MedDRA®
POINTS TO CONSIDER
COMPANION DOCUMENT

ICH-Endorsed Guide for MedDRA Users

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SECTION 1 – INTRODUCTION

The *MedDRA Term Selection: Points to Consider* (MTS:PTC) and *MedDRA Data Retrieval and Presentation: Points to Consider* (DRP:PTC) documents provide valuable guidance to MedDRA users worldwide on general term selection and data retrieval principles as well as specific examples of approaches to coding and analysis. However, there are certain topics where users could benefit from having more detailed information pertaining to the use of MedDRA other than what is covered in the MTS:PTC and DRP:PTC documents.

The purpose of this Companion Document is to supplement the other two Points to Consider (PtC) documents by providing additional details, examples, and guidance on specific MedDRA-related topics of global regulatory importance. It was developed and is maintained by the same working group that was charged by the ICH Management Committee to develop the PtC documents. The working group consists of representatives of ICH regulatory and industry members, the World Health Organization, the MedDRA Maintenance and Support Services Organization (MSSO), and the Japanese Maintenance Organization (JMO).

The Companion Document is intended to be a “living” document and is updated based on users’ needs, rather than being tied to MedDRA releases. The Companion Document is available in English and Japanese; however, if certain examples are not relevant or are difficult to translate, these will not be included in the Japanese version.

The contents of the document are agreed by all ICH parties; it does not specify regulatory requirements, nor does it address database issues. Organisations are encouraged to document their own coding and data retrieval conventions in organisation -specific guidelines which should be consistent with the PtC documents.

Users are invited to contact the MSSO Help Desk with any questions or comments about the MedDRA Points to Consider Companion Document.

SECTION 2 – DATA QUALITY

This section will discuss important data quality and data entry principles related to the use of MedDRA in the clinical trial and postmarketing environments. It will not address specific regulatory requirements, database structure issues, file format conventions, data workflow applications, or other topics which are beyond the scope of MedDRA.

In both the development and marketing of human medicinal products, data collection is a critical and ongoing process. As noted in the *MedDRA Term Selection: Points to Consider* (MTS:PTC) document, the quality of original reported information directly impacts the quality of data output.

Data are applied to make inferences, test hypotheses, draw conclusions, make statements, and report findings about the safety and efficacy of biopharmaceutical products. Since data are used for activities ranging from coding to information categorisation, retrieval, analysis, and presentation, ensuring access to high quality data is paramount. Quality data support safety functions including signal detection, data analysis, and product label development. This section will describe some of the practices and processes which should be part of an organisational data quality strategy.

2.1 The Importance of Data Quality

As the regulated biopharmaceutical industry strives for greater harmonisation of safety reporting regulations and standards, there is an increasing emphasis on safety surveillance and data quality. In addition to supporting patient/subject safety, increased data quality facilitates communication of complete and accurate information to those involved in clinical research and post-marketing processes (including regulatory bodies, sponsoring companies, study site personnel and marketing authorisation holders). Collection of high -quality data can also result in greater time and cost efficiency during product development and marketing (e.g., less querying of incomplete data, decreased site monitoring costs and reduced risk of delayed regulatory approval).

The quality of adverse event data is central to safety monitoring in clinical trials, to the risk assessment of marketing applications and in the evaluation of safety

signals within postmarketing data. Adverse events are typically reported by study subjects, patients or their caregivers and health care professionals. These reported events may be either coded manually or coded automatically with autoencoder tools by selecting MedDRA Lowest Level Terms (LLTs). Users need to be aware that some LLTs are rather non-specific, and that further clarification of the reported information may be necessary. Small deviations in coding can result in significant issues and produce misleading analyses. Coding selections may vary even in apparently simple cases. Given this variability, it is important to thoughtfully evaluate adverse event data.

2.2 Characteristics of Good Quality Data

Quality data have several common features. Foremost, these data should be both complete and accurate. Whenever possible, the most concise form of data should be collected, without compromising either completeness or accuracy. Within an organisation, data quality is fostered by comprehensive, consistent, transparent and documented data handling processes. Quality data is, by definition, supported by the available information. For example, clinical diagnoses should be consistent with the available medical history, physical findings, laboratory and investigational results. Furthermore, quality data should be capable, when appropriate, of supporting data-related associations (e.g., when performing a causality assessment of an adverse event which could be related to a product).

2.3 The Role of MedDRA in a Data Quality Strategy

As a standardised and validated clinical terminology used in both clinical development and postmarketing surveillance, MedDRA has a fundamental role in a sound data quality strategy. Since MedDRA is used to “code” information during data entry, it is important to consider the principles in the MTS:PTC document to ensure the selection of coding terms with the highest specificity and medical accuracy for analysis. The large number of available LLTs provides a high degree of granularity. However, the granularity of MedDRA cannot overcome “low quality” primary information.

2.4 Components of an Organisational Data Quality Strategy

The development and implementation of an organisational data quality strategy is a complex task which involves the input, support and collaboration of many stakeholders. Many of the principles of high-quality data collection are the same

in both the clinical trial and postmarketing environments. This section will discuss a framework for acquiring high-quality data.

2.4.1 Data collection

Whether in a clinical trial, a postmarketing safety call centre, or a healthcare professional's office, there is often only one opportunity to capture complete and accurate information. Since data output quality is determined by data input quality in a database, there are important consequences from these initial steps. For those collecting information (e.g., a study site physician/nurse, a postmarketing call centre employee, a dispensing pharmacist, an emergency room physician), certain practices will help to maximise the quality of the collected data:

- During data collection, completeness and accuracy need to be weighed against the risk of collecting nonessential information. It is advisable to minimise the amount of nonessential information placed in dedicated data fields for key concepts such as adverse events. In clinical trials, reporters should be encouraged to use consistent medical terminology to describe similar medical concepts. The best strategy is to carefully train study site personnel (especially investigators) about the importance of consistency in data collection.
- Data collection tools (whether they are electronic or paper case report forms) should be carefully designed to be easy to use, enduring and sufficiently comprehensive to gather all the necessary information. Since individual trials or clinical projects can span years, it is never possible to spend "too much" time developing quality data collection tools. Appropriate "subject matter experts" in data management, information technology, statistics, quality assurance, and regulatory compliance should be involved throughout the planning process. After years into development, it is difficult, if not impossible, to compensate for needed data which has not been adequately collected.
- With the passage of time, the ability to seek clarification of incomplete or vague information becomes limited and very often, a reporter's recollection of important facts can change dramatically. Therefore, it is crucial to start the "query" process as soon as possible to obtain clarification from the data source.
- When a report contains multiple diagnoses (such as a report of "broken finger and hand abrasion" or "urinary bladder obstruction and cystitis"), it is usually appropriate to record these as separate concepts on the data collection form.

- Attempt to minimise spelling errors and the use of abbreviations and acronyms. The table below illustrates the difficulty of interpreting such poor or ambiguous data:

Reported	Data Quality Challenge
Had MI	Does MI stand for myocardial infarction, mitral insufficiency, mental illness or mesenteric ischaemia?
Interperial	Was this word intended to represent “intraperitoneal” or “intraperineal”?
Nitro drip	Did this drip contain nitroglycerin or nitroprusside?

- Furthermore, without proper context, it is impossible to interpret other “vague” terms as shown in the table below:

Reported	Data Quality Challenge
Congestion	Nasal, hepatic, venous, etc.?
Obstruction	Bronchial, intestinal, ureteral, etc.?
Infarction	Myocardial, cerebral, retinal, etc.?

Clarification of such terms should be requested at the time of data collection.

2.4.2 MedDRA coding considerations

MedDRA can be used to accurately code many types of reported information. This includes not only diagnoses, signs and symptoms representing adverse reactions/adverse events but also concepts such as medical and social history, indications for product use, device -related events, surgical and medical procedures, investigations, exposures, misuse and abuse, off label use, medication errors, product quality issues, and manufacturing and quality system issues. For meaningful data review, it is important to ensure that all required

information is coded consistently. Important data quality considerations include the following:

- Steps should be taken to ensure that individuals responsible for MedDRA coding have familiarity with the terminology as well as the requisite training to utilise it effectively. Particular attention should be paid to the relevant coding principles outlined in the MTS:PTC document and supported by the examples in this PtC Companion Document. In environments where MedDRA coding is performed by a number of individuals, it is important to have a consistent organisational approach.
- Appropriately trained individuals should review MedDRA coding.
- To ensure that the selected MedDRA term accurately reflects the given scenario, all information that is relevant (including contextual) for term selection needs to be available (e.g., in the verbatim text) to coders, autoencoding systems and reviewers.

  This is true in all cases and may be of particular relevance for age or gender information as well as medication error, overdose, abuse, misuse, lack of effect, off label use or product defects scenarios.
- It is an important concept that all adverse events and adverse reactions from a report should be coded, regardless of causal association. Similarly, do not add information by selecting a term for a diagnosis if only signs or symptoms are reported (MTS:PTC Section 2.10).
- It is important that reported information is coded accurately; it is not appropriate to select terms for concepts which are less specific or less severe than the reported term (e.g., coding a convulsive seizure with LLT *Shakiness* or coding peritonitis with LLT *Belly ache*).
- It is advisable to follow the “preferred” coding options specified in the MTS:PTC document, especially for issues such as the coding of provisional and definitive diagnoses with associated signs and symptoms. If one chooses to use an “alternate” coding option from the MTS:PTC, it is a good practice to document why this was done and to be consistent in the use of this alternate choice.
- It is important to distinguish medical conditions (typically found in the SOC of the primary manifestation site) from laboratory and test terms (which are found in SOC *Investigations*).

- Verbatim terms may contain more than one medical concept (such as a report of “fall and contusion”). It is important to consider each of the reported events and code as appropriate. Consider the use of “split coding” (selecting more than one term) where there is no single LLT within MedDRA which captures all of the relevant reported information (MTS:PTC Section 2.8 and Section 3.5.4).
- Organisations may wish to create “synonym” lists of verbatim terms associated with pre-determined LLTs. An example of a synonym list is shown below:

Reported Verbatim	LLT
Aching all over head Terrible headache	In a synonym list, each of these verbatim reports would be coded using LLT *Headache*

- Synonym lists are helpful to support consistent and efficient coding and may be particularly useful in some circumstances, e.g. when used in combination with autoencoding systems or when coding is done in several geographical sites. It is important to ensure that verbatim terms designated as a synonym are truly synonymous with the coded medical concept. Also, users should address synonym list maintenance in their versioning strategy.
- Medical and surgical procedures are generally not adverse events. However, if only a procedure is reported, then an appropriate term is used to code the procedure (MTS:PTC Section 3.13.1). On the other hand, if a procedure is reported with a diagnosis, then the preferred option is to select appropriate terms to code both the procedure and diagnosis. The alternate option is to code only the reported diagnosis (MTS:PTC Section 3.13.2). Some organisations have data collection forms with separate data fields for adverse events and for procedures; this aids entry of data in the appropriate category.

- In the context of safety reporting, death, disability and hospitalisation are outcomes or seriousness criteria, not adverse events. Therefore, they are generally not coded with MedDRA. Instead, they are recorded in the appropriate data collection field for outcomes. An exception to this recommendation is when death, disability, or hospitalisation is the only reported verbatim. These concepts are coded with MedDRA while clarification of the underlying cause is sought (see MTS:PTC Section 3.2 for further information). In addition, death terms that add important clinical information (e.g., LLT *Sudden unexplained death in epilepsy*, LLT *Foetal death*) should be selected along with any reported ARs/AEs.
- When vague, ambiguous, or conflicting information is reported, MedDRA has codes which can be utilised while attempts are made to clarify the information. For example:

Vague information (see also MTS:PTC Section 3.4.3):

Reported	LLT Selected	Comment
Appeared red	*Unevaluable event*	"Appeared red" reported alone is vague; this could refer to a patient's appearance or even that of a product (e.g., a pill, a solution)

Ambiguous Information (see also MTS:PTC Section 3.4.2):

Reported	LLT Selected	Comment
Patient had medical history of AR	*Ill-defined disorder*	It is not known what medical condition the patient had (aortic regurgitation, arterial restenosis, allergic rhinitis?), so LLT *Ill-defined disorder* can be selected

Conflicting Information (See also MTS:PTC Section 3.4.1):

Reported	LLT Selected	Comment
Severe anaemia with a haemoglobin of 19.1 g/dL	*Haemoglobin abnormal*	LLT *Haemoglobin abnormal* covers both reported concepts (note: haemoglobin value of 19.1 g/dL is a high result, **not** a low result as would be expected in severe anaemia

2.4.3 Training

Appropriate ongoing training is a key part of a good data quality strategy. Training should be given to all persons involved in the collection, transcription, categorisation, entry, coding, and review of information. Organisational training practices and procedures should be documented in writing and continually reviewed for updates. Training should be performed by appropriately qualified individuals who are knowledgeable about the organisation's standardised procedures and focused on compliance. Cross-training of key functions is advisable to ensure a consistent approach and to preserve data quality standards during periods of unexpected personnel changes.

Given that organisations may commonly use unfamiliar or remote study sites for clinical trial conduct, it is also important to ensure that study site personnel (e.g., investigators, study nurses, clinical study coordinators, clinical research associates, site pharmacists) are well trained in all relevant aspects of clinical trial conduct including:

- Correct use of the assigned data collection tools
- Training in appropriate techniques for interviewing of study subjects/patients [e.g., the use of non-directed questioning, reporting of adverse events as diagnoses (when possible) rather than lists of signs and symptoms, precautions to avoid unblinding]
- Knowledge of relevant regulatory considerations related to quality data collection

- Adequate knowledge of the use of MedDRA for coding purposes, as applicable. This is particularly important for concepts such as coding of definitive versus provisional diagnoses (with or without symptoms) and not inferring diagnoses
- A thorough understanding of and compliance with an organisation's agreed-upon "data query" process to clarify information

The "Data Quality, Coding and MedDRA" presentation in the 'General/Basics' section of the "Training Materials" page of the MedDRA website (https://www.meddra.org/training-materials) is another useful resource. This customisable slide set is intended for use at investigator meetings and for training personnel involved with data collection (such as clinical research associates and clinical coordinators). It provides an overview of the importance and benefits of good quality data as it relates to MedDRA.

