Contains Nonbinding Recommendations

E2D(R1) POST-APPROVAL SAFETY DATA: DEFINITIONS AND STANDARDS FOR MANAGEMENT AND REPORTING OF INDIVIDUAL CASE SAFETY REPORTS

GUIDANCE FOR INDUSTRY

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

March 2024
ICH

Revision 1

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FOREWORD

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has the mission of achieving greater regulatory harmonization worldwide to ensure that safe, effective, and high-quality medicines are developed, registered, and maintained in the most resource-efficient manner. By harmonizing the regulatory expectations in regions around the world, ICH guidelines have substantially reduced duplicative clinical studies, prevented unnecessary animal studies, standardized safety reporting and marketing application submissions, and contributed to many other improvements in the quality of global drug development and manufacturing and the products available to patients.

ICH is a consensus-driven process that involves technical experts from regulatory authorities and industry parties in detailed technical and science-based harmonization work that results in the development of ICH guidelines. The commitment to consistent adoption of these consensus-based guidelines by regulators around the globe is critical to realizing the benefits of safe, effective, and high-quality medicines for patients as well as for industry. As a Founding Regulatory Member of ICH, the Food and Drug Administration (FDA) plays a major role in the development of each of the ICH guidelines, which FDA then adopts and issues as guidance to industry.

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GUIDANCE FOR INDUSTRY

1. INTRODUCTION

It is important to establish an internationally standardized procedure to ensure the quality of post-approval safety information and to harmonise, where feasible, the way of gathering and reporting information. The ICH E2D guideline provides guidance on definitions and standards for post-approval individual case safety reporting, as well as good case management practices. This guideline was originally based on the content of the ICH E2A guideline (which provides guidance on pre-approval safety data management), with consideration as to how the terms and definitions should be applied in the post-approval phase of the product life cycle. Detailed guidance on the specific structure, format, standards, and data elements for transmitting Individual Case Safety Reports (ICSRs) is provided in the ICH E2B guideline. Guidance on periodic reporting of aggregated safety data is covered in the ICH E2C guideline.

This guideline provides recommendations that are harmonised to the extent possible given differences in post-market safety reporting requirements among ICH regions. Where applicable, this guideline notes where local and regional requirements may vary and, as such, marketing authorization holders (MAHs) should refer to the relevant local or regional regulatory authority's requirements.

2. DEFINITIONS AND TERMINOLOGY

2.1 Basic Terms

2.1.1 Adverse Event (AE)

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

2.1.2 Adverse Drug Reaction (ADR)

Adverse drug reactions, as defined by local and regional requirements, concern noxious and unintended responses to a medicinal product.

The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (refer to the ICH E2A guideline). A reaction, in contrast to an event, is characterized by the fact that a causal relationship between the medicinal product and the occurrence is suspected. For regulatory reporting purposes, if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse drug reaction (see Section 5.1.1, AEs/ADRs).

2.1.3 Serious AE/ADR

In accordance with the ICH E2A guideline, a serious adverse event or reaction is any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening (NOTE: The term "life-threatening" in the definition of "serious" refers to an event/reaction in which the patient was at risk of death at the time of the event/reaction; it does not refer to an event/ reaction which hypothetically might have caused death if it were more severe);
- requires inpatient hospitalization or results in prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is a medically important event or reaction.

Medical and scientific judgment should be exercised in deciding whether other situations

should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events which may occur following the use of a medicinal product are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of dependency or substance use disorder.

2.1.4 Unexpected AE/ADR

MAHs should treat AEs/ADRs in ICSRs as unexpected if the reported AE/ADR is not included in any section of the local/regional product labeling (e.g., Prescribing Information or Summary of Product Characteristics). In addition, an AE/ADR in an ICSR whose nature, severity, or specificity is not consistent with the term or description used in the local/regional product labeling should be considered unexpected. When an MAH is uncertain whether an AE/ADR in an ICSR for a country or region should be treated as expected or unexpected, the AE/ADR should be treated as unexpected for that local country or region.

