pharmaceuticals and Medical Devices Agency (PMDA), Japan
Sue LE ROUX	CIOMS
Lynn MACDONALD	Health Canada/ retired
Christiane MICHEL	Novartis
Yutaka NAGAO	MedDRA Japanese Maintenance Organization (JMO)
Tomoko NARITA	MedDRA Japanese Maintenance Organization (JMO)

(continued)

Name	Organization
Members, advisors and observers who contributed to the MLG EWG (continued)	
Norbert PAESCHKE	Federal Institute for Drugs and Medical Devices (BfArM), Germany
Catherine PENFORNIS	Sanofi Aventis
Scott PROESTEL	U.S. Food and Drug Administration (FDA)
Lembit RÄGO	CIOMS
Radhika RAO	Abbvie
Jill ROBINSON	Amgen
Aniello SANTORO	European Medicines Agency (EMA)
Debbra SCOTTI	Pfizer
Alima TAPSOBA	Health Canada
Laurence TRINH-LA	Gilead
Omi WATANABE	Pharmaceuticals and Medical Devices Agency (PMDA), Japan

CIOMS MLG Expert Working Group meetings

Meeting	Date	Location	Venue
1	3–4 April 2019	Geneva, Switzerland	Domaine des Penthes, Pregny, Geneva, Switzerland
2	25–26 September 2019	Geneva, Switzerland	CIOMS offices, Le Grand-Saconnex, Geneva, Switzerland
3	25–26 August 2020	Virtual	Zoom
4	4 March 2021	Virtual	Zoom
5	8 December 2021	Virtual	Zoom
6	20 June 2023	Virtual	Zoom

CIOMS MLG Expert Working Group activities

13 Nov 2018	18th Annual Meeting of the International Society of Pharmacovigilance (ISoP), Geneva. *New use of clinical concepts in MedDRA: Can MedDRA labelling groupings help to standardise safety labeling?* **Presentations:** • *MedDRA Labeling Groupings (MLGs): A Harmonised Approach to Safety Communication* (William W Gregory, Sonja Brajovic) • *MedDRA Labeling Groupings (MLGs) Examples from a Pharmaceutical company* (Ilona Große-Michaelis) **Q & A Panel discussion** (Judith K Jones, chair)
25 Jun 2019	Drug Information Association (DIA) 2019 Global Annual Meeting. Session on *The Elephant in the Room: Meaningful Communication of Near Synonyms as Suspected Adverse Reactions* **Presentations**: • *A Perspicacious CIOMS View of a Sometimes Tangled Mass of Adverse Reaction Communication Challenges* (William W Gregory) • *MedDRA Labeling Groupings (MLGs): A New CIOMS Initiative* (Sonja Brajovic) • *MedDRA Labeling Groupings (MLGs): Practical Examples Underscore Feasibility* (Ilona Große-Michaelis) **Round table discussion** (Judith K Jones, chair)
18 Nov 2020	DIA-NIFDS Pharmacovigilance Workshop, Korea (virtual event), session on *Effective Presentation of Safety Data on Label-Near-Synonymous MedDRA Terms in Medical Product Labeling* **Presentations**: • *Rationale for Grouping Near-Synonymous MedDRA Terms* (William W Gregory) • *Practical Aspects of Grouping Near- Synonymous MedDRA Terms* (Ilona Große-Michaelis)
17 Sep 2021	Expert Working Group (EWG) meeting with the U.S. FDA Safety Analytics Control Board (SACB) (virtual event) **Presentations** (Ilona Große-Michaelis and Radhika M Rao) **Panel Discussion** (CIOMS MLG EWG and FDA SACB members)
8 Aug 2022	**Open-access article published** in *Therapeutic Innovation & Regulatory Science* (TIRS), official scientific journal of the Drug Information Association (DIA) Große-Michaelis I, Proestel S, Rao RM, Dillman BS, Bader-Weder S, Macdonald L, Gregory W. MedDRA Labeling Groupings to Improve Safety Communication in Product Labels. Ther Innov Regul Sci. 2023;57(1):1-6. https://doi.org/10.1007/s43441-022-00393-1
18 Oct 2023	PERI (Pharmaceutical Education and Research Institute) Global Labeling & Regulatory Symposium, USA, (virtual presentation) **Presentation:** • *CIOMS MedDRA Labeling Grouping (MLG)* (Ilona Große-Michaelis)

APPENDIX 3.