2.4.4 Quality assurance checks

A thoughtful and thorough quality assurance (QA) process supports the goal of maximising data quality. QA checks during the data management process ensure compliance with established organisational procedures and metrics. Examples of inaccurate MedDRA coding which QA checks could identify include:

Reported	Inaccurately Selected LLT	QA Review Outcome
Allergic to CAT scan	*Allergic to cats*	This inaccurate LLT was selected by an autoencoder which matched the words "**Allergic to CAT s**can" from the reported term

Reported	Inaccurately Selected LLT	QA Review Outcome
Feels pressure in eye	*Intraocular pressure*	This inaccurate LLT refers to the name of the test for intraocular pressure; the appropriate term to reflect the symptom being described in the report would be LLT *Sensation of pressure in eye*.

QA checks could also identify coding inconsistencies. When the reported scenario conveys the same event/incident, although worded differently, it is essential to code consistently.

The MSSO -maintained Unqualified Test Name Term List is a comprehensive collection of all unqualified test name terms at the Preferred Term (PT) and Lowest Level Term (LLT) levels in SOC *Investigations*. The Unqualified Test Name Term List can be found on the “Support Documentation” page on the MedDRA website. It may be applied by regulatory authorities and industry as a QA check of data quality in clinical trial and pharmacovigilance databases. Test name terms without qualifiers (e.g., LLT *Blood glucose*, LLT *CAT scan*) do not represent ARs/AEs but are intended to point to an actual value in a specific database field. For example, in the section for Results of Tests and Procedures in the ICH E2B ICSR electronic transmission standard, unqualified terms may be used in the data element capturing the test name. Unqualified Test Name terms are not intended for use in other data fields capturing information such as ARs/AEs. The Unqualified Test Name Term List is intended as a recommendation only, providing a standard tool for checking coding quality.

2.4.5 MedDRA versioning strategy

Given the twice -yearly releases of new MedDRA versions, organisations should have a documented versioning strategy to address these updates. The MSSO has created a Best Practice document which contains sections entitled “Recommendations for MedDRA Implementation and Versioning for Clinical Trials” and “Recommendations for Single Case Reporting Using Semi-annual

Version Control". This document is found on the "Support Documentation" page on the MedDRA website.

In addition, the MSSO has provided a MedDRA Version Analysis Tool (MVAT) which facilitates the identification and understanding of the impact of changes between any two MedDRA versions, including non-consecutive- ones (see the "Tools" Page on the MedDRA website).

SECTION 3 – MEDICATION ERRORS

The purpose of this section is to expand on the section on medication errors in the *MedDRA Term Selection: Points to Consider* (MTS:PTC) document and to provide guidance on scenarios that are medication errors as well as scenarios informative for medication errors or scenarios that are confused with medication errors. This section has two main sub-sections; the first sub-section provides answers to commonly asked questions about coding medication errors. The second sub-section provides examples for coding medication errors.

The document is a living document, and the content of this section will be updated based on user feedback. Users are invited to contact the MSSO Help Desk with any questions or comments about the MedDRA Points to Consider Companion Document.

Acknowledgments

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Manish Kalaria, Physician, CDER, Office of Surveillance and Epidemiology, FDA, United States

Jo Wyeth, Associate Director, CDER, Office of Surveillance and Epidemiology/Office of Medication Error Prevention and Risk Management, FDA, United States

Georgia Paraskevakos, Patient Safety Specialist, Health Canada, Canada

Background

For the purposes of this document, medication errors occur only within the medication use process, which encompasses activities after release of the product into the healthcare system including procurement, storage, prescribing, transcribing, selecting, preparing, dispensing, administering, and monitoring. The medication use process excludes activities related to the entire manufacturing process comprising manufacturer distribution and storage (up to wholesaler), further described in Sections 4 and 5. Errors within the manufacturing process are manufacturing issues and are not medication errors; however, if the affected product is in the medication use process, a manufacturing issue may potentially result in adverse events and/or medication errors.

For coding purposes, terms that reflect medication errors are grouped in the High Level Group Term (HLGT) *Medication errors and other product use errors and*

issues (from MedDRA Version 20.0 onwards). However, terms located elsewhere in the MedDRA hierarchy can also be used to code cases describing medication errors. To aid data retrieval of the widely dispersed coding terms, the Standardised MedDRA Query (SMQ) *Medication errors* was developed, with a narrow and a broad scope, as a tool for standardised retrieval of suspected medication error cases.

It is essential to code reported medication errors with the most specific LLT. The LLTs linked to medication error PTs are usually more than just synonymous terms and often contain more specific information. For example, PTs for errors reflecting a stage of the medication use process may contain LLTs for specific types of errors occurring within that stage.

The HLGT *Medication errors and other product use errors and issues* contains numerous terms:

- Terms for the type of error (e.g., LLT *Wrong drug*)
- Terms (for an error) specific to a stage of the medication use process (e.g., LLT *Product prescribing error*)
- Terms combining the type of error with a stage of the medication use process; these terms can be strictly LLTs (e.g., LLT *Wrong drug prescribed* under PT *Product prescribing error*, a PT specific only to stage) or both LLTs and PTs (e.g., PT *Wrong product administered*)
- Terms describing the potential for an error (e.g., LLT *Potential for medication error, wrong drug*)
- Intercepted errors that did not reach the patient (e.g., LLT *Intercepted wrong dosage form selected*)
- Terms for situations when it is uncertain whether the reported incident occurred in error (e.g., LLT *Product prescribing issue*)

Each PT is grouped into one of the High Level Terms (HLTs), either for accidental exposures, stages of the medication use process, product confusion, or the HLT grouping for various other PTs not elsewhere classified.

3.1 Coding Medication Errors – Points for Consideration

3.1.1 MedDRA Concept Description for medication error

There are multiple definitions of a medication error.

> For the purposes of term selection and analysis of MedDRA coded data, medication errors are defined as any unintentional and preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient or consumer. Such events may be related to professional practice, health care products, procedures and systems, including prescribing, order communication, product labelling, packaging and nomenclature, compounding, dispensing, distribution, administration, education, monitoring and use. Within the HLGT *Medication errors and other product use errors and issues*, MedDRA terms that include the word “wrong” refer to medication errors.

As a general principle, intentional uses such as abuse, misuse, overdose, off label use, and clinical decisions to alter medication use due to adverse drug reactions (ADRs) are not medication errors. However, whether a scenario is an error or not depends on the reason or cause.

For example:

- Confusion with an aspect of the product may cause or result in reports of incorrect product use or misuse (e.g., the device was confusing so the person administered an extra dose to make sure he got a full dose); this scenario would usually be considered an error instead of intentional misuse.
- Patient may decide to take their medication differently than prescribed or recommended (change in dose, schedule, duration, etc.); this scenario may be classified as misuse, depending on the provided information, and not a medication error.
- Occurrence of an ADR may cause the patient to stop therapy; this is generally not considered intentional misuse or an error.

Drug abuse and details describing how the drug is abused (route of administration, preparation) do not constitute medication errors.

Note that situations such as product quality or product supply issues outside one’s control are also not usually classified as medication errors but can result in

medication errors. For example, device malfunction or packaging defect (product quality issues) can result in an incorrect dose administered.

3.1.2 Medication error vs. misuse

For the purposes of term selection and analysis of MedDRA-coded data, misuse is the intentional use for a therapeutic purpose by a patient or consumer of a product – over-the-counter or prescription – other than as prescribed or not in accordance with the authorised product information.

Consider the full context of the report to determine whether the information is a medication error or a misuse. Relying on single words in the verbatim without considering the relevant context may lead to incorrect coding.

An example is a scenario where “a patient misused a product in error because he misunderstood the dosing instructions provided by the physician”.

Similar verbatims may be reported, as “accidental misuse”, “misused unintentionally”, or “misused drug by mistake”. Therefore, such scenarios should be coded to the most specific medication error term rather than to a misuse term.

For cases in which the context does support a misuse scenario (which is always for a therapeutic purpose, as per the concept description), select the most specific term describing the misuse.

When the information is insufficient to make the distinction, try to clarify the information. If not possible, then select the most applicable term without inferring what is not reported. Avoid double-coding a singular event by selecting a term for an error and a term for misuse when neither is stated but both are possible.

3.1.3 Medication error vs. off label use

For the purposes of term selection and analysis of MedDRA-coded data, the concept of “off label use” relates to situations where a healthcare professional intentionally prescribes, dispenses, or recommends a product for a medical purpose not in accordance with the authorised product information. When recording off label use, that product information and/or regulations/requirements may differ between regulatory regions.

Consider the following verbatim: a prescriber ordered a much higher dose than per label. It is not stated if this was a mistake or off label use; should terms for both possibilities be selected, as in differential diagnoses?

- Do not double code a singular event by selecting a term for an error and a term for off label use when neither is stated but both are possible; this approach is not helpful.
- When a scenario is unclear, try to obtain clarification; if still unknown, select the most applicable term for what is reported without inferring what is not reported. For example, if it is only reported that Drug X was prescribed at a higher dose than per label (no information that it was in error or off label use), select LLT *Prescribed overdose* (HLT *Overdoses NEC*).
- Off label use terms should only be selected when off label use is specifically mentioned in the reported verbatim information.
- Terms for “suspected off label use” may be selected when medical judgment indicates that the product was used off label although not stated in the reported verbatim information.
- A medication error should be ruled out if suspecting an off label use scenario.
- ARs/AEs and medication errors such as dosing errors can occur in the context of off label use and should be coded when reported.

Reported Information	**Contextual Information for Coding**	**LLT**	**Comments**
Drug was prescribed to a 2-year-old child.	Drug is only approved for adults, but treatment of paediatric patients is an accepted medical practice.	*Suspected off label use in unapproved age group*	Although off label use is not explicitly stated, it is suspected based on medical knowledge.
Drug was prescribed to a 2-year-old child.	Drug is only approved for adults; no medical knowledge about use in paediatric patients.	*Drug prescribed for unapproved age group*	

Reported Information	Contextual Information for Coding	LLT	Comments
Drug was prescribed to a 2-year-old child. During reconstitution the caregiver did not add the necessary amount of liquid in error.	Drug is only approved for adults, but treatment of paediatric patients is an accepted medical practice.	*Suspected off label use in unapproved age group* *Product reconstitution error*	Medication errors can still also occur in the context of suspected or stated off label use and should be coded when reported.

3.1.4 Intercepted medication errors

How should terms be selected for reports that describe intercepted errors?

For example, a report stated that 'the wrong drug strength was dispensed to the ward because of similar packages, but the nurse immediately realized the mistake and alerted the pharmacist'.

For the purposes of term selection and analysis of MedDRA coded data, an intercepted medication error refers to the situation where a medication error has occurred but is prevented from reaching the patient or consumer. The intercepted error term should reflect the stage at which the error occurred, rather than the stage at which it was intercepted.

- Select LLTs that represent information about the intercepted error, the error type that occurred, and the contributing factor(s), if reported. Some LLTs contain information about both the intercepted error and the type of error (e.g., LLT *Intercepted wrong drug strength selected*, LLT *Intercepted wrong route of administration selected*). If such a specific LLT is unavailable for the reported scenario, select a separate term for each.

- For the above example, select terms to capture:
    - the intercepted error (LLT *Intercepted drug dispensing error*)
    - the type of error that occurred (LLT *Wrong drug strength dispensed* under PT *Product dispensing error*)
    - the contributing factor (LLT *Look alike packaging*)

3.1.5 Potential medication errors

How should terms be selected for reports that describe the potential for error?

For example, a report stated that ‘two drug labels look alike and could result in someone getting the wrong drug’.

Select terms that represent information of a potential for an error to occur, the contributing factor(s) and the potential error type.

- Potential for an error should be captured by selecting the closest LLT under PT *Circumstance or information capable of leading to medication error*.

  It is essential to capture information on the specific potential error of concern, not only that there is a potential for an error, if information is available in the verbatim. Terms that only capture a potential for an error and not the type of error, should be used as stand-alone terms only if no further information on the type of error is reported.

  Some LLTs combine the potential for error and the type of error within a single term; if such a term is not available for the reported scenario, select a separate term for each.

  For the above example, select terms:

    - For the potential for an error including the type of error (LLT *Potential for medication error, wrong drug*)
    - For the contributing factor (LLT *Drug label look-alike*)

3.1.6 Use of LLT Medication error

When is it acceptable to use the Lowest Level Term (LLT) Medication error? Can the term be selected if there is no appropriate MedDRA term for the error?

- The use of LLT *Medication error* should be avoided unless there is **no other** information reported about the specific type or stage of error.
- Check all the LLTs in HLGT *Medication errors and other product use errors and issues* for the most specific term possible.
- If a specific error is reported but no suitable LLT is available, the procedure for a change request should be followed (see the Change Requests page on the MedDRA website). In the interim, select the closest available term to code the reported error. There may be rare instances when LLT *Medication error* is the closest term and can be selected.

3.1.7 Selecting more than one term

Should terms for all reported errors related to the same incident be selected?

Sometimes the ‘originating error’ (also referred to as the initial error) results in consequent errors. For example, it was reported that “a prescribing error for the wrong drug consequently resulted in the wrong drug being dispensed and administered.”

- The ‘originating’ error, as well as additional or ‘consequent’ errors and contributing factors should be coded if they are stated in the report. In the above example, code LLT *Wrong drug prescribed* and code LLT *Wrong drug dispensed* and LLT *Wrong drug administered* as consequent errors.
- Avoid ‘double coding’ the same error when this does not add information. In other words, do not use multiple LLTs to capture a singular error that is reported with both a general and a specific verbatim; code only the specific error. For example, if it is reported that there was an administration error in that the wrong drug was administered, select only LLT *Wrong drug administered* for the specific error. Do not use an additional LLT *Drug administration error* for the general description because this would not add any meaningful information (even though the two LLTs are linked to different PTs). Examples describing when double coding is necessary can be found in Section 3.1.5.

