MedDRA® and Product Labeling: "Best Practices" Recommendations

I. Introduction

The purpose of this document is to present a set of general recommendations on how MedDRA-coded data should be used in biopharmaceutical product labeling. These recommendations take into account the multiple purposes of product labeling and the characteristics of MedDRA. They also recognize that product labeling can take several forms, each addressed to a different set of end users. Any recommendations made should be considered in the light of local regulations governing product labeling content.

Purpose and scope of MedDRA

MedDRA was developed for use by regulators and the biopharmaceutical industry for the following areas[1]:

- Clinical studies
- Spontaneous adverse event/reaction reporting
- Regulatory submissions
- **Regulated product information**

MedDRA was developed to support encoding of several types of clinical information collected during the clinical development and marketing phases for biopharmaceutical products. Besides adverse events (including diseases, diagnoses, signs and symptoms), MedDRA supports encoding of medical and social history, indications, investigations, and physical examination findings. MedDRA is required for communication of safety information in the framework of electronic regulatory reporting of single cases (E2B). Increasingly, MedDRA-coded data are the basis for product labeling.

While recognizing MedDRA's obvious strengths for data input (coding), use of MedDRA may require a set of approaches and ancillary tools for data presentation and analysis (e.g., Standardised MedDRA Queries to aid in case identification). Similarly, optimal use of MedDRA in product labeling may require additional elements.

Purpose of product labeling

In all three ICH regions, product labeling takes similar forms and is designed to serves multiple functions. First, national/regional health professional (HP) and patient/consumer labeling serves to communicate information on the benefits and risks as well as advice on the effective and safe use of a product to various end-users. The national/regional HP labeling is also used by biopharmaceutical companies to determine whether a suspected adverse drug reaction is considered expected or unexpected (in terms of nature, severity, specificity, or outcome) for purposes of expedited reporting to local regulatory authorities[2].

Specific labeling content of national/regional labeling is generally negotiated between biopharmaceutical companies and regulatory authorities.

In addition to using labeling to inform HPs and patients/consumers, biopharmaceutical companies use labeling documents for various internal purposes. For example, approved labeling of one country can be given to an affiliate in another country as a reference model for their own local labeling. Many companies use a "Company Core Data Sheet" (CCDS) as internal reference labeling for local affiliates. The content of a CCDS is not negotiated between biopharmaceutical companies and regulatory authorities. With respect to safety information, the CCDS generally contains a defined set of data and advice that the company intends to have reflected in national/regional labeling worldwide. This reference safety information is commonly designated as Company Core Safety Information (CCSI). As outlined by CIOMS, the CCSI information is typically designed to reflect the company's view of the essential safety information that will assist in the selection and use of the medicine by healthcare professionals.[3] However, the CCSI may not necessarily be the minimum information required for safe use of a product. Compared to the CCSI, national/regional HP labeling may contain more, less or different safety information.

The CCDS is usually also used as a global reference document for the determination of "listedness" for periodic safety reporting (i.e., as reference labeling for Periodic Safety Update Reports [PSURs]). However, in the absence of a CCDS, companies may use approved national/regional HP labeling of one country as the global reference document for the determination of "listedness".

Many countries/regions have a two-tiered labeling system in place, with patient/consumer information and HP labeling. Canada has a three-tiered system in place, with a layer of detailed and scientific information beyond what is included in the "regular" HP labeling[4].

Safety information needs to be summarized and presented for all end-users to understand and use. Since MedDRA is intended for the encoding and analysis of safety data, MedDRA-coded data will eventually need to be reflected in product labeling in a language that readily represents as exactly as possible the medical concepts intended to be described.

The focus of the recommendations in this document is primarily HP labeling (with additional discussion of the CCDS where appropriate). Using MedDRA terms in the patient/consumer labeling could be challenging as most MedDRA terms (PT level and above), like some terms from prior terminologies, are generally not readily interpretable by patients/consumers without some degree of medical/healthcare training. Although patient information is based upon and must be consistent with the information provided in the HP labeling, this labeling

must use language that is easily understood by non-professionals, rather than medical terminology.