COMPARISON OF SMQ AND MLG

Medical Dictionary for Regulatory Activities (MedDRA) Labeling Groupings (MLGs) and Standardised MedDRA Queries (SMQs) are both based on MedDRA terminology and are a combination of Preferred Terms (PTs), but with different aims (see also Section 1.2.2 Differences between SMQs and MLGs). The principle of grouping MedDRA PTs that describe the same or similar adverse reactions (ARs) also applies to searching, analyzing and presenting MedDRA-coded data during safety data analysis. The value of SMQs in aggregating related PTs into clinically relevant concepts has been shown. Some institutions have developed their own MLG-like custom PT groupings and report benefiting from them, but an internationally agreed set of MLGs does not exist at the moment.

Combining the AR terms in medically meaningful ways greatly facilitates the interpretation of data displays in study reports, Integrated Summaries of Safety (ISS), or benefit-risk assessments. These data are subsequently distilled and condensed for communication of important safety concepts to healthcare providers in product safety labeling (PSL).

Parallels can be drawn between SMQs and the proposed MLGs. Both are based on MedDRA terminology and are combinations of MedDRA PTs, although with different aims. Both are intended as tools to promote harmonization and simplification by use of a standardized approach and are developed based on need. The Council for International Organization of Medical Sciences (CIOMS) MLG Expert Working Group (EWG) proposed approach of MedDRA PT grouping of near-synonymous terms is anticipated to achieve a clinically meaningful representation of adverse reactions in the product safety label for healthcare providers. MLGs are not intended to be used for safety signal detection or to alter the approach to safety data analyses. Due to heterogeneous nature, one SMQ may contain a combination of MedDRA PTs related to a medical concept presenting signs and symptoms, diagnosis, and diagnostic and therapeutic measurements. Hence when an SMQ is utilized for data retrieval, the output is more sensitive, although less specific. Whereas an MLG by nature is homogenous and intended to contain MedDRA PTs that are near-synonymous to an individual medical concept such as signs or symptoms only or diagnosis only, or diagnostic and therapeutic measurements only. Therefore, an MLG may be too specific and little sensitive for the purposes of data retrieval and would generally be expected to be contained in an SMQ for the same concept, but not always, due to the requirement of different inclusion/exclusion criteria of the medical concepts of both groupings. However, SMQs would typically be expected to contain many more PTs given their use for safety signal detection and lower threshold for similarity.

SMQs are used for safety signal detection in MedDRA-coded adverse event (AE) data sets, while MLGs would be used to communicate the ARs in product safety labeling.

The CIOMS MLG EWG believes that SMQs and MLGs would serve different primary purposes as shown on the next page, the former for signal detection and the latter for labeling. MLGs would have merit on their own as tools for improving safety communication in PSL.