An ADR included in the local/regional product labeling should be considered unexpected when it is reported with a fatal outcome in an ICSR unless the labeling specifically states that the ADR might be associated with a fatal outcome.

Product labeling may include information related to ADRs for the pharmaceutical class to which the medicinal product belongs. This situation is often referred to as ‘‘Class ADRs’’, and such class ADRs should not automatically be considered “expected” when reported in an ICSR for one of the medicinal products. In this instance, MAHs should refer to the relevant local or regional requirements.

NOTE: In contrast to the term “unexpected”, the term “unlisted” is not applicable to individual case safety reporting but is used to characterize the ADR according to the Company Core Safety Information (refer to the ICH E2C guideline for definitions).

2.1.5 Other Observations

“Other observations” refers to certain occurrences associated with use of a medicinal product, including: use in pregnancy/lactation; lack of efficacy; overdose, abuse, misuse, medication error, occupational exposure; and off-label use. In some cases, “other

observations" can occur without any associated AEs/ADRs, while in other cases "other observations" can occur with an associated AE/ADR.

2.1.6 Reporting Terminology

Throughout this guideline, the term "reporting", unless specifically indicated otherwise, refers to MAHs submitting ICSRs to a regulatory authority (i.e., regulatory reporting), as opposed to MAHs receiving or collecting information about a case from a primary source.

For the purpose of reporting, requirements in some regions refer only to ADRs, whereas other regions refer to AEs. For simplicity, the term AE(s)/ADR(s) is used throughout this guideline. Refer to local and regional requirements for specifications and requirements on the reporting of AEs or ADRs to each Regulatory Authority. The term "AE(s)/ADR(s)" includes AE(s)/ADR(s) or other observations, unless specifically stated otherwise.

2.2 Individual Case Safety Report (ICSR) including Minimum Criteria for Reporting

An ICSR is a description of an AE/ADR or other observation in an individual patient at a specific point of time.

The minimum criteria for reporting ICSRs are:

- At least one AE/ADR – see Section 5.1.1, or other observation – see Section 5.1.3;
- At least one suspect or interacting[1] medicinal product;
- An identifiable patient – see Section 6.1;
- At least one identifiable reporter – see Section 6.1;

A case is the information received by an MAH or regulatory authority about an AE/ADR or other observation. Cases missing any of the above criteria do not qualify for reporting; due diligence should be exercised to collect the missing criteria.

While these criteria are the minimum needed for a case to be eligible for reporting, regulatory authorities may have additional criteria, as specified by local and regional requirements, for reporting of a case to be required. See Section 5, Standards for Reporting, for more information

[1] The term suspect medicinal product includes interacting medicinal products. "Interacting" medicinal products are products for which the reporter indicates a suspected interaction with other medicinal products. All interacting medicinal products are considered to be suspect medicinal products (See ICH E2B).

on what should be reported.

An ICSR can be a description of at least one AE/ADR, or other observation (see Section 5.1.3, Other Observations), or both.

2.3 Expedited Report

An expedited report is an individual case safety report that meets the requirements for reporting as soon as possible, but no later than 15 calendar days after day zero (see Section 5.2, Reporting Timeframes).

2.4 Primary Source

A primary source(s) is a person who provides facts about a case. Primary sources, often referred to as "reporters", include healthcare professionals and consumers who provide facts about a case to the MAH or regulatory authority. Primary sources should be distinguished from senders who gather information on a case from primary sources and transmit it (e.g., MAH to regulatory authority). Several sources, such as healthcare professionals and/or consumers, may provide information on the same case. The 'primary source' for regulatory purposes is the person who first provided facts on the case (see ICH E2B). In the case of a literature article, the author(s) is/are a primary source.