II. *Data Presentation and Retrieval: Points to Consider*

The same ICH Working Group that drafted the "*MedDRA Term Selection: Points to Consider*" document has a remit to create a complementary document dealing with data retrieval and presentation (titled "*MedDRA Data Retrieval and Presentation: Points to Consider*"). The new document is expected to address best practices for data retrieval including proposals for how MedDRA-coded data could be optimally presented in tables, e.g., frequency tables. As of March 2005, this document is in a draft stage and has been posted on the ICH, MSSO, and JMO websites for user comments.

The MSSO fully supports the development of this new document by the Points to Consider (PTC) Working Group. In general, the labeling recommendations herein follow the principles outlined in the draft "*MedDRA Data Retrieval and Presentation: Points to Consider*" document. The ICH-endorsed recommendations in that document should supersede any of the recommendations made in this present paper, if any are found to be in conflict.

III. Adverse Events/Adverse Reactions (Undesirable Effects in SPC), including Regulatory Requirements

Recognizing that information concerning the safety profile of a product is presented in multiple sections of product labeling, this document is focused on MedDRA's role in the sections of labeling directly pertaining to adverse events/reactions primarily in HP labeling.

In HP labeling, this section lists, and often elaborates on, suspected adverse events or adverse reactions (depending on local requirements).

In the CCDS, this section typically focuses on suspected adverse reactions, except for specific products and circumstances where lists of events are considered appropriate. Lists of events may also be provided in addition to lists of reactions.

In HP labeling, a general overview of AEs/ADRs is usually provided, followed by tabular presentations of AEs/ADRs. In some countries, more common AEs/ADRs are listed with more detail on reporting rates than less common AEs/ADRs. The tabular presentation may be followed by a narrative description of some AEs/ADRs.

The EU SPC guideline states that tables of adverse reactions should be presented according to a standard system organ class such as in MedDRA, and that they should be presented in the internationally agreed

MedDRA SOC order[5]. In March 2005, a proposal for the revision of the SPC guideline does specify the use of MedDRA and that adverse reaction descriptions be based on the most suitable representation within the terminology. It states that this will usually be at the Preferred Term (PT) level, although there may be instances where the use of LLTs or, grouping terms, such as High Level Terms (HLTs) or other "groupings" of terms may be appropriate. Additionally, the proposed revision states: "As a general rule, MedDRA terms should be classified according to the most relevant SOC related to the target organ. A pragmatic approach to the location of terms should be taken in order to make the identification of adverse reactions simpler and clinically appropriate for the reader." For example, on occasion – solely in the context of the SPC - secondary SOC locations or other SOC locations could be used (e.g., "liver function test abnormal", although located in SOC *Investigations*, could be grouped in the SPC [under "Hepatobiliary disorders"] with "hepatitis" and "hepatic encephalopathy", which haveprimary links to SOC *Hepatobiliary disorders* and SOC *Nervous system disorders*, respectively.

In the MHLW Notification on MedDRA Usage, it is noted that the Japanese version of MedDRA could be used for ADR terms in the Precaution section (which includes the adverse reactions) of the package insert[6].

The recent Health Canada guidance document *Guidance for Industry: Product Monograph,* states that MedDRA "will be used as the preferred terminology to describe adverse drug reactions. This will usually be at the Preferred Term Level, although there may be instances where the use of a Lowest Level Term or a High Level Term may be appropriate". The guidance further outlines that tables of adverse reactions should be categorized by MedDRA SOCs[4].

The US prescribing information regulations/guidelines does not specify that a particular terminology be used[7-8].

IV. General principles on the use of MedDRA in labeling

The following section describes the MSSO's recommendations on the use of MedDRA in labeling. As noted above, patient information does not require the use of formal medical terms and will not be discussed here.

CCDS (Manufacturer/regulator document)

This document is used as a reference document and common communication tool within the company and between a company and a regulator that requires submission of PSURs. For this reason, the MSSO recommends the use of the standardized MedDRA terminology in this document for both narrative and tabular presentations of information.