Characteristics	Standardised MedDRA Queries (SMQ)	Proposed MedDRA Labeling Groupings (MLG)
Purpose	Safety signal detection in MedDRA-coded adverse event data sets	Safety communication in product safety label
Status	International MedDRA Preferred Term (PT) groupings exist	To be established
Content	Consist of MedDRA PTs that reflect a range or different aspects of a medical concept (heterogeneous concept)	Consist of MedDRA PTs that are nearly synonymous (homogeneous concept)
	Typically contain many more PTs than MLGs, given the lower threshold for similarity	Typically contain less number of PTs than SMQs given the higher threshold for similarity
	May contain a combination of MedDRA PTs related to a medical concept presenting: – signs and symptoms, and – diagnosis, and – diagnostic and therapeutic measurements	Contain MedDRA PTs related to a medical concept presenting: – signs or symptoms only, or – diagnosis only, or – diagnostic measurements only, or – therapeutic measurements only
Output when used for data retrieval	More sensitive than MLGs, but less specific	Too specific, not very sensitive
Example	**SMQ *Acute renal failure*** (narrow scope)*	**Proposed MLG *Acute kidney injury***
	Consists of the following 19 PTs from MedDRA v24.0: PT *Acute kidney injury* PT *Acute phosphate nephropathy* PT *Anuria* PT *Azotaemia* PT *Continuous haemodiafiltration* PT *Dialysis* PT *Foetal renal impairment* PT *Haemodialysis* PT *Haemofiltration* PT *Neonatal anuria* PT *Nephropathy toxic* PT *Oliguria* PT *Peritoneal dialysis* PT *Prerenal failure* PT *Renal failure* PT *Renal failure neonatal* PT *Renal impairment* PT *Renal impairment neonatal* PT *Subacute kidney injury*	Consists of the following 2 PTs from MedDRA v24.0: PT *Acute kidney injury* PT *Subacute kidney injury*

* SMQ *Acute renal failure* (broad search) consists of 51 PTs (including 19 PTs of narrow scope)

APPENDIX 4.

EXAMPLES OF ADR PRESENTATION IN APPROVED LABELS

To demonstrate the lack of consistency in grouping adverse drug reaction (ADR) terms across different jurisdictions for the same substance, a spontaneous literature review was performed by the Council for International Organization of Medical Sciences (CIOMS) Medical Dictionary for Regulatory Activities (MedDRA) Labeling Grouping (MLG) Expert Working Group (EWG) members.

This appendix consists of two parts: an overview as presented at the Drug Information Association (DIA) meeting of 25 June 2019 (Appendix 4.1), and a random sample review performed by the CIOMS MLG EWG in 2019 (Appendix 4.2). The different drugs are anonymized.

Appendix 4.1.
Current approaches in presenting ADRs in a label & challenges with ADR groupings in current labels:
Overview of examples as presented at the DIA 2019 Global Annual Meeting

Reproduced from reference: DIA 2019 Global Annual Meeting. Session on *The Elephant in the Room: Meaningful Communication of Near Synonyms as Suspected Adverse Reactions*, William W Gregory, Sonja Brajovic, & Ilona Große-Michaelis (all CIOMS MLG Expert Working Group Activities are listed in Appendix 2).

Adverse drug reaction (ADR) in table	Drug	Included Preferred Terms (PTs) in footnote	Challenges with the groupings
Edema	A	Includes terms *Edema, Edema peripheral, Pitting edema, and Generalized edema*	Different etiologies
	B	Edema includes the following terms: *Edema*, *Peripheral edema*, *Localized edema*, *Face edema*	
	E	Edema (*Face edema*, *Generalized edema, Local swelling, Localized edema, Edema, Edema peripheral, Periorbital edema*)	

(continued)

Adverse drug reaction (ADR) in table	Drug	Included Preferred Terms (PTs) in footnote	Challenges with the groupings
(Appendix 4.1, continued)			
Abdominal pain	B	Abdominal pain includes the following terms: *Abdominal pain, Upper abdominal pain, Lower abdominal pain, Abdominal tenderness, Gastrointestinal pain, Abdominal discomfort*	Different severity and prognosis
	C	Includes *Abdominal discomfort, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness,* and *GI pain*	
	D	Includes the following terms: *Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal rigidity, Abdominal tenderness, Acute abdomen, Esophageal pain*	
	E	Abdominal pain (*Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness*)	
	F	No terms mentioned	
Dyspnea	H	Includes *Acute respiratory failure, Dyspnea, Dyspnea exertional, Respiratory failure, Respiratory distress, Bronchospasm, Bronchial hyperreactivity, Tachypnea,* and *Wheezing*	Different severity
Cardiac failure	A	Includes terms *Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy,* and *Ejection fraction decreased*	Different etiology
Rash	B	Rash includes the following terms: *Rash, Macular rash, Pruritic rash, Generalized rash, Papular rash, Maculo-papular rash*	Includes terms of broad scope and different etiology