- Bear in mind that some organisations will have their database configured in a way that counts at LLT level and therefore if two LLTs which map to the same PT are used, this may impact signal detection.

3.1.8 Selecting the most specific term

How should terms that have overlapping concepts with other terms be used?

For example, a report described a patient who did not exchange the needle for repeated use.

- The most specific available LLT should be selected for the reported information. For the above example, select LLT *Needle reusage* (PT *Multiple use of single-use product*) because it is more specific than LLT/PT *Wrong technique in device usage process*. Coding a singular incident by selecting two terms is useful only when this provides meaningful additional information, i.e., when the single LLT cannot describe the entire reported scenario.

3.1.9 Stages of the medication use process

When is it appropriate to use a medication error term without the stage of the medication use process?

Some MedDRA terms have both the type of error and stage of the medication use process (e.g., LLT *Wrong drug prescribed*); some terms have only the type of error (e.g., LLT *Wrong drug*); and some terms have only the stage (e.g., LLT *Drug prescribing error*). PTs for the stage of the medication use process contain specific LLTs for error types at that stage, but not necessarily for all types (e.g., PT *Product prescribing error* contains LLTs for prescribing a wrong drug (LLT *Wrong drug prescribed*), a wrong dose (LLT *Drug dose prescribing error*), a wrong schedule (LLT *Drug schedule prescribing error*), but not for a wrong strength).

- Using a single LLT

For example, a report stated that ‘the pharmacy dispensed the wrong drug’. It is important to highlight both the stage and the type of error where it is known. In this example, this is possible using a single LLT *Wrong drug dispensed* (instead of two LLTs: LLT *Wrong drug* and LLT *Drug dispensing error*).

- Using more than one LLT

For example, a report of ‘mistakenly prescribed the wrong strength’ should be coded with LLT *Wrong strength* and LLT *Drug prescribing error* because no available single term captures the complete reported information.

If the stage is not known, there are terms for the type of error only, such as LLT *Wrong drug*, LLT *Wrong schedule*, LLT *Wrong strength*, etc.

3.1.10 Coding contributing factors/causes for medication errors

What is a contributing factor? Is it recommended to code the contributing factor if stated in the case report?

The MedDRA Concept Description for contributing factor is adapted from the World Health Organization[1] and is as follows:

> A contributing factor is a circumstance, action or influence which is thought to have played a part in the origin or development of a medication error or to increase the risk of a medication error.

MedDRA contains terms for capturing contributing factors related to the product (e.g., product label confusion, use of error-prone- abbreviations, product quality issues leading to errors).

However, organisational system issues such as noise level, fatigue, and staffing levels may also contribute to medication errors. These factors may not have specific MedDRA terms and should be recorded in free text (e.g., narrative section). For these organisational system issues, an overarching term (LLT *Organisational systems issue contributing factor*) can be used for coding.

When contributing factors are provided, select a term for the contributing factor and the error.

- For example, a product quality issue may lead to a medication error; in such a case, the product quality issue is the contributing factor for the error. Select terms for both the quality issue and the error.

[1] Conceptual Framework for the International Classification from Patient Safety. WHO, 2009 The International Classification for Patient Safety,3 under development by the World Health Organization. Available at: https://apps.who.int/iris/bitstream/handle/10665/70882/WHO_IER_PSP_2010.2_eng.pdf

- For example, a communication issue, such as a patient not receiving the product instructions for use, may lead to a medication error; in such a case, the communication issue is the contributing factor to the error. Select terms for both the communication issue (e.g., LLT *Product information not provided to patient*) and the error.

3.1.11 Do not infer a medication error

Is it acceptable to use specific medication error codes for information not explicitly stated in the case report?

The selected LLTs should reflect only the information stated in the case report; it should not be assumed that a medication error occurred if this is not clearly reported as such.

For example, the report that only stated 'The nurse administered 50 mg of Drug X' is not an informative report and should not be submitted as such; further information should be sought or a dose qualification referencing the prescribing information should be provided in the narrative.

Ideally, at the point of data capture, the reason for reporting as a medication error should be included in the narrative and verbatim, e.g., 'the patient was accidentally given 50 mg which is more than the prescribed dose'. Alternatively, if it is not possible to clarify with the reporter but the prescribing information recommends a smaller dose, then the report should reference the prescribing information in the narrative, e.g., "the nurse administered 50 mg of Drug X, whereas the recommended dose in the prescribing information is 25 mg."

Reported	LLT	Comment
Drug X 50 mg administered	-	This verbatim is uninformative. Additional (e.g. contextual) information is needed.
Drug X 50 mg administered, which is different from the labelled dose	*Unapproved dose administered*	No information to distinguish if an error or intentional, code to LLT *Unapproved dose administered*

Reported	LLT	Comment
Drug X 50 mg administered by mistake	*Wrong dose administered*	Medication error
Drug X 50 mg administered by patient because his usual dose had no effect	*Intentional misuse by dose change* *Lack of drug effect*	Intentional misuse
Drug X was partially administered because of premature locking of needle shield	*Partial dose delivery by device* *Safety mechanism activated prematurely*	Medication error and specific device issues

3.1.12 Medication errors related to products with a drug delivery device

An increasing number of marketed products are intended for use with a drug delivery device and may be available as a single drug device- product, co--packaged in a kit, or separately distributed but labelled for use with a specific device. There are numerous types of drug delivery devices, including autoinjectors, pens, patient controlled- injectors, prefilled syringes, on-body injectors/wearable injectors, transdermal and topical delivery systems, metered dose inhalers, etc. A delivery device may have a unique or complex product design, instructions for use, packaging, and safety features, any of which may cause confusion and lead to a medication error. Further, the same drug is often marketed as several distinct products, each with a different delivery device (e.g., Drug A supplied as pen, prefilled syringe, and autoinjector).

When processing a medication error report involving a drug delivery device, it is important to capture the specific device related contributing factors that led to the error. Such factors can be problems with:

- the labelling (e.g., confusing packaging, device name, or instructions for using the device)
- the device itself (e.g., device malfunction, poor design, failed to activate)
- the way the device is used (e.g., injector positioned upside down, needle cap not removed)

Some reports do not have enough information to determine if the incident is related to a device issue/malfunction or a device use error. Clarification should be sought since these are very important distinctions to inform case coding and retrieval. Considerations relating to good data collection can be found in Section 2.4.1. Attempt to code the verbatim information and avoid inferences.

Safety reports involving a drug delivery device may reflect medication errors (e.g., prescribing or dispensing the incorrect product or using the device incorrectly), complications with using the delivery device (e.g., needlestick injury), product design or other product quality issues, malfunction, or adverse events.

Medication error terms can be those specific to products with a drug delivery device, or applicable to all products. The same adverse event or error may occur consequent to different preceding events and may further lead to a new error. For example, “pen jammed” scenario could result from using the device incorrectly (medication error category) or due to a malfunction (device issues category). Regardless of why the “pen jammed”, there may or may not be a reported consequence, such as a missed or delayed dose (medication error category) or an adverse event.

Scenario	Medication error?	LLT	Comment
Pen jammed.	Unknown	*Device mechanical jam*	
Patient used the pen correctly, but the pen jammed.	No	*Device mechanical jam*	The reported information clarifies that the patient used the pen correctly, ruling out a medication error. A potential consequent medication error should not be inferred as it is not reported.
Pen jammed and patient missed his dose.	Yes	*Drug dose omission by device* *Device mechanical jam*	Unknown if the device was used correctly, only that a device issue resulted in a medication error.
Patient thought the new pen is used the same way as his prior one. He did not use it correctly and the pen jammed.	Yes	*Device use error* *Device mechanical jam*	Incorrect use, which is a device use error; this error resulted in the device function issue.

Scenario	Medication error?	LLT	Comment
Patient followed the product leaflet instructions for use but misunderstood the steps as they were not clear, and the pen jammed.	Yes	*Product leaflet instructions confusion* *Device use error* *Device mechanical jam*	Unclear instructions for use resulted in use error and device function issue.
Due to a new design a pen was difficult to activate. A patient pushed the plunger button as hard as he could but managed to deliver only a partial dose.	Yes	*Product design issue* *Delivery device component difficult to use* *Partial dose delivery by device*	A product design issue resulted in a medication error.

How does MedDRA group concepts related to devices?

There are multiple types of events related to devices, and they are grouped in different MedDRA sections. The terms need to be searched for in several HLTs/HLGTs.

- **Device errors** and **Device use issues** are generally grouped in HLGT *Medication errors and other product use errors and issues*.
- **Device issues** are generally contained in the HLGT *Device issues*.
- **Complications associated with device** are generally grouped in HLGT *Complications associated with device*.
- **Product quality issues**: Existing terms for product quality issues are applicable to products with a device, and are generally grouped in HLGT *Product quality, supply, distribution, manufacturing and quality system issues*.

3.2 Examples for Coding Medication Errors

This sub-section provides examples for coding medication errors in various categories.

The LLTs may fall into more than one category and the concepts presented may overlap across tables.

3.2.1 Accidental exposures to products

Scenario	Medication error?	LLT	Comment
Parent accidentally injected himself in the thumb while using an auto-injector to administer the drug to the child.	Yes	*Accidental exposure while administering drug*	The parent was not the intended patient and was accidentally exposed to the drug. The selected LLT captures the reported information with specificity, e.g., that the accidental exposure occurred while administering the drug.
Patient experienced choking after accidentally swallowing a desiccant tube that was the same colour and similar size as the tablets in the bottle.	Yes	*Accidental ingestion of product desiccant* *Product appearance confusion* *Choking*	Accidental exposure is the error. Although a product desiccant is considered a part of product packaging, the LLT Product appearance confusion is the closest term available to capture the reported contributing factor to the accidental ingestion.

Scenario	Medication error?	LLT	Comment
2-year-old child took some antibiotics that were accidentally left on the kitchen counter.	Yes	*Accidental drug intake by child*	This is an example of an accidental exposure.
Adolescent died of overdose after taking 200 doses of a nasal inhalant in under 15 minutes, in an attempt to get high.	No	*Drug abuse* *Overdose*	Overdose in the context of drug abuse is neither a medication error nor intentional misuse which implies therapeutic use (see MTS:PTC, Section 3.16). Death would be captured as an outcome and seriousness criterion.
Adult intentionally ingested 2 tablets of 100 mg strength for his back pain instead of the recommended 1 tablet.	No	*Intentional misuse by dose change*	This is an example of intentional misuse and is not a medication error.
A person tried to commit suicide by overdosing on heroin and prescription opioids.	No	*Multiple drug overdose intentional* *Attempted suicide*	This is not a medication error but a scenario of an intentional overdose in the context of a suicide attempt.

Scenario	Medication error?	LLT	Comment
Person took street heroin to get high but died of a heroin overdose.	No	*Overdose* *Opioid abuse*	It is not known that the overdose was intentional; do not code as accidental overdose because the scenario is in the context of drug abuse, not a medication error. Death would be captured as an outcome and seriousness criterion.

3.2.2 Miscellaneous medication errors/issues

Scenario	Medication error?	LLT	Comment
Pharmacist reported that the product label was confusing and that it could result in a patient receiving the wrong dosage form.	Yes	*Circumstance or information capable of leading to medication error* *Product label confusion* *Wrong dosage form*	This is an example of a potential medication error since the report does not state that the wrong product was actually dispensed or administered. The LLT *Circumstance or information capable of leading to medication error* captures that the error is potential. The most specific code for the reported type of potential medication error should be selected and the contributing factor, label confusion.

Scenario	Medication error?	LLT	Comment
Patient drew her insulin out of the pen with a syringe because she was confused by the numbers marked on the pen to select the dose, and did not want to mistakenly take too much insulin using the pen.	Yes	*Inappropriate drug extraction with syringe* *Device markings confusion*	The initial confusion is with the graduation markings on the pen. Product design confusion may cause device use confusion, which may result in an administration error. In the example scenario, the patient intentionally extracted the drug with a syringe to prevent such a dosing error. The confusion and the consequent wrong technique in product usage are both within a scenario of a medication error, so there is no need to add Intentional device misuse. Do not infer a missed or incorrect dose, since it is not reported in the narrative.

Scenario	Medication error?	LLT	Comment
Patient experienced hypoglycaemia after he used his insulin pen cartridge as a vial. He reported that he did so because he had leftover insulin syringes and did not want to waste them.	No	*Intentional device misuse* *Hypoglycaemia*	This is an example of intentional misuse: there is a therapeutic purpose but there is no mention of a medication error.
The pharmacist used a wrong adapter device that was incompatible with the drug; the device started dissolving when it was used to transfer the drug from the vial to the bag for administration.	Yes	*Wrong device used* *Drug-device incompatibility*	Capture both that the wrong device was used and that it is incompatible with the drug.

Scenario	Medication error?	LLT	Comment
Patient did not hold the injector on the skin for the recommended 10 seconds during administration because he misunderstood how to use the pen.	Yes	*Delivery device removed before complete product administration* *Device use confusion*	In considering coding options for this scenario, both LLT *Device use error*, and LLT *Wrong technique in device usage process* are more general terms then the selected LLT *Delivery device removed before complete product administration* - PT *Product administration interrupted*.
The patient forgot to have her hormonal intra-uterine device (IUD) replaced after the recommended 5 years. In the 7th year after device was originally inserted, she became pregnant.	Yes	*Unintentional device use beyond labelled duration* *Pregnancy with IUD*	LLT *Unintentional device use beyond labelled duration* (PT *Device use error*) represents a broad error in using the device appropriately according to recommendations for its intended use.