We advocate flexibility in this approach because the word order of some MedDRA terms may not be suitable for HP communication where the use of natural language and word order would be more appropriate. Additionally, in the US, terms with American spelling would need to be used in labeling (MedDRA terms at the PT level and above are spelled using British spelling). However, we do recommend the use of MedDRA terms, generally PTs, in the Adverse Reactions section.

The advantages of using MedDRA terms in the Adverse Reactions section include:

- standardization
- specificity
- much of the information from clinical trials and spontaneous reports would be already coded in MedDRA; no further conversions are needed

When appropriate, standardized term groupings relevant for summarizing information in the context of product labeling may be used to represent a particular condition. In some instances, MedDRA High Level Group Terms (HLGTs) and HLTs may serve this purpose adequately. When HLGTs and HLTs do not suffice (e.g., if they contain linked terms beyond the medical concept intended for the label), a different type of standardized term grouping (proposed, but not yet developed; provisionally called "MedDRA Labeling Entities" [MLEs]) could be used. MLEs must be defined so that their subordinate terms reflect exactly the concepts that HPs would understand as being covered by the MLE term. MLEs could also serve as a communication tool to regulators when specifying cases that meet certain criteria defined by the groupings. For example, if there is no existing HLGT or HLT to adequately summarize instances of bundle branch block for the purpose of labeling, an MLE for "bundle branch block" would be used.

Additionally, the term content of the MLEs could serve to develop "listedness" tables by companies, mapping the MLEs to their subordinate MedDRA PTs. These tables must be updated with each new version of MedDRA to account for movement of terms related to maintenance activities. A pragmatic approach is advocated; the use of such tables is no substitute for sound medical judgment in determining "listedness" or "expectedness", and additional information may have to be reviewed in context to make this determination. For example, there may be instances where certain terms on this list would be considered not listed because context information makes the event/reaction more specific or more severe[3]. For MLEs representing syndromes (e.g., "anaphylactic reaction"), the various manifestations represented by MedDRA terms would have to be considered in light of a "case definition".

The MSSO recommends that MLEs be developed within the ICH process; specifically, the remit of the ICH PTC Working Group should be expanded to

cover the development of MLEs. MLEs would then become part of MedDRA and be maintained by the MSSO; as such, they would become a standard communication tool between the various organizations involved in product labeling.

HP labeling

The MSSO recommends the use of familiar medical wordings and logical medical groupings of such words supplemented as appropriate by specific MedDRA terms or term groupings (i.e., HLGTs, HLTs or MLEs). In some circumstances, therefore, it may be necessary to "translate" MedDRA terms into more familiar and understandable medical terms.

We propose the use of logical groupings of related terms to summarize data: in some instances, existing MedDRA HLTs, HLGTs or MLEs may be applicable. If an appropriate MLE is not available, a request to the organization creating or maintaining such groupings (e.g., the ICH PTC Working Group or the MSSO) should be considered. "MLE" groupings created by companies, or even by regulatory authorities, will be inevitable as long as no standard groupings are available. Additionally, the list of standard MLEs may not be complete at any given time, or a company may not feel comfortable with the breadth of a grouping and prefer more granular groupings. Some national or regional groupings may also develop. In any case, in the absence of standard MLEs, companies and regulators should be advised to invent/define groupinss for AEs/ADRs strictly based on an HP's expected understanding of the term.

V. Special considerations

As the biopharmaceutical industry transitions to the use of MedDRA, inevitably, newly acquired safety information encoded in MedDRA will coexist with label information coded in older terminologies. This may occur under the following circumstances:

- Studies supporting new indications for a marketed product
- Spontaneous adverse event cases (MedDRA-coded) compared to labeling with older terminology terms
- During product development, as CCDSs are being developed, and data from multiple studies are being analyzed in aggregate
- When databases of different companies have been merged

The MSSO does not feel that a complete revision of labeling (e.g., a CCDS) to reflect MedDRA-coded data is necessary or useful under most circumstances; in fact, unless verbatim terms from old studies are readily available for conversion, this may be impossible. Even if this information were available, the costs in terms of resources would need to be weighed against the potential benefit.