Additional examples of ADR groupings in current labels included terms of broad scope and different severity:

- Depression: included *Depressed mood*, *Depression*, *Suicidal ideation*, and *Completed suicide*.
- Neutropenia: included *Agranulocytosis*, *Febrile neutropenia*, *Neutropenia*, *Neutrophil count decreased*.
- Neuropathy: included *Dysaesthesia*, *Formication*, *Gait disturbance*, *Hyperaesthesia*, *Hypoaesthesia*, *Hypotonia*, *Motor dysfunction*, *Muscle atrophy*, *Muscular weakness*, *Neuralgia*, *Neuritis*, *Neuropathy peripheral*, *Neurotoxicity*, *Paraesthesia*, *Peripheral motor neuropathy*, *Peripheral sensorimotor neuropathy*, *Peripheral sensory neuropathy*, *Peroneal nerve palsy*, *Polyneuropathy*, *Sensory disturbance*, *Skin burning sensation*.

Appendix 4.2.
Current approaches in presenting ADRs in a label & challenges with ADR groupings in current labels:
CIOMS MLG EWG random sample review

The Council for International Organization of Medical Sciences (CIOMS) Medical Dictionary for Regulatory Activities (MedDRA) Labeling Grouping (MLG) Expert Working Group (EWG) conducted a random review of product information (PI) from European public assessment reports (EPARs) and the United States (U.S.) Food and Drug Administration (FDA)-approved labels to broadly characterize current practices in presentation of adverse drug reactions in labels through the use of MedDRA Preferred Terms (PTs). A few examples from this review are described below to demonstrate that groupings in approved labels differ between jurisdictions and similar terms were not grouped. Additionally in some approved labels, grouping was performed, but grouped terms were not documented.

The review demonstrated a broad variability in the groupings in approved labels.

This appendix shows examples of the types of grouping challenges identified. The examples are categorized as follows:

- No grouping of near-synonymous terms
- Grouping was performed, but grouped terms were not documented
- Grouping with varying detail
  - Grouped terms represent a broad concept
  - Grouped terms represent different severity
  - Grouped terms represent different etiology
  - Grouped terms represent different scope
  - Differences in PT groupings between sections of the same approved label
- Groupings were different in the label for the same product within different jurisdictions.

Notes:
(1) The products are numbered with consecutive Roman numerals within each category. The same numbers in different sections do not necessarily refer to the same product.
(2) Additional types of grouping challenges could apply to the examples shown under each category.

1 No grouping of near-synonymous terms

The reviewed example Product I showed that the terms *"Gastrointestinal perforation, Large intestine perforation, Intestinal perforation"* were individually listed in the European Union (EU) label, while they could have been grouped to avoid possible dilution of the medical concept of Gastrointestinal perforations. However, in the U.S. label, *Intestinal perforation* was listed in a footnote for *Enterocolitis* in the table on severe and fatal outcome ADRs.

Product I

Example: *Gastrointestinal perforation*

EPAR product information:

The following are listed individually, under monotherapy, "Uncommon", System Organ Class (SOC) *Gastrointestinal disorders*: *Gastrointestinal perforation, Large intestine perforation, Intestinal perforation*

(Note: Under combination therapy: "*Intestinal perforation*" is listed instead, but not the other terms listed under monotherapy).

FDA label:

Intestinal perforation is listed in a footnote for *Enterocolitis*.