Scenario	Medication error?	LLT	Comment
Pharmacy application software had a built-in dose calculator that was misprogrammed by the pharmacy. The error resulted in a child getting the wrong dose.	Yes	*Device programming error* *Dose calculation error associated with device* *Wrong dose administered*	
While hospitalized, patient experienced an unspecified medication error but no adverse event.	Yes	*Medication error*	This is not an informative report but is an example where the verbatim is captured with LLT *Medication error*. According to the MTS:PTC, if a medication error report specifically states that there were no clinical consequences, the preferred option is to select only a term for the medication error. Alternatively, a term for the medication error and the additional LLT *No adverse effect* can be selected (see MTS:PTC, Section 3.21).

Scenario	Medication error?	LLT	Comment
Nurse administered the wrong dose after using a faulty mobile medical device (app) that miscalculated the patient's insulin needs.	Yes	*Mobile medical application issue* *Dose calculation error associated with device* *Wrong dose administered*	The issue with the mobile application is the cause of the dose calculation error and the subsequent administration of the wrong dose.
Patient split the tablet (labelling doesn't advise against splitting the tablet).	No		The report does not mention an error; instead, it confirms that this is not a medication error because the label does not advise not to split. There is nothing to code in the provided text.
Provider prescribed half a tablet once daily, unaware that the labelling states to swallow the tablets whole. Patient split the tablets.	Yes	*Product prescribing error* *Tablet split by mistake*	.

Scenario	Medication error?	LLT	Comment
Prescriber advised patient to split tablet. The labelling states that tablets should be swallowed whole.	Unknown	*Product prescribing issue*	Select LLT *Product prescribing issue* since it is not known whether this is unintentional (a medication error) or intentional (off label use). The report does not indicate whether the prescriber was aware that the tablets should be swallowed whole.
Patient should be on Drug A but instead got Drug B; it is unclear where the error occurred.	Yes	*Wrong drug*	This is a “Wrong drug” medication error; the stage where the error occurred is not stated (e.g., at prescribing, dispensing, selection, or administration).

Scenario	Medication error?	LLT	Comment
A generic was incorrectly substituted for the brand name product although the physician specifically prescribed the brand name product with no substitution.	Yes	*Product substitution error*	This is a scenario of a substitution error coded with an “error” term, PT *Product substitution error*, HLT *Medication errors, product use errors and issues NEC*. Another term, LLT-PT *Product substitution*, HLT *Therapeutic procedures NEC*, signifies neither an error nor an issue, only product substitution.
Patient had thrown medicated opioid patches in the open waste bin instead of disposing as recommended in the label. Their child experienced an overdose after playing with the patches.	Yes	*Incorrect disposal of medication* *Accidental exposure to product by child* *Accidental overdose*	The route of exposure is not specified in the verbatim information and therefore cannot be coded.

3.2.3 Product administration errors/issues

3.2.3.1 Dose omission

As per the MedDRA Concept Description, dose omission refers to an event where an ordered dose is not administered before the next scheduled dose, if any.

Dose change and discontinuation of therapy due to an adverse event do not represent dose omissions, and are usually captured elsewhere, so only the adverse event should be coded.

Circumstances define the type of dose omission. Scenarios where dose omission occurs can be generally grouped as follows:

- Dose omission unintentional (error; e.g., dose missed because patient misunderstood instructions, pen device jammed and patient could not deliver the dose, patient forgot to take dose)
- Dose omission intentional (dose omission for clinical reasons, e.g., patient skips a dose of an antidiabetic because of low blood sugar, medication held one day prior to surgery)
- Dose omission that is unspecified (cause / contributing factors unknown, e.g., dose was not administered)
- Therapy interruption (neither an error nor intentional, due to external factors; e.g., supply, insurance, financial issues).

The cause or contributing factors for the dose omission are necessary to determine if the omission is a medication error or not, and consequently to select the appropriate MedDRA term(s). A variety of terms exist to capture the different scenarios accurately.

Scenario	Medication error?	LLT	Comment
Health care provider reported a problem that resulted in leakage where the two syringes were connected. This led to the dose not being given.	Yes	*Drug dose omission by device* *Syringe connection issue* *Leak at device connection*	This is an example of a device-related contributing factor leading to a medication error.
Patient was not given the dose of the drug, as the nurse accidentally administered the diluent to the patient instead of using the diluent to reconstitute the vial containing the active ingredient.	Yes	*Missed dose in error* *Active ingredient not added to diluent* *Single component of a two-component product administered*	In this scenario, dose omission is an error caused by failure to reconstitute the vial with the diluent. The specific term LLT *Missed dose in error* should be selected if the report indicates that the dose omission is an error. The originating error is the product preparation error.
Missed dose.	Unknown	*Missed dose* (PT *Product dose omission issue*)	No other information available.

Scenario	Medication error?	LLT	Comment
Patient couldn't take medication for a day because the pharmacy was out of the medication.	No	*Temporary interruption of therapy* *Product availability issue*	This event is neither intentional nor a medication error. Use LLT *Temporary interruption of therapy* and capture that an external factor caused the interruption of therapy.
Patient missed her dose because she did not notice that one of the dosage units in the package was empty.	Yes	*Missed dose in error* *Package empty units* (PT *Product packaging quantity issue*)	This event of missing a dose is unintentional, because it is due to a product packaging quantity issue.
Patient did not take medication last week because he could not afford it.	No	*Temporary interruption of therapy* *Inability to afford medication*	This is neither a dose omission in error nor an intentional dose omission. Use LLT *Temporary interruption of therapy* and capture that an external factor caused the interruption of therapy.
The afternoon dose was held because the patient was scheduled for a medical procedure.	No	*Product dose omission by medical indication*	This is an example of an intentionally omitted dose.

Scenario	Medication error?	LLT	Comment
Patient's blood sugar was low so he decided to skip the prescribed evening dose of insulin.	No	*Product dose omission by medical indication*	This is an example of an intentionally omitted dose by the patient for a clinical reason.
Patient took the drug as prescribed but broke out in a red itchy rash and did not take the remaining doses.	No	*Itchy rash*	Stopping or adjusting therapy because of an adverse event does not represent an error or intentional misuse. Discontinuation or adjustment of therapy may be captured elsewhere in the database/case report.
Patient was nonadherent with his antituberculosis regimen.	No	*Treatment nonadherence*	
The on-body infuser fell off the patient's arm and she missed the dose.	Yes	*Missed dose in error* *Drug delivery device fell off skin*	Capture the unintentional missed dose and that it occurred because the delivery device fell off. In this case it is not stated whether this is an adhesion issue.

Scenario	Medication error?	LLT	Comment
Patient forgot to take his medication on one day during the week.	Yes	*Forgot to take product*	

3.2.3.2 Other administration errors/issues

Scenario	Medication error?	LLT	Comment
Patient had difficulty removing the tablet from the thick blister pack; she managed to force it out, but the tablet crumbled into many pieces that fell to the floor. She was only able to find and take a few pieces of the dose.	Yes	*Product blister packaging issue* *Incorrect dose administered*	There is an issue with the blister packaging which should be coded. "Tablet crumbled" in this scenario may or may not be a product quality issue and coding can be considered depending on the specific circumstances.

Scenario	Medication error?	LLT	Comment
Syringe plunger couldn't be completely pushed down so the patient received only half of his scheduled dose.	Yes	*Partial dose delivery by device* *Syringe issue*	Capture both the device issue and the consequent medication error. There are multiple reasons (e.g., malfunction, product design) why the plunger couldn't be pushed down so LLT *Syringe issue* is the appropriate term.
A patient reported that he followed the directions for use, but the device jammed and most of the injection sprayed all over his hands.	Yes	*Accidental exposure while administering drug* *Device mechanical jam* *Accidental contact of product with skin*	The example indicates the patient followed the directions, so a use error appears to be ruled out. LLT *Device mechanical jam* is the appropriate term to capture the event. Do not infer a missed dose since it is not reported in the narrative. The reported medication error is the accidental exposure to the product.

Scenario	Medication error?	LLT	Comment
Patient unknowingly taking a drug that is contraindicated with his disease.	Yes	*Contraindicated drug administered* *Labelled drug-disease interaction medication error*	The report states that the patient is taking a contraindicated drug; provided circumstances clarify that this is a medication error.
The drug was administered in the abdomen rather than the arm muscle as recommended.	Unknown	*Drug administered at inappropriate site*	
Patient asked her health care provider about possible overdose symptoms because she unintentionally took an extra dose.	Yes	*Accidental dose increase*	The patient is only inquiring about overdose symptoms (not reporting an overdose). Even though there is a more detailed issue term available for the extra dose in LLT *Extra dose administered*, it is important to cover the accidental nature of the event.
Patient reported taking an expired drug.	Unknown	*Expired drug used*	

Scenario	Medication error?	LLT	Comment
Patient experienced respiratory arrest after the nurse misprogrammed the infusion pump to deliver the drug over 5 minutes instead of the intended 50 minutes.	Yes	*Drug administration rate too fast* *Pump programming error* *Respiratory arrest*	
The patient used a cracked insulin cartridge which resulted in a partial dose administered.	Yes	*Partial dose delivery by device* *Cartridge cracked*	

3.2.4 Product confusion errors/issues

Scenario	Medication error?	LLT	Comment
Patient was dispensed Drug Y instead of Drug X. The two drugs had similar looking packaging.	Yes	*Look alike packaging* *Wrong drug dispensed*	

Scenario	Medication error?	LLT	Comment
Patient purchased over the counter (OTC) Drug A, 10 mg strength instead of intended Drug A 5 mg strength because of label confusion.	Yes	*Product label confusion* *Wrong drug strength selected*	
Patient accidentally took the wrong drug for a week because the tablets looked identical to his daily vitamin tablets.	Yes	*Wrong drug administered* *Look alike pill appearance*	
Mix-up of 5 mg/ml with 50 mg/ml product.	Yes	*Product strength confusion*	It is unclear whether the patient was administered the drug. 'Strength' pertains to the product itself; 'dose' is the amount of drug the patient receives / should receive.
Patient was dispensed 'Drillo' instead of 'Millo', as the pharmacist misheard the name of the drug as 'Drillo" when the physician ordered it over the telephone.	Yes	*Wrong drug dispensed* *Drug name sound-alike*	

Scenario	Medication error?	LLT	Comment
Patient experienced skin ulceration after applying the wrong topical medical cream. Error attributed to the creams packaged in the same size tube with similar red font and black background labels.	Yes	*Wrong drug administered* *Look alike packaging* *Drug label look-alike* *Skin ulceration*	
Patient with known hypersensitivity to Drug A experienced a serious allergic reaction after using Drug A. The error was attributed to the labelling that used an abbreviation for Drug A instead of the complete name of the drug.	Yes	*Use of error-prone abbreviation* *Documented hypersensitivity to administered drug* *Allergic reaction to drug*	

3.2.5 Dispensing errors/issues

Scenario	Medication error?	LLT	Comment
Patient complained that the generic didn't work as well as the innovator drug.	No	*Product substitution issue brand to generic* *Drug effect decreased*	This is a product quality complaint.
A generic was substituted for the brand name product.	Unknown	*Product substitution* (HLT Therapeutic procedures NEC)	Code only what is stated. The report does not specify an error.
Patient received expired patches from the pharmacy.	Yes	*Expired drug dispensed*	
Patient took the drug daily instead of on the intended weekly schedule because the clinic wrote the wrong directions on the vial.	Yes	*Wrong directions typed on label* (PT *Product dispensing error*) *Once weekly dose taken more frequently*	
Drug was not dispensed in the original container, although the labelling advises that the drug must be kept in the original container.	Yes	*Drug not dispensed in original container*	

Scenario	Medication error?	LLT	Comment
The prescription was illegible and resulted in the pharmacy dispensing the wrong strength.	Yes	*Wrong drug strength dispensed* *Written prescription illegible*	
Pharmacy dispensed drug with the pharmacy label obscuring the recommended storage information. Product stored at wrong temperature.	Yes	*Pharmacy label placed incorrectly* (PT *Product dispensing error*) *Product storage error*	This is a specific dispensing error captured by LLT *Pharmacy label placed incorrectly*. There is no need to also select LLT *Drug dispensing error*, a less specific term that does not add information.

3.2.6 Monitoring errors/issues

Scenario	Medication error?	LLT	Comment
Patient was hospitalized with thromboembolism because his INR wasn't monitored as recommended in the labelling.	Yes	*Drug monitoring procedure not performed* *Thromboembolism*	

Scenario	Medication error?	LLT	Comment
Literature report hypothesised a possible drug interaction caused the patient to experience hypotension.	No	*Drug interaction* *Hypotension*	
Patient experienced type I hypersensitivity after receiving amoxicillin during surgery. Only the patient's e-health record had a documented history of amoxicillin allergy, but due to a lack of interoperability between the anaesthesia software and the hospital's e-health record, this information was not transferred.	Yes	*Medication error in transfer of care* *Software interoperability issue* *Hypersensitivity type I* *Documented hypersensitivity to administered drug*	

Scenario	Medication error?	LLT	Comment
Patient on anticoagulant undergoing surgery but due to an oversight, it was not stopped prior to surgery as recommended in the labelling and patient experienced postoperative bleeding.	Yes	*Failure to suspend medication* *Postoperative bleeding*	
Provider prescribed two drugs with known drug interaction because he was unaware of the interaction potential.	Yes	*Labelled drug-drug interaction medication error* *Drug prescribing error*	
Patient's lithium level was not monitored.	Unknown	*Therapeutic drug monitoring analysis not performed*	
Patient's ANC (absolute neutrophil count) was monitored monthly and not weekly as recommended in the label by mistake.	Yes	*Drug monitoring procedure incorrectly performed*	

3.2.7 Preparation errors/issues

Scenario	Medication error?	LLT	Comment
Caregiver wasn't aware to remove the inner cover from an insulin pen needle when preparing the pen.	Yes	*Product assembly error during preparation for use*	
Product was reconstituted with the wrong diluent.	Yes	*Wrong solution used in drug reconstitution*	
Pharmacy compounded the wrong strength product.	Yes	*Product compounding error* *Wrong strength*	
Patient received only one component of a two-component product because the nurse wasn't aware that the two components needed to be mixed together before administration.	Yes	*Product preparation error* *Single component of a two-component product administered*	

Scenario	Medication error?	LLT	Comment
Pharmacy prepared incorrect concentration because of confusion related to the way the strengths for the two active ingredients were stated on the label.	Yes	*Wrong concentration prepared* *Product label strength confusion*	
The technician didn't follow the instructions to mix the contents of the vial for 5 minutes after reconstitution.	Yes	*Product preparation error*	LLT *Product preparation error* (HLT *Product preparation errors and issues*) is more specific than LLT *Wrong technique in product usage process* (HLT *Medication errors, product use errors and issues NEC*).