2.5 Healthcare Professional (HCP)

Healthcare professional is defined as a primary source who is medically-qualified such as a physician, dentist, pharmacist, nurse, coroner (if medically trained), or as otherwise specified by local or regional requirements.

2.6 Consumer

Consumer is defined as a primary source who is not a healthcare professional. Examples include a patient, patient representative (including a legal representative), caregiver, friend, or relative of a patient.

2.7 Digital Platform

A digital platform is the software and technology used to enable transmission of information between users (see Section 4.3, Digital Platforms).

2.8 Organized Data Collection System (ODCS)

An organized data collection system (ODCS) is an activity that gathers data in a planned manner,

thereby enabling review to be performed.

Local or regional regulatory authorities may require a protocol for certain types of ODCS (i.e., clinical trials and non-interventional studies). In this context a protocol means a document that describes the objectives, design, methodology, statistical considerations and organization of a clinical trial or study.

For MAH ODCS activities that are not conducted according to a protocol (e.g., a market research program, a patient support program), the MAH should have documentation that describes the:

1. Objectives of the ODCS activity;
2. Source(s) of the data;
3. Dataset that the MAH will collect or receive and review in order to meet the objectives of the activity detailed under item 1, including the time period that will be represented by the data;
4. Method the MAH will use to review the dataset to meet the objective of the activity;
5. Process for collection and management of any AEs/ADRs that may be identified.

For the purposes of this Guideline, ODCS excludes the MAHs' standard procedures for the surveillance, receipt, evaluation, and reporting of spontaneous postmarketing AEs/ADRs and other postmarketing AEs/ADRs managed as spontaneous reports (i.e., the MAH's routine pharmacovigilance operations for spontaneous reports), see Section 4.

Specific examples of ODCS in the context of this Guideline include clinical trials, non-interventional studies (e.g., pharmacoepidemiologic, drug utilization studies, registries), patient support programs, and market research programs. Other examples include: an MAH activity using a patient forum on a digital platform to assess patient perceptions of the safety of disease treatments; and a product-specific analysis of consumer positivity or negativity about the product (i.e., a sentiment analysis) conducted by an MAH using posts on social media networking sites.

2.9 Patient Support Program (PSP)

PSPs are ODCSs initiated by an MAH, in which patients enroll for the purpose of supporting their use of the MAH's medicinal product, or the management of their medical condition, and which include a mechanism for two-way communication between the MAH (or third party acting on the MAH's behalf) and patients or healthcare professionals. Examples of PSPs include

adherence support, disease management, and certain reimbursement, and educational programs. See Section 4.4, Sources of ICSRs, PSPs, for further details.

Programs meet the definition of a PSP if 1) they solicit medical information about the patient's use of a medicinal product and/or 2) the design of the program is such that the MAH (or a third party acting on the MAH's behalf) would foreseeably receive medical information about the patient's use of a medicinal product (e.g., when a program involves HCP interaction with a patient to administer medication or provide medical advice).

MAH-initiated programs that do not meet the criteria above (e.g., delivery of a product to a patient's home, provision of vouchers or coupons) are not considered to be PSPs, as long as the MAH does not request medical information about the patient's use of a medicinal product. PSPs exclude: clinical trials; non-interventional studies, such as post-authorization safety studies which have a scientific intent or are testing a hypothesis; all forms of compassionate use; and named patient supply.

2.10 Market Research Program (MRP)

MRPs are ODCSs which are used for planned collections of healthcare professional and/or consumer insights by an MAH, on medicinal products and/or a disease area, for the purpose of marketing and business development.

3. TYPES OF INDIVIDUAL CASE SAFETY REPORTS

3.1 Spontaneous Reports

A spontaneous report is a direct communication by an HCP or consumer to an MAH, regulatory authority or other organization (e.g., World Health Organization Uppsala Monitoring Center, Regional Pharmacovigilance Center) that describes one or more AEs/ADRs in a patient who was exposed to one or more medicinal products and that was not gathered as part of an ODCS.