2 Grouping performed, but grouped terms not documented

Product II

EPAR product information:

e.g., *Stomatitis*, Pneumonia*, Sinusitis*, Rash*, Bruising*, Musculoskeletal pain*, Skin infection*, Hypertension*, Interstitial lung disease*, Non-melanoma skin cancer*,*

Footnote for all terms with *****: "**includes multiple adverse reactions terms**"

FDA label:

e.g., *Stomatitis*, Pneumonia*, Sinusitis*, Rash*, Bruising*, Musculoskeletal pain*, Skin infection*, Hypertension*, Neutropenia*, Thrombocytopenia*, Hemorrhage**.

Footnote for all terms with *****: "**Includes multiple ADR terms**"

3 Groupings with varying detail

3.1 Grouped terms represent a broad concept and variability across jurisdictions

Product IV

Example: *Neuropathy*

EPAR product information:

It includes: *Burning sensation, Dysaesthesia, Formication, Gait disturbance, Hyperaesthesia, Hypoaesthesia, Hypotonia, Motor dysfunction, Muscle atrophy, Muscular weakness, Neuralgia, Neuritis, Neuropathy peripheral, Neurotoxicity, Paraesthesia, Peripheral motorneuropathy, Peripheral sensorimotor neuropathy, Peripheral sensory neuropathy, Peroneal nerve palsy, Polyneuropathy, Sensory disturbance, Skin burning sensation*.

FDA label:

It includes: *Gait disturbance*, *Hypoesthesia*, *Muscular weakness*, *Neuralgia*, *Neuropathy peripheral*, *Paresthesia*, *Peripheral sensory neuropathy*, *Polyneuropathy*, *Sensory disturbance*.

3.2 Grouped terms represent different severity

Product V

Example: *Abdominal discomfort*

EPAR product information:

Individual terms of *Abdominal discomfort*, *Abdominal pain* and *Abdominal distension* are listed without grouping.

FDA label:

Abdominal discomfort combines *Abdominal tenderness*, *Abdominal rigidity*, *Gastrointestinal discomfort*, *Stomach discomfort*, and *Abdominal discomfort*.

Product VI

Example: *Dyspnea*

EPAR product information:

Dyspnoea includes *Dyspnoea*, *Dyspnoea exertional*, *Respiratory distress* and *Respiratory failure*.

FDA label: (also note that PT is included in more than one grouping:)

Dyspnoea "includes *Dyspnea* and Respiratory distress, Respiratory failure".
"Additional important adverse reactions that did not meet the threshold criteria for inclusion: *Respiratory, thoracic, and mediastinal disorders*: *Respiratory distress* (6%), *Respiratory failure* (6%), *Acute respiratory distress syndrome* (4%), *Oropharyngeal pain* (6%)".

3.3 Grouped terms represent different etiology

Product IV

Example: *Edema*

EPAR product information/FDA label:

Oedema: It includes: *Face oedema*, *Generalised oedema*, *Local swelling*, *Localised oedema*, *Oedema*, *Oedema peripheral*, *Periorbital oedema*.

3.4 Grouped terms represent different scope

Product IV

Example: *Blood testosterone decreased*

EPAR product information:

It includes: *Blood testosterone decreased*, *Hypogonadism*, *Secondary hypogonadism*.

From FDA label:

"*Decreased blood testosterone* (1%; *Hypogonadism*)."

3.5 Differences in PT groupings between sections of the same approved label

Product VIII

Example: *Diarrhea*

EPAR product information:

Diarrhea and *Colitis* are listed separately, but they are each grouping terms.

Diarrhea, includes *Diarrhoea*, *Frequent bowel movements*, and *Gastrointestinal hypermotility*;

Colitis, includes *Colitis*, *Autoimmune colitis*, *Colitis ischaemic*, *Colitis microscopic*, *Colitis ulcerative*.