3.2.8 Prescribing errors/issues

Scenario	Medication error?	LLT	Comment
Drug prescribed in error for unauthorised use.	Yes	*Drug prescribing error*	This is a prescribing error.

Scenario	Medication error?	LLT	Comment
Unintentionally prescribed Drug X instead of Drug Y because the names sounded alike.	Yes	*Drug prescribing error* *Drug name sound-alike*	It is important to be able to identify the name confusion as a contributing factor for the error.
Prescribed 4 mg/kg instead of 0.4 mg/kg. Prescriber realised immediately and called nurse but nurse had already administered the drug.	Yes	*Drug dose prescribing error* *Wrong dose administered*	Even though the error was detected it was not intercepted in time.
Patient was switched to different insulin product but dose adjustment was not written on the prescription. Patient administered the wrong dose and experienced hypoglycaemia.	Yes	*Drug dose prescribing error* *Wrong dose administered* *Hypoglycaemia*	
Patient was prescribed 2 times the appropriate dose due to computerised prescriber order entry (CPOE) error.	Yes	*Drug dose prescribing error* *CPOE error*	

Scenario	Medication error?	LLT	Comment
Patient taking multiple drugs was prescribed a contraindicated drug.	Unknown	*Contraindicated drug prescribed*	
Patient prescribed 1 tablet daily for insomnia for many years. The product directions state that the product should not be taken for more than 2 weeks.	Unknown	*Medically prescribed prolongation of labelled treatment duration* (PT *Product prescribing issue*)	The selected LLT captures both the "prescribing" concept and the "duration" concept
Patient decided to maintain dose at Step 2 of weekly titration schedule for another week (and not titrate up further) due to hypoglycaemia.	No	*Hypoglycaemia*	Stopping or adjusting therapy because of an adverse event does not represent an error or intentional misuse. Discontinuation or adjustment of therapy is usually captured elsewhere in the database/case report, and only the adverse event/adverse drug reaction is coded in that case.
Patient prescribed 0.25 mg (off label starting dose).	No	*Off label dosing*	

Scenario	Medication error?	LLT	Comment
Physician ordered the wrong rate of administration for the IV drug, and the patient experienced hypotension.	Yes	*Drug prescribing error* *Incorrect drug administration rate* *Hypotension*	
Drug approved only for IV administration was used off label via the oral route.	No	*Off label use in unapproved route of administration*	
Patient accidentally received duplicate therapy because the prescriber didn't realise the 2 drugs had the same active ingredient.	Yes	*Duplicate drug prescription error* *Duplicate therapy with same active substance*	

3.2.9 Product selection errors/issues

Scenario	Medication error?	LLT	Comment
The elderly patient confirmed that due to the cataract, the patient did not see well and ended up buying the infant formulation.	Yes	*Product selection error*	This is not a product name confusion. Cataract would be captured as concurrent condition.

Scenario	Medication error?	LLT	Comment
Pharmacist selected the wrong drug because of name confusion, but the error was caught and corrected before the drug was dispensed.	Yes	*Intercepted wrong drug selected* *Drug name confusion*	It is important to capture the cause of the error, the error type, and that the error was intercepted. In this scenario, LLT *Intercepted wrong drug selected* captures both the intercepted selection error and the error type (wrong drug) in a single term.
The hospital selected the wrong bag and the patient received a transfusion of the wrong blood type prior to and during surgery.	Yes	*Wrong product selected* *Transfusion with incompatible blood*	
Clerk ordered the wrong drug from the wholesaler because the drugs were listed next to each other in the catalogue and the names looked very similar.	Yes	*Wrong drug procured* *Drug name look-alike*	

3.2.10 Product storage errors/issues

Scenario	Medication error?	LLT	Comment
Healthcare facility reported storing reconstituted drug in syringes past the recommended 30 days, and administering it to patients. One of these syringes was used by a patient who reported that the drug didn't work.	Yes	*Improper storage of unused product* *Expired drug administered* *Lack of drug effect*	LLT *Poor quality drug administered* should not be selected because the selected LLT *Expired drug administered* is more specific.
Vaccine product was stored in the pharmacy at excessive temperatures.	Yes	*Product storage error temperature too high*	This is a medication error, as the error occurred in the medication use process.
The pharmacy staff member could not find drug as it had inadvertently been placed on the wrong shelf.	Yes	*Drug stored in wrong location*	

Scenario	Medication error?	LLT	Comment
Boxes of the drug sent from the manufacturer were left outside at excessive temperatures over the weekend when the wholesaler was closed.	No	*Manufacturing product storage issue* (HLT *Product distribution and storage issues*, SOC *Product issues*)	This storage problem is not a medication error because it occurred under manufacturing distribution and storage activities, prior to the product reaching the medication use process.
Pharmacy delivered the drug to the patient's home while the patient was hospitalised. The package was outside at temperatures below freezing for two days (drug should not be frozen).	Yes	*Product storage error temperature too low*	This is a medication error, as the error occurred in the medication use process.
Manufacturer issued a recall of certain lots of Drug X that were found to be exposed to inappropriate storage conditions by the wholesaler.	No	*Manufacturing product storage issue* *Recalled product*	This storage problem is not a medication error because it occurred under manufacturing distribution and storage activities, prior to the product reaching the medication use process.

Scenario	Medication error?	LLT	Comment
Pharmacy mistakenly stocked the wrong drug in the automated dispensing system. Reporter attributed the error to both drugs being packaged in similar sized vials with look-alike container labels.	Yes	*Wrong drug stocked* *Drug label look-alike* *Product packaging confusion*	

3.2.11 Product transcribing errors/communication issues

Scenario	Medication error?	LLT	Comment
Healthcare provider called in a prescription for Drug A, but pharmacy wrote down the prescription as Drug B.	Yes	*Transcription medication error* *Wrong drug*	
Pharmacy dispensed 800 mg strength instead of 600 mg due to data entry error.	Yes	*Product data entry error* *Wrong drug strength dispensed*	

Scenario	Medication error?	LLT	Comment
Physician ordered insulin pens, but a transcription error occurred at the pharmacy and the patient was dispensed insulin in a vial with syringes instead.	Yes	*Transcription medication error* *Wrong device dispensed*	
Patient had an issue communicating and was given the possible diagnosis of autism.	No	*Communication disorder* *Autism*	Despite the terms "issue" and "communicating" in the example, this is not a medication error and should not be captured under LLT *Product communication issue*, but rather should be captured under LLT *Communication disorder*.

SECTION 4 – PRODUCT QUALITY ISSUES

The overarching topic of product quality issues encompasses product quality, supply, distribution, manufacturing and quality system issues. This topic is addressed in Sections 4 and 5 which expand on the product quality issues section in the *MedDRA Term Selection: Points to Consider* (MTS:PTC) document.

Section 4 addressed term selection for product quality issues for distributed products reported in the clinical setting or through customer complaints.

Section 5, Manufacturing and quality system issues, addresses manufacturing deviations or non-conformances.

Section 4 has three main sub-sections:

- Background: concept of product quality issues in medical products
- Examples for coding product quality issues (based on MedDRA Version 27.1)
- Data search and retrieval strategies: guidance and considerations

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Kirubel Assegid, Chemist, FDA, United States

Elise Murphy, Supervisory Consumer Safety Officer, FDA, United States

Maria R. Thomas, Consumer Safety Officer, FDA, United States

Georgia Paraskevakos, Patient Safety Specialist, Health Canada, Canada

4.1 Background

It is important to recognise product quality issues as they may have implications for patient safety. Product quality issues are defined as abnormalities, also known as non-conformances (failures to conform with established product specifications), that may be introduced in any phase of the supply chain. These include the manufacturing, labelling, packaging, shipping, handling or storage of the products. Product quality terms may be used to report product defects to regulatory authorities and may also be used in organisations' internal databases to track and trend quality issues or deviations. Product quality issues may occur

with or without clinical consequences. Not all product quality issues are readily detectable to the user.

Product quality issues may be reported in the context of adverse events or as part of a product quality monitoring system. Likewise, patient safety data may facilitate surveillance for evidence of product quality issues. MedDRA coding conventions for product quality issues promote consistency in data entry, facilitating data retrieval that is required to support health risk assessment when a non-conforming product is detected in the marketplace.

Other important concepts that may be reported into a product quality monitoring system include consumer preference complaints in which the reporter makes no allegation against the product quality, but communicates dissatisfaction with the product or packaging design. Examples include request for a liquid form of a solid dosage form, a suggestion to change the package configuration from bottle to blister or to increase the quantity of tablets per bottle, and a request for a dye-free version of a children's suspension. While these may not represent product quality non-conformance and/or there is no reported clinical consequence, these may be valuable to inform enhancements to the product and packaging design and labelling, and may influence the product benefit-risk profile.

SOC *Product issues* contains two HLGTs, one of which is HLGT *Product quality, supply, distribution, manufacturing and quality system issues*. Under this HLGT are the HLT categories including HLT *Product packaging issues*, HLT *Product physical issues*, HLT *Counterfeit, falsified and substandard products*, and HLT *Product contamination and sterility issues*. MedDRA Lowest Level Terms (LLT) that most accurately reflects the reported verbatim information should be selected. This may be achieved by use of the search function or by use of the SOC window of a browser to navigate the MedDRA hierarchy down to the appropriate LLT.

SOC *Product issues* is focused on issues related to products rather than clinical or patient related concepts and therefore, the majority of terms in this SOC are single-axial and have no need for multi-axial links to other patient related "disorder" SOCs. However, there are a few product quality terms that also denote a patient related issue and are multi-axial to preserve the link to patient safety. For example, PT *Transmission of an infectious agent via product* is linked to primary SOC *Infections and infestations* and has a secondary link to SOC *Product issues*. The fact that most product quality terms are single-axial and are

located only in SOC *Product issues* should be taken into consideration when designing queries and other retrieval strategies.

Description of certain product quality issue terms (e.g., “Product coating incomplete”) are found in the MedDRA Introductory Guide (Appendix B, MedDRA Concept Descriptions).

4.2 Examples for Coding Product Quality Issues

4.2.1 Product physical issues

Scenario	LLT	Comment
Pharmacist opened bottle of tablets and detected an irregular odour that was due to mould.	*Product odour abnormal* *Product contamination mould*	A term has been added for the reporter’s statement that the abnormal odour is the result of contamination with mould. This is also a form of biocontamination (see Section 4.2.2).
Patient stated chewable tablets were excessively hard and he suffered a broken tooth. He suspects the product was defective.	*Medication too hard to chew* *Tooth fracture* *Tablet physical issue*	Product quality issue, LLT *Tablet physical issue*, is based on reporter verbatim. In the absence of this information, a product quality issue should not be inferred.

Scenario	LLT	Comment
Mother states she gave her child a suspension labelled as cherry flavoured and it had a distinct taste of mint instead.	*Product taste abnormal*	Note that LLT-PT *Product taste abnormal* links to HLT *Product physical issues*, indicating a product issue. A different term, LLT *Taste abnormality* – PT *Taste disorder*, indicates a "patient disorder", and is linked to HLT *Sensory abnormalities NEC* and HLT *Taste disorders*. Hierarchy should always be checked to confirm correct term selection.
When the nurse opened the vaccine carton, the vial was observed to contain yellow liquid. The product label states it should be colourless.	*Product colour issue*	In scenarios referring to a discrepancy between labelled colour/taste (or other) and actual colour/taste (or other), either the product content is incorrect, or the label is incorrect. A term from HLT *Product label issues* should be selected only if the reporter indicates that the label is incorrect.
The pharmacist opened the medication bottle and discovered some of the tablets were broken.	*Tablet chipped*	

Scenario	LLT	Comment
Patient found intact tablets in her stool and complained that the tablet must be of poor quality.	*Tablet in stool* *Product quality complaint*	LLT *Tablet in stool* is under PT *Product residue present* and located in the SOC *Investigations*. Although this is not typically a product non-conformance, it is the patient perception that something is wrong, or that the tablet is of poor quality.
A female patient noticed that her contraceptive medication smelled bad and tasted differently than before.	*Product smell abnormal* *Product taste abnormal*	

4.2.2 Product contamination/sterility issues

Scenario	LLT	Comment
Upon opening the sterile packaging for a venous catheter, the surgeon noticed an insect present in the inner packaging. She discarded the unit and retrieved an alternate package that was clean and intact.	*Product contamination insect*	This information may require collection and reporting by the user facility, with or without evidence of patient involvement.

Scenario	LLT	Comment
Upon inspection of a prefilled syringe, the nurse detected particles floating in the liquid. This was the last available prefilled syringe for this drug at the clinic. The patient's treatment was delayed until the following week when the product was available again.	*Particle present in liquid product* *Temporary interruption of therapy* *Product availability issue*	The reported information does not specify the reason for the unavailability of the product. Although product unavailability is frequently a consequence of a supply disruption, LLT *Product supply issue* should not be inferred in this example because it is not stated.
A consumer reported that while examining the drug provided in an ampoule, she noticed that there was a piece of glass inside.	*Product contamination glass*	
The patient reported contracting fusarium keratitis of her left eye. She suspected contamination of her contact lens solution was the source.	*Fusarium infection* *Keratitis fungal* *Suspected product contamination* *Suspected transmission of an infectious agent via product*	LLT-PT *Suspected transmission of an infectious agent via product* is multi-axial, linking to SOC *Infections and infestations* as primary and SOC *Product issues* as secondary.