In certain situations, public communication about an AE/ADR (e.g., a "Dear Healthcare Professional" communication, litigation, or publication or reporting in the media) results in stimulated reporting (i.e., increased reporting by primary sources regarding the AE/ADR). Stimulated reports should be considered spontaneous reports.

Local or regional requirements may require HCPs to report AEs/ADRs not gathered as part of an ODCS to regulatory authorities; these reports should also be managed as spontaneous reports.

3.2 Solicited Reports

Solicited reports are those derived from ODCSs (see Section 2.8, ODCS). For the purposes of reporting, solicited ICSRs should be classified as "report from study" in ICH E2B format and should have a causality assessment (see Section 5.1.1, AEs/ADRs).

4 SOURCES OF INDIVIDUAL CASE SAFETY REPORTS

4.1 Communications by HCPs and Consumers

Communications by HCPs and consumers are reports from an HCP or consumer to an MAH, regulatory authority, or other organization (e.g., World Health Organization Uppsala Monitoring Center, Regional Pharmacovigilance Center) that describes one or more AEs/ADRs. These reports may be spontaneous or they may have been gathered as part of an ODCS. For the purposes of ICSR reporting, if spontaneous, then the "Type of Report" in ICH E2B format should be classified as "spontaneous report". If gathered as part of an ODCS (i.e., solicited), then the "Type of Report" in ICH E2B format should be classified as "report from study".

4.2 Literature

Each MAH is encouraged, and in some regions required, to regularly monitor the worldwide scientific literature for safety information concerning their products by conducting a search and literature review using large reference databases with broad coverage. MAHs should follow local and regional requirements regarding their obligations to perform literature screening and the frequency of such screening.

MAHs should assess whether AEs/ADRs from scientific literature, including relevant published abstracts from meetings and draft manuscripts, qualify for reporting. Whether or not AEs/ADRs from literature are required to be reported as ICSRs depends on local and regional requirements. Once a determination is made to submit a literature ICSR, follow the ICH E2B Guideline for instructions on designating the "Type of Report": if a case in the literature arises from spontaneous observations, "Type of Report" in ICH E2B format should be classified as "spontaneous report" if a case in the literature arises from a study, "Type of Report" in ICH E2B format should be classified as "report from study". In this context, spontaneous observations are descriptions of AEs/ADRs in a patient or group of patients (i.e., individual case report or case series) which the author(s) identified in their clinical experience. In contrast, literature cases arising from a study are AEs/ADRs identified from publications where the author(s) gathered the

cases only as part of an ODCS (for example, an author who plans and conducts a search of a dataset for cases meeting pre-specified criteria). See Section 2.8, ODCS. If it is unclear from the literature report whether or not the case(s) cited are spontaneous observations or whether they arise from a study, then this item should be classified as "other".

When submitting ICSRs from literature, an ICSR with relevant medical information should be provided for each identifiable patient (see Section 6.1, Assessing Patient and Reporter Identifiability). The literature reference should be included in the ICSR[2], and the first listed author (or the corresponding author, if one is specified) should be given as the primary source; information about co-authors does not need to be documented. Additionally, regulatory authorities may request, and in some regions require, a copy of the article to accompany the ICSR. MAHs are encouraged, and in some regions required, to include in their literature screening scientific journals or other publications available in their local region or language.

MAHs may conduct literature searches themselves or use external services (i.e., third parties acting on behalf of the MAH) to conduct literature searches. MAHs and/or the third parties acting on their behalf should review the literature search results without undue delay to identify AEs/ADRs. When required, follow-up activities should be initiated in a timely manner to collect missing data on the minimum criteria for reporting and/or to obtain additional medically relevant information (see Sections 2.2, ICSR, and 6.4, Follow-up Information). The regulatory time clock for the reporting of ICSRs from the scientific literature starts (day zero) as soon as the MAH or third party acting on their behalf identifies sufficient information to determine that the criteria for ICSR reporting (i.e., the minimum criteria for reporting (refer to Section 2.2, ICSR, and 5.2, Reporting Timeframes)) are met, and not necessarily on the date of the search. If follow-up is required to determine that the criteria for ICSR reporting are met, then day zero is the date the MAH receives sufficient follow-up information to determine that these criteria are met.