FDA label:

Adverse Reactions section lists "*Diarrhea*" as a grouped term in some tables and as a single term in others; "*Colitis*" is only in the footnote displaying events included in the term "*Diarrhea*" in Tables 2 and 6 (of this label):
Table 2 (of this label): *Diarrhea*, includes *Diarrhea*, *Colitis*, *Frequent bowel movements*, *Autoimmune colitis*
Table 4 (of this label): *Diarrhea*
Table 6 (of this label): *Diarrhea*, includes *Diarrhea*, *Gastroenteritis*, *Colitis*, *Enterocolitis*
Table 8 (of this label): *Diarrhea*
Table 10 (of this label): *Diarrhea*.

3.6 Approved labels differ between jurisdictions

Product IX

EPAR product information:

No *Abdominal pain* under SOC *Gastrointestinal disorders*,
Listed only under SOC *General disorders*: *Pain* (including *Mouth*, *Abdominal*, *Bone*, *Tumour pain* and *Headache*).

FDA label:

Abdominal pain: Includes the following terms: *Abdominal pain*, *Abdominal discomfort*, *Hepatic pain*, *Esophageal pain*, *Esophageal discomfort*, *Abdominal pain lower*, *Abdominal pain upper, Abdominal tenderness, Abdominal rigidity*.

Health Canada Monograph:

No *Abdominal pain* under SOC *Gastrointestinal disorders*,
Listed only under SOC *General disorders*: *Pain* (including *Mouth*, *Abdominal, Bone, Tumour pain* and *Headache*).

Conclusion and next steps

The review highlighted a broad variability in the groupings in approved labels. This identifies the need for CIOMS MLG WG to promote globally harmonized principles for voluntary consideration for consistent and standardized communication of the product safety labeling (PSL).

APPENDIX 5.

EXAMPLES OF MLG DEVELOPMENT

To inform its work, the Council for International Organization of Medical Sciences (CIOMS) Medical Dictionary for Regulatory Activities (MedDRA) Labeling Grouping (MLG) Expert Working Group (EWG) conducted a feasibility exercise by creating some examples of MLGs, shown in this appendix.

Disclaimers and Clarifications: Throughout this report, unless indicated otherwise, the MedDRA versions used are MedDRA versions 24.0 and 24.1. (See also the Disclaimers and clarifications on page x).

MLG *Hyperkalemia*

	Preferred Terms (PT)	Discussion
Included	PT *Blood potassium increased* (SOC *Investigations*) PT *Hyperkalaemia* (SOC *Metabolism and nutrition disorders*)	These two PTs belong to two different MedDRA SOCs but are seen as describing same medical concept.*
Excluded	PT *Blood potassium abnormal* PT *Pseudohyperkalaemia*	PT *Blood potassium abnormal* is clinically meaningful in both directions of laboratory abnormality and hence is not included under MLG *Hyperkalemia.* The PT *Pseudohyperkalemia* represents a false elevation in potassium that reflects a different medical concept than hyperkalemia. Therefore, is not included in the MLG *Hyperkalemia*.

* The System Organ Class (SOC) information and the explanation of included Preferred Terms (PTs) is provided only for this MLG example for illustrative purposes. For the rest of the MLG examples, this explanation is provided for only excluded PTs.

MLG *Abdominal pain*

	Preferred Terms (PT)	Discussion
Included	PT *Abdominal pain* PT *Abdominal discomfort* PT *Abdominal pain lower* PT *Abdominal pain upper* PT *Gastrointestinal pain* PT *Abdominal tenderness* PT *Epigastric discomfort*	
Excluded	PT *Abdominal rebound tenderness* PT *Oesophageal pain* PT *Abdominal migraine* PT *Abdominal rigidity* PT *Acute abdomen* PT *Enteric neuropathy* PT *Intestinal spasm* PT *Perihepatic discomfort* PT *Spleen pain*	PT *Abdominal rebound tenderness* was seen as more clinically important, based on a different etiology PT *Oesophageal pain* was seen as questionable for localization of abdominal pain