4.2.3 Product distribution issues

Scenario	LLT	Comment
A patient complained that the medication shipment to her home was delayed. As a result, she ran out of medication, missed several doses and developed hyperglycaemia.	*Product shipment delay* *Therapy interrupted* *Hyperglycaemia*	Missed doses due to external circumstances are not considered medication errors and are coded as *Therapy interrupted* or *Treatment delayed*. Code LLT *Patient ran out of medication* (HLT *Medication errors, product use errors and issues NEC*) when this is the **only** information provided without clarification why.

4.2.4 Product label issues

Scenario	LLT	Comment
The patient was unable to read the expiration date on the medication bottle because it had faded in colour.	*Product expiration date illegible*	
A consumer opened a carton containing infant suspension in a bottle. The accompanying package insert was for the adult tablet form.	*Product package insert incorrect*	

Scenario	LLT	Comment
A patient stated he read the dosing schedule on a tube of ophthalmic ointment incorrectly because the print was illegible. As a result, he used product twice a day instead of the recommended once a day. He developed irritation in his eyes.	*Product label text illegible* *Once daily dose taken more frequently* *Irritation of eyes*	

4.2.5 Counterfeit

Scenario	LLT	Comment
A patient was contacted by the infusion facility to inform her that she had been treated with counterfeit medication. She was advised to return for treatment.	*Counterfeit product administered*	This LLT links to SOC *Injury, poisoning and procedural complications* as the primary SOC and to SOC *Product issues* as the secondary SOC. LLT *Counterfeit product administered* should only be selected if a counterfeit product has been confirmed. Otherwise, LLT *Suspected counterfeit product* should be selected.

Scenario	LLT	Comment
When inspecting a carton of vaccines from a new supplier, the clinic manager noted that the product branding was different from previous cartons. He suspected that the material was not authentic.	*Suspected counterfeit product*	
A consumer had been using a drug for several years. The newly purchased unit was ineffective compared to past experience. She suspected that the product was counterfeit.	*Suspected counterfeit product* *Drug ineffective*	
The manufacturer received a customer complaint about a batch that showed a slight difference in the font size of the secondary packaging. The batch number corresponded to a legitimate batch, however, during investigation, the material code stated on the secondary packaging was found to be different than the one used in the production of the legitimate batch.	*Spurious product*	

4.2.6 Product supply and availability

In general, a “drug shortage” indicates a period when the demand or projected demand for the drug exceeds the supply of the drug. Supply disruptions can occur associated with manufacturing or product quality problems, for unknown reasons, associated with unanticipated increases in demand, natural disasters, or product discontinuations.

Scenario	LLT	Comment
A patient was told by her pharmacist that her medication was not available due to a shortage in supply following closure of several manufacturing facilities. Her physician prescribed an alternative therapy.	*Supply shortage* *Product availability issue* *Drug therapy changed*	The supply shortage resulted in unavailability of the medication.
The pharmacist informed the patient that his medication was not available due to the COVID-19 pandemic.	*Product unavailable due to pandemic*	

4.2.7 Packaging issues

Scenario	LLT	Comment
When the patient removed the medication bottle from the carton, the tamper evident seal was absent.	*Product container seal issue*	

Scenario	LLT	Comment
On inspection of a medication bottle, a customer noticed that the child resistant cap did not work.	*Failure of child resistant product closure*	
A nurse noticed that the blister package was not completely sealed.	*Product blister packaging separated*	
A woman reported that her contraceptive medication was missing the placebo tablets.	*Package dosage units missing*	

4.3 Data search and retrieval of product quality issues

Product quality issues may result in patient safety concerns, but safety concerns are not always detectable to the manufacturer or the patient. When detected, an opportunity is created to remediate the non-conformance.

Appropriate data entry practices facilitate detection and retrieval of product quality issues in safety data. It is also important to be aware that multiple databases might be used to capture product quality complaints, e.g., a safety database and a quality database. Consider potential database specifics including differences in data coding of adverse events and quality complaints between the databases (e.g., different dictionaries or data that is not coded).

Broadly, medical safety data review may detect product quality deviations on a continuous, periodic and ad hoc basis. During continuous, real-time review product quality issues can be detected based on single Individual Case Safety Reports (ICSRs) or based on batches/lots when these have a disproportionate number of adverse event reports.

The periodic review for product quality issues is generally product specific. Dependent on the scope of the review this can be done by means of aggregate adverse event review performed on a fixed schedule, or by a review of events reported to the quality system. If data is coded in MedDRA, the retrieval and data

output may be enhanced by developing and applying a customised data filter based on MedDRA product quality issue terms. When creating and maintaining a data review strategy, it is important to document the review strategy and terms, and to also document review and update of the terms with each MedDRA release. Periodic review is usually performed to find anomalies in the data. Thus, an increase in certain quality complaints might lead to the generation of a new hypothesis. Further validation could then become necessary by searching for adverse event terms suspected to occur with this type of quality issue.

Data review may be lot specific (i.e., all adverse events for the material in scope) and/or problem specific (i.e., all material, with or without a lot number, for a defined list of adverse event terms). Distribution dates and locations may also be incorporated into this type of data review strategy. The adverse event term list should reflect the medical conditions that may result from exposure to non-conforming product. For example, assessment of a product containing an undocumented potential allergen should include MedDRA terms reflecting hypersensitivity concepts. SMQ *Hypersensitivity* could be applied to achieve this with efficiency. Assessment of a product subject to biocontamination should include MedDRA terms reflecting infection concepts, both broad and specific to the contaminant, if known.

Whether data assessment for product quality is continuous, periodic, or for cause, description of quality issues using MedDRA facilitates detection and retrieval. This improves the integrity of the medical assessment.

SECTION 5 – MANUFACTURING AND QUALITY SYSTEM ISSUES

The purpose of this section is to expand on the product quality issues section in the *MedDRA Term Selection: Points to Consider* (MTS:PTC) document to facilitate term selection for manufacturing and quality system issues. This section may be applied to characterization of issues for in-process materials or distributed products that have not met specifications, or for related issues not associated with a specific product or material. Manufacturing and quality system issues usually originate from industry in the form of technical assessments which may have the potential to impact product integrity and adherence to established specifications. This PtC does not mandate any regulatory reporting requirements. Adoption of the MedDRA terminology for manufacturing and quality system issues is at the discretion of users, whether industry or regulator. Applicable regional regulatory requirements should be considered.

The section contains three main sub-sections:

- Background: concept of manufacturing and quality system issues
- Terminology use and reporting
- Examples for coding manufacturing and quality system issues (based on MedDRA Version 27.1)

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Tom Brusselmans, Scientific Administrator – GMP and Manufacturing, Human Medicines Inspections Office, EC, Europe

Kirubel Assegid, Chemist, FDA, United States

Jean Ennis, Regulatory Specialist, FDA, United States

Elise Murphy, Supervisory Consumer Safety Officer, FDA, United States

Shahla Parvizi, Pharmacist, FDA, United States

Maria R. Thomas, Consumer Safety Officer, FDA, United States

Hui-l Tom, Senior Chemist, FDA, United States

Alison Dawson, Senior Director, QA Leader - EU External Advocacy & Collaborations Global Quality Systems, Eli Lilly and company, EFPIA

Janeen Skutnik-Wilkinson, Senior Director, Regulatory Intelligence and Advocacy, Lilly, EFPIA

Tomasz Zawislak, Senior Director, Head of Audits and Inspections Management, Merck KGaA Darmstadt, Germany, EFPIA

Nina S. Cauchon, Director Regulatory Affairs, Amgen Inc., PhRMA

Julia Diniz Calatrone, Health Regulation Specialist, ANVISA, Brazil

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Dimitri Yakunin, Roszdravnadzor, Russia

Jing Cui, Biologics Pharmaceutical Reviewer, NMPA, China

5.1 Background

MedDRA terminology was developed under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

The use of a single standardised international terminology facilitates consistency in regulatory reporting and surveillance activities, regulatory communication, and evaluation of data, as well as exchange of data across companies, clinical research organizations and external databases. The MedDRA Maintenance and Support Services Organization (MSSO) was appointed by ICH and tasked to maintain, develop and distribute MedDRA. Under the governance of the MedDRA Management Committee, MedDRA is continuously enhanced to meet the evolving needs of regulators and industry around the world. The decision to use MedDRA is at the discretion of organisations or may be determined by regional regulatory authorities.

As stated elsewhere, the quality of the manufacturing and quality system issue information directly impacts the quality of term selection, which impacts the quality of surveillance. Likewise, accuracy in term selection is dependent upon the availability of terms, which is dynamic and will evolve over time as more use cases are established. Clarification should be obtained for information that are ambiguous, confusing, or unintelligible. If clarification cannot be obtained, refer to

Section 2 of this document and Section 3.4 of the *MedDRA Term Selection: Points to Consider* document for additional guidance.

HLGT *Product quality, supply, distribution, manufacturing and quality system issues* belongs to SOC *Product issues*. This HLGT contains several HLTs specific to manufacturing and quality system issues, such as HLT *Manufacturing materials issues*, HLT *Manufacturing production issues*, and others. Each HLT groups specific PTs with their linked LLTs, including terms for improper equipment qualification, cleaning and sanitisation of product contact surfaces, manufacturing and testing methods, calibration and maintenance, and computer qualification, validation and security. Manufacturing and quality system issues may or may not result in a product quality defect. Any associated or resulting defect would require the inclusion of an additional term, as described in Section 4 Product Quality Issues of this Companion Document.

Introduction of MedDRA terminology for classification of manufacturing and quality system issues is a complex process. The initial steps include incorporation of MedDRA terms, and the publication of this new section of the Companion Document to guide term selection. Both the terminology and the coding guide will be further developed through regulator and industry collaboration, examples and user feedback.

The purpose of the Manufacturing and Quality System Issues section of the Companion Document is to provide examples and clarification when coding post-market defects associated with manufacturing, analytical or microbial testing, production, and distribution of marketed products. This allows the manufacturer as well as the regulator to observe signals and trends in product quality defects.

Originally, the terminology and the example-scenarios focused on small molecules and issues common to all products (e.g., contamination, packaging, distribution). The scope has now been expanded to include biologics, vaccines and advanced therapy medicinal products, which may involve more complex manufacturing environments and modalities.

Similarly, device components of a product, whether device or combination product, may have manufacturing non-conformances, and issues with device operation. Current MedDRA terminology contains the HLGT *Device issues* with terms that facilitate capture of reported quality issues.

The LLTs linked to manufacturing and quality system issue PTs are usually more than just synonymous terms and often contain more specific information. Coding

at the LLT level of granularity enables specific capture of reported information, and data analysis at LLT, PT and HLT levels for signal detection and trending.

A product quality defect may lead to an adverse event or medication error. Coding both types of reports with MedDRA terminology enables the linking of product quality and adverse event domains.

5.2 Terminology Use and Reporting

5.2.1 Regulatory reporting

MedDRA is a standardised terminology available in multiple languages. Thus, MedDRA facilitates communication of information, including manufacturing and quality system issues. The use of a shared terminology renders data more accessible for analysis by external audiences, including regulators and other stakeholders. It also facilitates interactions between the manufacturing quality organizations and the safety organizations, in both the regulatory and industry context.

5.2.2 Terminology features, harmonisation, surveillance and quality risk management

The comprehensive and dynamic nature of MedDRA allows users to leverage broadly accepted terminology and request additions to suit the full range of manufacturing technologies and products. MedDRA is global, flexible, extensible and version controlled. Company-specific terminology can be granular and can feature a hierarchy, but administrative control of categories can be cumbersome and difficult to maintain in a validated state. Terms need to be added to accommodate new processes, products and product types (e.g., packaging image, delivery device). MedDRA has a specific change request process (see the Change Requests page on the MedDRA website).The use of a single terminology for quality and safety concepts also enables data analysis across the spectrum of both.

An effective quality risk management approach can provide a proactive means to identify potential quality issues contributing to product safety and efficacy throughout the product lifecycle. Manufacturing and quality system issues may manifest as product non-conformance or product quality issues that may only be detected through patient outcomes. In this manner, safety data may correlate with manufacturing data, identifying adverse event patterns that are rooted in quality fluctuation. Quality data may inform root cause in safety signal

assessment. For example, an out of specification result for dissolution may manifest as a lack of therapeutic effect.

5.3 Examples for Coding Manufacturing and Quality System Issues

The scenarios provided in this section focus only on the manufacturing and quality system issues. Patient consequences potentially arising from use of products affected by these manufacturing and quality systems issues are out of scope of the coding guidance in this section.

5.3.1 Manufacturing facilities and equipment issues

These examples feature terms to classify information related to physical environment, utilities, and equipment used in the production of drug products.

Scenario	LLT	Comment
A formulation tank used for multiple products was cleaned and prepared for the next product. During an audit, it was discovered that the cleaning verification was not conducted as required in four previous batches. Cleaning verification performed following the fifth batch revealed the following: the lab analyst noted that one of the samples taken from the tank exceeded the allowed limit for drug substance residue.	*Manufacturing equipment cleaning issue* *Suspected product contamination*	Additional LLT *Suspected product contamination* should be selected if one formulation tank for more than one product was used. LLT *Manufacturing materials contamination*, might be added after outcome of examination, if confirmed.