How this situation can be handled depends on the original format and content of the adverse reactions section. For adverse event tables, "legacy" data could be left in its original terminology and MedDRA-coded data appended in new tables or other formats. A side-by-side comparison of the old and new safety information based on individual or aggregated events may be then accomplished (only in very exceptional cases might this be an option for HP texts). The company may consider making note of any discrepancies, especially those related primarily to terminology attributes (e.g., "rash" events may be represented by several MedDRA terms but only a single legacy term).

One might consider an actual "conversion" of labeling adverse event data under very limited circumstances. For example, if a CCDS has been created early in development and contains only a few studies, a company may wish to consider converting this labeling to MedDRA as the effort involved would likely be minimal. Additionally, if the only way to achieve clarity of critical safety information is to convert it all to one terminology, this should be considered. However, this would likely be a rare occurrence.

Whenever existing labeled adverse event terms are considered for recoding or replacement, it is essential to preserve their clinical meaning unless new data necessitate a conceptual change. When a MedDRA term (resulting from recoding) differs from the original, non-MedDRA label term, especially one that represents an important suspected adverse reaction or warning about possible risks, the new term must be shown to represent the concept as well as, or better than, the original wording.

VI. Summary and conclusions

Based on the input made by the expert members of the Blue Ribbon Panel, the following are the MSSO's specific recommendations:

- A flexible and pragmatic approach to the use of MedDRA for labeling is advocated, keeping in mind relevant local regulations governing content
- MedDRA Labeling Entities (MLEs) are proposed as a new concept:
  - MLEs should be developed within the ICH framework to enforce harmonization
    - Extend the remit of PTC Working Group to address this task. (Nomination of labeling experts from each ICH party would be essential for this new remit)
  - MLEs should be maintained by MSSO and distributed with MedDRA to all subscribers
  - Whenever suitable, an existing MedDRA term (e.g., an HLT or HLGT) should be used to summarize information in the context of labeling; however, when these grouping terms are inadequate, MLEs should be used instead

        - Implementation of MLEs should not create "conversion" issues (i.e., difficulties for companies to adapt from current labeling practices to MedDRA groupings/MLEs). Implementation/conversion issues will occur if groupings are not provided rapidly. If their availability is delayed, companies and regulators will create *ad hoc* groupings that may result in conversion issues (possibly even issues of a legal nature).
    - MedDRA terms and – if accepted by regulators – MLEs can be used as a basis for assessment of listedness/expectedness, but they are not a substitute for medical judgment
        - For example, there may be product-specific instances where certain subordinate terms in an MLE would be considered <u>not</u> listed because context information makes the event/reaction more specific or more severe[3]

- Natural language is recommended for labeling (HP and patient/consumer labeling)
    - SPC guideline recommends MedDRA
        - MedDRA translations are useful, especially if LLTs or modified LLTs are used for patient/consumer labeling
    - MSSO should review MedDRA terms for more natural language representation in the context of the ongoing HLT/HLGT feasibility study

- For labels developed with legacy terminologies but with present-day data being coded using MedDRA:
    - Document the method of data conversion, if this has been performed
        - Verbatim conversion *vs.* legacy term conversion
    - Labeling may not need to be rewritten with the change to MedDRA, however, exceptions may occur
    - A pragmatic approach is recommended
    - It is acceptable to combine MedDRA and legacy terms in a single table if necessary when new information is received
    - In all instance, minimize confusion for end-user (e.g., add explanations where needed)

- For both the CCDS and HP labeling:

    - Encourage the use of term groupings – hierarchy terms such as HLTs and HLGTs and other standard groupings such as "MLEs"
        - Link conceptually covered PTs (and LLTs) under a single concept term (e.g., "diarrhea") based on a physician's understanding of that concept (not too broad, but not as granular as single PTs)

- Groupings should be used when needed to more easily communicate a particular concept to the end-user

- Typically, unmodified MedDRA terms should not be used for patient/consumer product labeling

VII. References

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