MLG *Headache*

	Preferred Terms (PT)	Discussion
Included	PT *Headache* PT *Head discomfort* PT *Tension headache*	
Excluded	PT *Basilar migraine* PT *Cervicogenic headache* PT *Chronic paroxysmal hemicrania* PT *Cluster headache* PT *Drug withdrawal headache* PT *Exertional compression headache* PT *Familial hemiplegic migraine* PT *Medication overuse headache* PT *New daily persistent headache* PT *Primary headache associated with sexual activity* PT *Sinus headache* PT *Vascular headache*	PTs with specific etiology were considered not fitting to the general concept of unspecific headache PT *New daily persistent headache* describes a primary headache syndrome which can mimic chronic migraine and chronic tension-type headache

MLG *Acute kidney injury*

	Preferred Terms (PT)	Discussion
Included	PT *Acute kidney injury* PT *Subacute kidney injury*	
Excluded	PT *Acute phosphate nephropathy* PT *Anuria* PT *Azotaemia* PT *Crystal nephropathy* PT *Blood creatinine abnormal* PT *Blood creatinine increased* PT *Cardiorenal syndrome* PT *Glomerular filtration rate decreased* PT *Nephropathy toxic* PT *Oliguria* PT *Prerenal failure* PT *Renal failure* PT *Renal impairment*	PT *Blood creatinine abnormal,* PT *Blood creatinine increased,* PT *Blood urea increased,* PT *Creatinine renal clearance decreased,* PT *Glomerular filtration rate decreased,* PT *Hypercreatininaemia and* PT *Renal function test abnormal* are not included as they fit to other diagnoses too PT *Nephropathy toxic* has a different etiology, and PT *Oliguria* can be seen as symptom fitting to several medical diagnoses PT *Prerenal failure,* PT *Renal failure,* PT *Renal failure neonatal,* PT *Renal impairment,* PT *Renal impairment neonatal* are too unspecific or represent a different medical concept

MLG *Renal impairment*

	Preferred Terms (PT)	Discussion
Included	PT *Blood creatinine abnormal* PT *Blood creatinine increased* PT *Blood urea increased* PT *Creatinine renal clearance decreased* PT *Glomerular filtration rate abnormal* PT *Glomerular filtration rate decreased* PT *Hypercreatininaemia* PT *Renal impairment*	
Excluded	PT *Renal impairment neonatal* PT *Glomerulonephritis chronic* PT *Nephrogenic anaemia* PT *End stage renal disease*	PT *Renal impairment neonatal:* as per MLG convention to exclude PTs referring to specific age groups. PT *End stage renal disease* is considered more severe PT *Glomerulonephritis chronic* and PT *Nephrogenic anaemia* are considered different medical entities

The Medical Dictionary for Regulatory Activities (MedDRA) is a terminology developed by the International Council for Harmonisation (ICH). While it is useful for precise coding of adverse events of medicines for data analysis, its high granularity can obscure the communication of adverse reactions in product labeling for healthcare practitioners. Many sponsors and regulators have therefore begun to develop their own approaches to clustering similar adverse reaction terms in medical product prescribing information on a product-by-product basis. However, there are no agreed-upon conventions that describe which adverse reaction terms may be appropriate to group together. To improve safety communication to patients and healthcare providers, there is an urgent need for a harmonized international approach to the creation and use of groups of MedDRA terms, or "MedDRA Labeling Groupings (MLGs)", in medical product prescribing information.

Given its long-standing contributions towards the design of Standardised MedDRA Queries (SMQs), the Council for International Organizations of Medical Sciences (CIOMS) convened an Expert Working Group with involvement of multiple major stakeholders, to produce a consensus document on principles and points to consider in the development of MLGs. It is envisaged that the use of the consensus recommendations proposed in this report would be voluntary and applied to product labels in a manner that is consistent with existing regulatory frameworks.

Introduction to MedDRA Labelling Grouping (MLG): A standardized approach to grouping adverse reactions in product safety labels. Geneva: Council for International Organizations of Medical Sciences (CIOMS), 2024.

This publication is freely available on the CIOMS website at:
https://doi.org/10.56759/hmku5307

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