Scenario	LLT	Comment
During routine six-month requalification of high efficiency particulate air (HEPA) filters for supply air to the filling space for an aseptic filling line, eight HEPA filters did not meet efficiency requirements.	*Manufacturing equipment high efficiency air filter issue*	Although the LLT *Manufacturing equipment filter issue* may be used in this scenario, the LLT *Manufacturing equipment high efficiency air filter issue* provides greater specificity.
The bioreactor impeller motion stalled during the bulk incubation step. Impact assessment on the marketed product is pending.	*Manufacturing equipment issue*	
Mould was detected in the Grade A/B area. The expanded investigation detected mould in additional areas of the facility where marketed product may be impacted.	*Manufacturing facilities issue* *Suspected product contamination*	If the investigation confirms the presence of mould in marketed product through sample testing, it is appropriate to select LLT *Product contamination mould*.
During periodic scheduled bioreactor maintenance, inverted impeller orientation was noted. An investigation was launched to determine the root cause and potential impact to material produced since the last documented maintenance activity.	*Manufacturing equipment issue*	

Scenario	LLT	Comment
HEPA filters in a cell culture facility were found to have microbial contamination, potentially exposing live viral vaccine production to contamination.	*Manufacturing facility high efficiency air filter issue*	
A bioreactor temperature sensor malfunctioned, leading to suboptimal fermentation conditions for monoclonal antibody production.	*Manufacturing process control procedure temperature issue*	Many biologics rely on strict temperature control during production, affecting cell growth and protein yield.
During the review of environmental monitoring data for batch release of a sterile biological, a count of 1 colony forming unit (CFU) was detected in a settle plate located in the A grade critical zone of the aseptic filling line.	*Manufacturing process control procedure environmental monitoring issue*	
Anomalies were detected during routine requalification of a sterile filling line for vaccines. It was detected that the air flow was reversed with contamination risk.	*Manufacturing process control procedure aseptic processing issue* *Equipment qualification issue*	

5.3.2 Manufacturing laboratory controls issues

These examples feature terms used to classify information related to laboratory controls, Out of Specification (OOS) product attributes and testing issues. The OOS results include all test results that fall outside the specifications or acceptance criteria established by the manufacturer in drug applications, drug master files (DMFs), or official compendia. This also includes stability tests results that do not meet acceptance criteria.

Scenario	LLT	Comment
The manufacturing laboratory analytical testing relies on software algorithms to generate test results. In the data analysis software, the raw data files are preserved. When the raw data files are processed, the methods for the data processing are also preserved, and the data outputs are named with sequential letters added to the end of the original file name. However, if an initial set of processed results are then required to be reprocessed, the original processed results electronic file is not saved and is overwritten. Only the last set of reprocessed results is retained in the analytical analysis software. Data integrity is not maintained and results cannot be verified potentially also including distributed batches.	*Manufacturing laboratory data control issue*	

Scenario	LLT	Comment
Stability sample testing was not performed at the time interval defined in the protocol due to insufficient on-site personnel during the pandemic.	*Manufacturing laboratory analytical testing issue due to pandemic manpower disruption*	
During audit of the batch record review post distribution, an error was found in the test for identity.	*Manufacturing laboratory analytical testing issue, identity incorrectly performed*	
Batch release specifications documented in the product regulatory filing require identification testing for sodium. However, a review of the batch release records indicates that this identification test for sodium was not performed and material was potentially distributed.	*Manufacturing laboratory analytical testing issue, identity not performed or documented*	

Scenario	LLT	Comment
During an audit of the batch record for X product, after distribution, it was noted that the approved test method had not been executed properly. The chromatogram used to calculate the concentration of the active had been manually integrated; the result was reported as 118 µg/mL. No explanation for the manual integration was recorded on the instrument printout and visual examination of the original (automatically integrated) chromatogram did not indicate that manual integration was necessary. When the concentration of analyte was calculated using the peak area from the original chromatogram, the result was 190 µg/mL which is greater than the acceptance criterion of Not More Than (NMT) 120 µg/mL.	*Out of specification test results potency* *Manufacturing laboratory data control issue*	

Scenario	LLT	Comment
The drug product monograph states potency for two active ingredients are Active A and B. A review of the batch release tests indicates that the potency test was performed only for Active A. The potency test for Active B was not performed. This issue was discovered post-distribution.	*Manufacturing laboratory analytical testing issue, potency not performed or documented*	
During high performance liquid chromatography (HPLC) analysis for related substances, peaks generated with relative retention time range of 4.5 to 5.5 minutes and having areas above the integration inhibition level have been disregarded as diluent or placebo peak instead of reporting the peaks as an unknown impurity. This could potentially affect distributed batches.	*Manufacturing laboratory analytical testing method management issue* *Manufacturing laboratory analytical testing issue, purity incorrectly performed*	While *Manufacturing laboratory controls issue* may be used in this scenario, the LLT *Manufacturing laboratory analytical testing method management issue* provides greater specificity.

Scenario	LLT	Comment
Samples of Product Y were placed under controlled temperature and humidity storage conditions for long-term stability testing. The protocol required sample retrieval and testing at six-month intervals to measure assay of active ingredient and levels of degradation products. The 12-month samples were retrieved and tested with significant delay. However, degradation products testing was not performed and the stability protocol deviation was not documented. At the previous testing interval, the result for degradation products was approaching the upper limit of acceptance, but within specification.	*Manufacturing laboratory analytical testing issue, purity not performed or documented* *Stability protocol deviation not documented*	
An internal audit revealed that Controlled Room Temperature stability samples for batch X were not withdrawn or tested for stability at 9 months and at 15 months, as required per respective protocol.	*Manufacturing laboratory analytical testing issue, stability not performed or documented*	

Scenario	LLT	Comment
Sterility testing sample collections were not performed as per site standard operating procedure. Operator did not collect a representative sample of finished product vials. While the number of samples collected was consistent with the method, the distribution of sample collection was isolated to the beginning of the batch fill. All collected vial samples passed sterility testing, however, the sample was not representative for the entire batch. This was not detected during the routine batch release process.	*Manufacturing laboratory analytical testing issue, sterility incorrectly performed*	
During audit of contract manufacturing organisation, it was discovered that on one occasion the sterility test media samples for product release testing were discarded before the required incubation period (14 days) was completed, without record of growth observed at time of discard.	*Manufacturing laboratory analytical testing issue, sterility not performed or documented*	
A discrepancy was identified in the periodic calibration record for a hardness testing apparatus in the compression suite.	*Manufacturing laboratory controls calibration issue*	

Scenario	LLT	Comment
An audit observation noted that the quality control laboratory retested out of specification (OOS) samples from rejected drug product and obtained new results that were within specification. The initial OOS result was invalidated and the product was reclassified as passing release testing without a full-scale investigation to identify the root cause and a scientifically sound retest plan.	*Manufacturing laboratory controls issue*	
An out of specification test result was observed at completion of the 6-month accelerated stability study, for a known product impurity. The observed result was 0.54%, which is above the established specification limit Not More Than (NMT) 0.50%.	*Manufacturing stability testing chemical analysis purity issue* *Out of specification test results stability*	
During stability sample testing of a liquid suspension product (18-month 25°C/60% Relative Humidity, horizontal storage condition), product residue was noted around the neck of the bottle. Upon removing the cap, the inside liner of the cap was wet, and the seal was not intact in all places.	*Manufacturing stability testing container closure issue* *Product leakage*	

Scenario	LLT	Comment
Upon retrospective review of manufacturing transfer documentation, the product did not meet the requirement for content uniformity at the 48-month stability test point.	*Manufacturing stability testing content uniformity issue*	
An Out of Specification osmolality result was obtained upon testing of stability samples.	*Manufacturing stability testing issue* *Out of specification test results osmolality*	
Specification for water content is Not More Than 4.0%. An out of specification water content result of 4.1% was generated upon testing of stability samples.	*Manufacturing stability testing moisture issue* *Out of specification test results moisture*	
The pH specification for Drug N is 6.0 to 7.5. The stability testing pH result for Lot X at 60 month 25°C/60% Relative Humidity is 8.0.	*Manufacturing stability testing pH issue* *Out of specification test results pH*	
An Out of Specification assay test result was obtained at 36 months under long-term storage conditions. The assay results obtained were 89.9% and 90.4% with an average of 90.2%. The Shelf-Life Specification for Assay is 92.5 to 107.5%	*Manufacturing stability testing potency issue* *Out of specification test results potency*	

Scenario	LLT	Comment
For a batch of ophthalmic solution, the preservative assay result was below the lower limit (90.0%) of the specification during the long-term stability study (25°C ± 2°C/60% ± 5% Relative Humidity). The observed result at 12 months was 84.6.	*Manufacturing stability testing preservative issue* *Out of specification test results preservative content*	
An out of specification result for assay was observed during retained sample testing for ophthalmic cream drug product associated with a consumer complaint investigation. The sample locations and results are as follows: Head: 88.7%; Mid: 92.5%; Crimp: 96.2% (Specification: 90.0-110.0%).	*Out of specification test results assay*	The complaint investigation in this scenario is providing the detection context.
While performing container-closure integrity testing for lot Y, two of the ten sample blister packages showed evidence of dye ingress into a blister cell at the same position on both samples, thereby resulting in a failing result.	*Out of specification test results container closure* *Product blister packaging issue*	

Scenario	LLT	Comment
During a customer complaint investigation, the Delivered Fill Volume test for a single unit was 0.16 mL. The approved specification is 0.23-0.42 mL.	*Out of specification test results fill volume*	
Sterile water for injection syringes featured in the lyophilized product kit failed release testing for oxidizable substances. Root cause investigation revealed that batches in distribution may be implicated.	*Out of specification test results for component packaged with final product* *Out of specification test results impurity*	
An out of specification result was observed in related substances when testing the finished product. This result was as follows: Impurity C = 0.59% [Limit: Not More Than 0.5%].	*Out of specification test results impurity*	
A repeated examination of release testing samples performed in the context of response to inspection finding revealed that four out of twenty samples of injectable solution had formed precipitates that settled to the bottom of the vial. The specification for appearance is “clear, colourless solution.”	*Out of specification test results precipitates*	

Scenario	LLT	Comment
Two lots of ophthalmic solution failed testing for preservative content. The preservative specification range is 0.28-0.48%. The lot results were as follows: Lot X: 0.23% Lot Y: 0.26% During investigation, it was determined that batches in distribution were impacted.	*Out of specification test results preservative content*	
An Out of Specification Conductivity test result was recorded for buffer solution. According to the Standard Operating Procedure, buffer solution is tested for conductivity every 14 days.	*Out of specification test results*	If no exact matching term is available, code to the nearest matching existing term and submit a change request. (see the Change Requests page on the MedDRA website).
During continued process verification, the assay of one of the active ingredients contained in the second layer of a bilayer tablet batch was found to be out of trend. On investigation, this pattern was confirmed for additional batches and high weight variability of the first layer was identified as a root cause.	*Out of trend test result assay* *Product process control issue*	

Scenario	LLT	Comment
Long term stability dissolution test results of a tablet product failed at Stage 1 and 2, and passed only at Stage 3 at 12 and 18 months' time point.	*Out of trend test result dissolution* *Out of trend test result stability*	
Routine calibration of the cell counter and analyser revealed erroneous results. There was no detectable impact to cell culture yield or finished product adherence to release specifications.	*Manufacturing laboratory controls calibration issue*	
Stability testing of a gene therapy viral vector showed a decline in potency beyond the expected rate.	*Manufacturing stability testing potency issue*	Gene therapies rely on viral vector integrity, and potency degradation can affect therapeutic effectiveness.
Sterility testing for Chinese Hamster Ovary (CHO)-cell-derived monoclonal antibody drug product was not performed due to incorrect sample handling. Impact on released and distributed product is pending	*Manufacturing laboratory analytical testing issue, sterility not performed or documented*	

Scenario	LLT	Comment
An OOS was detected in a sterility sample of a sterile monoclonal antibody product. During investigation, no assignable laboratory error was detected, and the manufacturer decided to resample the batch for re-testing.	*Out of specification product testing issue* *Out of specification test results contamination*	It is both a testing issue (OOS procedure is incorrect allowing for resampling) and a contamination issue.
During summer vacation time Polymerase Chain Reaction (PCR) testing for mycoplasma of cell culture was not performed weekly but only every other week due to availability of lab staff.	*Manufacturing process control procedure incorrectly performed*	
Company distributed drug product lots that were manufactured using drug substance lots tested at a contract research organization which is an unapproved testing site using unvalidated host cell protein and Oligosaccharide (NP-HPLC) test methods.	*Manufacturing laboratory analytical testing issue* *Management of outsourced manufacturing activities issue*	

Scenario	LLT	Comment
An investigation identified trend of atypical results for fluorescent-based polymerase chain reaction-based reverse transcriptase (F-PBRT) testing that is performed on cell banks to assess for the presence of viral contaminants and ensure the cell bank material is safe for use. A review of the qualification protocols and qualification data indicated that the validity criteria for the Ct cut-off values were not fully defined and/or supported by the qualification package data, which in turn contributed to an analyst-based variability in the analysis and interpretation of the control data.	*Manufacturing laboratory analytical testing issue, safety incorrectly performed* *Cell bank viral safety evaluation issue*	
An investigation into the unexpected results has determined that the test methodology for stability testing was not optimized to support cell growth following passage 3 for working cell bank. The data shows the rate of growth decreased in passages 4 and 5 following transfer of the cell culture to the spinner flasks.	*Cell bank characterization issue, stability issue* *Manufacturing laboratory analytical testing method management issue*	

Scenario	LLT	Comment
A retrospective review of Master Cell Bank (MCB) and Working Cell Bank (WCB) testing identified two minor changes to the media used for the mycoplasma and sterility testing of the MCB.	*Manufacturing laboratory analytical testing issue* *Cell bank characterization issue, purity issue*	

5.3.3 Manufacturing materials issues

These examples feature terms to classify information related to issues with incoming materials, including active substances, raw materials, excipients, components, containers and closures.