In some literature articles, a suspect product is identified by its active substance, and the product source, brand, or trade name is not specified. Unless otherwise specified by regional requirements, the MAH is not required to collect or submit ICSRs from literature if the MAH

[2] See ICH E2B for the standard format to be used for literature citations: citations should be provided in the style specified by the Vancouver Convention, known as "Vancouver style", which has been developed by the International Committee of Medical Journal Editors. The conventional styles, including styles for special situations, can be found in the following reference: International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med 1997; 336:309-15.

can determine, based on the country, product name, active substance name, pharmaceutical form, batch number, marketing status, or other characteristics, that the product is not the MAH's product. If unable to make this determination, then the MAH should presume that the product is the MAH's product and therefore should collect and report ICSRs as appropriate. The MAH should indicate in their ICSRs that the specific brand was not identified.

Literature cases may differ from information from other sources, particularly concerning causality, as authors may reference many events and many medicinal products, and the author may not necessarily suspect the products to be causally related to the events described in the article; MAHs should consider the relationship between products and events in this context. If an author explicitly states in an article that an event is not associated with a medicinal product, or the event occurred before the patient was exposed to the product, the MAHs should not submit it as an ICSR.

If multiple products are mentioned in an article, an ICSR should be submitted by the MAH(s) whose product(s) is/are suspected, by the article's author, to be associated with one or more AEs/ADRs. (Note that more than one MAH may have suspect products, and thus each MAH should submit ICSR(s), for a single article).

For regions where translations of a literature article are required to be submitted with the ICSR, translation of the abstract or only pertinent sections of the article should be acceptable if it captures all the relevant information for an ICSR, including at least the four minimum criteria for reporting (see Section 2.2, ICSR), especially for long articles whose subject matter may be largely outside the scope of the case(s) in question. The full translation of a publication should be provided upon request by a regulatory authority. Unless specifically otherwise required, translation into English is the accepted standard.

A publication may duplicate or provide follow-up to a report previously received by an MAH or regulatory authority via other means (e.g., spontaneously). Duplicate detection and management should be performed when articles are identified in scientific literature, to establish whether the AE/ADR has previously been reported. The literature reference[2] should be adequately recorded in the ICSR; this will help recipients of the ICSRs to detect possible duplicate reports when ICSRs of the same case are reported by multiple MAHs (see Section 6.6, Duplicate Management). If the article is referring to information that is in a pre-existing case, then the MAH should add the

publication's citation to the pre-existing case, along with additional relevant medical details, if available, and report as a follow-up ICSR as appropriate. For reporting purposes, new information from a literature source should be managed as with any other follow-up report.

See Section 4.6, Regulatory Authority Sources, regarding publications containing cases that the authors obtained from a regulatory authority's publicly available National or Regional AE/ADR database.

Literature which presents the results from non-interventional studies, meta-analyses, or systematic literature reviews may be excluded from reporting as ICSRs depending on local and regional requirements. For literature where the cases do not qualify for ICSR reporting, but which represent new or significant safety findings, the MAH should consider including the findings in the literature section of their next relevant periodic report, where applicable. MAHs should also follow the advice in Section 5.1.2, Important Safety Findings, about communicating safety findings to regulatory authorities.

4.3 Digital Platforms

A digital platform is the software and technology used to enable transmission of information between users. Digital platforms include but are not limited to social media, websites, internet forums, chat rooms, and software applications (apps).

A general distinction should be made between those digital platforms that are under the responsibility of the MAH, and those that are not under the responsibility of the MAH.