Scenario	LLT	Comment
The starting material used in the drug substance synthesis was not tested for assay as per the registered titration method prior to release for use in production batches.	*Manufacturing material testing deviation*	
Fine particulate foreign material was observed in the Active Pharmaceutical Ingredient (API) during the sieving process and drug manufacturing proceeded without appropriate impact assessment.	*Manufacturing active pharmaceutical ingredient contamination*	

Scenario	LLT	Comment
During dispensing, six fibrous particles consistent with plant material were observed at the bottom of a drum of the polyethylene glycol 400 liquid. The investigation of impact to finished product released to the market is pending.	*Manufacturing excipient contamination*	
Audit finding identified that two finished lots had accidentally been formulated with material from a rejected excipient lot. The excipient was rejected for presence of *Burkholderia cepacia*. Test of retain samples from potentially impacted (and distributed) batches confirmed presence of this organism.	*Manufacturing excipient contamination* *Product contamination microbial*	
During supplier audit, it was discovered that incoming testing of resin used in API purification revealed contamination with solvent residual at levels exceeding the upper limit of the specification. This was not reported to the API manufacturer and batches in scope had been distributed. During the subsequent investigation, API testing was within specification for the solvent.	*Manufacturing materials contamination*	The LLT *Out of specification test results residual solvent* may be selected if there is evidence that the solvent is present in finished product.

Scenario	LLT	Comment
During a supplier audit for polylactide (PDLLA) used in orthopaedic implant antibiotic coating, the presence of shiny particles was detected in both empty and filled raw material drums. Follow up investigation performed by the supplier revealed a systemic contamination issue impacting multiple distributed finished product implant batches.	*Manufacturing raw material contamination*	
Incoming material inspection of vial stoppers determined that the stoppers were purple, however the bill of materials statement and respective specification require the stoppers to be yellow. Re-inspection of other, potentially impacted batches of finished product in distribution also revealed incorrect stopper colour had been used.	*Incoming material container closure out of specification* *Product closure issue*	
Bottles received from a supplier were found to have excessive flash material at the bottle mouth threads. The bottles may have been used for marketed batches prior to detection of the defect. Investigation pending.	*Incoming material container defective*	

Scenario	LLT	Comment
Communication was received from a supplier of primary packaging material. Containers delivered by the supplier over the past nine months were manufactured using a different material than what is currently in the packaging specifications.	*Incoming material container out of specification*	If additional information is available regarding the specific impact to product, e.g., stability or compatibility, additional LLTs may be selected to describe those details.
An API manufacturer has notified the firm that API from an unapproved site had been shipped to the Drug Product manufacturer. It was confirmed that the API met the release specifications. This material was used in manufacturing of distributed product.	*Manufacturing active pharmaceutical ingredient issue*	
Investigation performed in the context of a supplier complaint featuring needle hubs that are splitting during assembly of the drug delivery device revealed 12 batches of needle hubs impacted by this quality failure. Three out of 12 batches were used in manufacturing of distributed products.	*Manufacturing component issue*	

Scenario	LLT	Comment
The excipient supplier notified Quality Assurance that an incorrect grade excipient was provided for the manufacturing of the drug product that was distributed.	*Manufacturing excipient issue*	
Unidentified impurities were present in the cell culture media. These were not revealed until after the product had been distributed.	*Manufacturing material impurities*	If there is evidence that finished product quality is impacted, an appropriate, most specific LLT for the quality issue may be added.
A supplier process deviation in the raw material was responsible for non-conforming particle size distribution in the active pharmaceutical ingredient used in the manufacture of distributed product batches.	*Manufacturing raw material issue* *Manufacturing active pharmaceutical ingredient issue*	
Environmental exposure of a batch of polysorbate excipient resulted in excessive formation of peroxide impurities, causing aggregation in a recombinant protein.	*Manufacturing excipient contamination*	Peroxides can degrade biologics, leading to instability and loss of potency.

Scenario	LLT	Comment
A lot of single-use bioreactor bags used for vaccine production had elevated leachables detected from the plastic material during an investigation.	*Manufacturing materials leachables issue*	
On-site audit of specific pathogen free (SPF) egg supplier used for vaccine production has not been performed as a part of the supplier qualification process.	*Material from non-qualified supplier used* *Oversight of external materials supply issue*	
Sterile ready-to-use single-use bags, used as the primary packaging of a low bioburden recombinant protein API were not tested for sterility at appropriate intervals based on risk.	*Manufacturing material testing deviation*	
Whilst checking delivery of CHO medium it was found to contain serum and was contaminated with mycoplasma.	*Manufacturing raw material contamination*	

Scenario	LLT	Comment
Selective antibiotic (SA) is not listed in Section 3.2.A.2, Adventitious Agents Safety Evaluation for the product. It was considered by the company to be animal origin (AO) free; however, it has recently been determined that some lots of the SA, used to produce the drug substance were indirectly of AO, due to AO components used in fermentation medium for SA production.	*Manufacturing raw material issue*	

Scenario	LLT	Comment
According to certification of origin received by suppliers, the Biologics License Application (BLA) of the drug state that “No materials of human or animal origin are used in the inoculum, fermentation, harvest and recovery process steps.” Company received updated information from drug substance contract manufacturing organization (CMO), that the L-cysteine in a bioprocessing fermentation material, was despite the supplier certification, derived from duck feathers. This bioprocessing fermentation material is used for the inoculation media for seed train initiation in drug substance manufacturing and used during the establishment of the working cell banks.	*Manufacturing cell culture management issue* *Manufacturing raw material issue*	
Commercial finished product, currently in distribution, used raw material HCl batch that have had an OOS result for appearance of solution on stability, during the manufacture of the Drug Substance.	*Manufacturing raw material issue*	

Scenario	LLT	Comment
During initial cell bank qualification, identity testing was performed, and the test did not result in appropriate biomarkers previously established for the cell line.	*Cell bank characterisation issue, identity issue*	

5.3.4 Manufacturing production issues

These examples feature terms to classify information related to failure in activities to control the manufacture of products, including in-process sampling and testing, and process validation. Also included are terms used to describe failures in establishing, following, and/or documenting performance of approved manufacturing procedures.

Scenario	LLT	Comment
During compliance monitoring aseptic activities, some sterile production employees were observed failing to comply with aseptic techniques; such as: speed of operator movement, handling of forceps, and conformance to gowning requirements. Investigation of distributed batches is ongoing.	*Inadequate aseptic technique in manufacturing of product*	

Scenario	LLT	Comment
A review of the batch record indicates that the temperature exceeded the maximum allowed in the ointment homogenizer during formulation and blending of ointment batch number X. Subsequent investigation revealed detection failure for other distributed batches.	*Manufacturing process control procedure incorrectly performed*	
Review of batch records of X Injection performed during a customer audit revealed that number of operators present in the aseptic core during filter assembly was higher than allowed by procedure and simulated during media fill.	*Manufacturing process control procedure aseptic processing issue*	
Environmental monitoring media plate results were recorded incorrectly as passing the CFU specification; however, the results were actually out of specification. Impact investigation of distributed batches is ongoing.	*Manufacturing process control procedure environmental monitoring issue*	

Scenario	LLT	Comment
A calibration technician discovered that calibration of an autoclave pressure sensor was overdue. This autoclave is used to sterilize production equipment parts. Upon calibration, the results did not meet the acceptance criteria, indicating that faulty equipment was in use during the interval since the last passing calibration measurement. An investigation was launched to assess the impact.	*Manufacturing process control procedure equipment calibration issue*	
Multiple turbid vials were found during media fill activities. Identification of microorganism and route of entry is ongoing.	*Media fill issue*	
After batch distribution, it was identified that the temperature in the vaccine incubator surpassed the maximum temperature range for 31.5 hours.	*Manufacturing process control procedure temperature issue*	
The sterilizer load configuration procedure for distributed batches was not performed as described in the validated process instructions.	*Manufacturing process control procedure not performed*	

Scenario	LLT	Comment
During the mixing process of the oral suspension, an electrical power outage caused the mixer to stop. Power was not restored for two hours, allowing the suspended material to settle to the bottom of the mixing tank. Material was used in a distributed batch.	*Manufacturing production issue*	
Production at three facilities is on hold until pandemic restrictions are eased.	*Manufacturing production temporarily discontinued due to pandemic*	
The Bioreactor Dissolved Oxygen (DO) sensor was replaced with an updated version that was not compatible with the process control software. This was detected during a system audit. An investigation was initiated to determine potential impact to distributed product.	*Product process control issue*	
After obtaining an OOS for endotoxins, the manufacturer determined this occurred due to filling technique and decided to rework a recombinant protein API batch by performing a chromatography step to remove endotoxins.	*Inadequate aseptic technique in manufacturing of product* *Product contamination endotoxin*	

Scenario	LLT	Comment
During routine maintenance, a sterile drug manufacturer discovered that a HEPA filter in an aseptic filling line had failed integrity testing.	*Manufacturing equipment high efficiency air filter issue*	
During an investigation of downstream purification chromatography operations as part of the biological active substance manufacturing process, it was determined the chromatography skid software design resulted in return of the waste outlet to the product collection pool.	*Manufacturing process control procedure issue* *Computerized system validation issue*	
A biologic product deviation regarding a discrepancy associated with the concentration of the selective reagent used in the bioreactor step for preparation of Working Cell Bank (WCB). The scope of this event includes product that was distributed to market and produced from WCB.	*Cell bank production issue*	
Incorrect colour of flip-off caps was used in packaging of the finished product. The product lot was packaged with blue colour caps instead of grey colour caps as stated in the manufacturing batch record.	*Incorrect component used in manufacturing* *Product closure issue*	

Scenario	LLT	Comment
Investigation revealed omission of mandatory bioburden testing prior to sterile filtration of an aseptically filled product.	*Manufacturing process control procedure aseptic processing issue*	

5.3.5 Product distribution and storage issues

These examples feature terms to classify information related to manufacturing quality control procedures governing issues and control of product packaging, storage, shipping and distribution.

Scenario	LLT	Comment
A newly approved vaccine for use in some regions was distributed for sale in a different region prior to its approval.	*Inappropriate release of product for distribution*	
Material was placed on quarantine pending quality review of a process deviation. An erroneous entry in the material control system allowed the product to enter distribution to the market.	*Product distribution prior to quality control unit release*	If the reason for quarantine had been provided, a more specific LLT may be selected, as in *Product distribution prior to required testing*.
A finished goods lot was released for commercial distribution without finished product bioburden testing as required per specification	*Product distribution prior to required testing*	

Scenario	LLT	Comment
A finished goods lot was found to have been released to market in error prior to completion of validation report for scale up to a larger batch size.	*Product distribution prior to validation of process*	
Shipment tracking of several manufacturing products revealed that material was lost in transit for 15 days until it was discovered at the facility of the incorrect manufacturer. The manufacturing product was returned to the distribution channel. The impact investigation is pending.	*Manufacturing product shipping issue*	

Scenario	LLT	Comment
Lots distributed were potentially exposed to temperatures outside labelled storage statement at the firm site.	*Product temperature excursion issue*	The selected LLT-PT *Product temperature excursion issue* links to HLGT *Product quality, supply, distribution, manufacturing and quality system issues* and is specific to a temperature storage issue during the manufacturing and supply phase. Another term, LLT *Product temperature deviation error* - PT *Product storage error*, links to HLGT *Medication errors and other product use errors and issues* and is specific to a temperature storage error in the medication use process.
During a review of product distribution history, it was determined that one lot had been distributed beyond the 2-year expiration date entered in the inventory control system.	*Product distribution issue* *Product expiration date issue*	

Scenario	LLT	Comment
Product awaiting customs clearance has resulted in a shipment delay, raising concerns about stability.	*Product shipment delay*	
The autoinjector component subassembly process was transferred from the component supplier to the market authorization holder filling site. Validation studies were conducted to demonstrate equivalence. Finished goods were distributed to wholesale customers prior to completion of validation sample testing.	*Product distribution prior to validation of process*	
Vaccine product was inadvertently stored overnight outside the warehouse of the manufacturing site.	*Manufacturing product storage issue*	
A cold chain product that should be stored at 2 to 8 degrees Celsius is required to be shipped using an overnight delivery service. The product was not shipped using the approved overnight delivery service and was exposed to excessive heat. As a result, the product quality and safety may have been compromised.	*Product temperature excursion issue* *Manufacturing product shipping issue*	

Scenario	LLT	Comment
Five batches of an oral suspension were shipped to customers before the quality unit release of the batches. Investigation revealed the root cause to be human error in the warehouse.	*Product distribution prior to quality control unit release*	

5.3.6 Quality system issues

These examples feature terms to classify information related to quality system issues, the framework that enables and promotes a state of control and compliance.

Scenario	LLT	Comment
Following an OOS test result, laboratory investigation was performed. However, no root cause related to the testing could be identified. Subsequently, the extended investigation process was initiated. Retesting was performed in the framework of the extended investigation without establishing a retest protocol.	*Improper management of out of specification result*	

Scenario	LLT	Comment
An OOS result for an assay was reported by a Quality Control analyst. A laboratory investigation was initiated according to the respective procedure, and a hypothesis was made that a dilution error was the root cause. A decision was made to perform the repeat testing, which yielded an in-specification result. The initial OOS result was invalidated without conducting hypothesis testing or further investigation to confirm or reject the root cause hypothesis.	*Out of specification result invalidated without appropriate rationale*	
Following an OOS assay result, the test was repeated. The new result was accepted, and original result was invalidated without proper investigation.	*Out of specification result invalidated without investigation*	
Release testing for particulate matter on a sterile parenteral product in vials was out of specification. The batch was discarded without conducting an investigation to understand root cause, e.g., product stability or manufacturing process.	*Out of specification result not investigated*	

Scenario	LLT	Comment
The granulate drying temperature for a tablet formulation was recorded as within the approved range. However, this did not reflect actual conditions recorded on the drying equipment during the operation.	*Inappropriate batch production records*	
During buffer solution processing, pH measurements were not recorded at the designated intervals as required.	*Incomplete batch production record*	
Investigation of a customer product quality complaint revealed that no batch record is available for review.	*Missing batch production record*	