4.3.1 Digital Platforms Under the Responsibility of the MAH

The MAH is responsible for the content of, and communications made available via digital platforms, that are owned, controlled, or operated by, or on behalf of, the MAH. A donation (financial or other) by an MAH to an organization that owns the digital platform does not necessarily mean that the MAH is responsible for the content of and communications made available via that digital platform, provided that the MAH does not control any content or communications made available via the digital platform.

MAHs should regularly screen digital platforms under their responsibility for AEs/ADRs. The frequency of the screening should allow for the MAH to identify and report AEs/ADRs within the required reporting timeline (see Section 5.2, Reporting

Timeframes). AEs/ADRs should be managed as spontaneous or solicited depending on the context in which the MAH received the report: for example, AEs/ADRs spontaneously reported by patients on any part of an MAH's product website should be managed as spontaneous reports (see Section 3.1 Spontaneous Reports); and AEs/ADRs identified from an ODCS conducted on a digital platform under the MAH's responsibility should be considered solicited reports (see Section 3.2, Solicited Reports) and managed according to the documentation describing the ODCS activity (see Section 2.8, ODCS).

4.3.2 Digital Platforms Not Under the Responsibility of the MAH

MAHs are not expected to screen or review digital platforms not under their responsibility for AE(s)/ADR(s).

However, if an MAH screens or accesses data from a digital platform not under its responsibility, and the MAH's activity is conducted in a planned manner consistent with an organized data collection, the MAH should consider the activity to be an ODCS (see Section 2.8, ODCS).

If accessing data on a digital platform in the context of an ODCS, the MAH should have documentation in place as detailed in Section 2.8, ODCS. The source of the data described in the ODCS documentation should specify the digital platform(s) being accessed. The timeframe that the MAH will conduct the activity (including review of the dataset) should also be specified in the documentation.

When accessing data from a digital platform not under its responsibility in the context of an ODCS, an MAH is not expected to search for AEs/ADRs beyond conducting its planned review of the dataset collected for the activity as detailed in its documentation. If the MAH identifies AEs/ADRs during the course of the review, the AEs/ADRs should be recorded, managed, assessed for causality and reported in accordance with the requirements applicable for solicited reports (see Section 5.1.1, AEs/ADRs), or as otherwise required by local or regional requirements.

The regulatory time clock for reporting starts (day zero) as soon as the MAH (or third party acting on their behalf), when reviewing the accessed data, identifies an AE/ADR and has sufficient information to determine that the criteria for reporting (i.e., the

minimum criteria as defined in Section 2.2, ICSR) are met; day zero is not necessarily the date the digital platform data was accessed. If follow-up is conducted, then day zero is the date of receipt of follow-up information sufficient to determine that criteria for ICSR reporting are met. See Section 5.2, Reporting Timeframes, for additional guidance on the time clock for reporting.

If an AE/ADR collected from a digital platform in the context of an ODCS meets reporting requirements to a regulatory authority, the "Study Type" data element in ICH E2B should be used to reflect the origin of the report as "Digital Platform". This designation enables these ICSRs to be distinguished from ICSRs originating from studies and other ODCS. Note: if the AE/ADR was collected in the context of a PSP or MRP, then the "Study Type" data element in ICH E2B should be used to reflect the origin of the report as PSP or MRP, as appropriate, instead of digital platform (see Sections 4.4, PSP, and 4.5, MRP).

If an MAH becomes aware of AEs/ADRs on a digital platform not under the MAH's responsibility, and the MAH received the information outside of the context of an ODCS (e.g., an MAH employee is viewing a website to identify possible answers/solutions to a business question and sees an AE/ADR mentioned), the MAH is expected to review the safety information and collect AEs/ADRs; although these cases are not direct communications to the MAH, they should be managed as spontaneous reports unless local or regional requirements indicate otherwise (see Section 5, Standards for Reporting, for information on standards and timeline for reporting).

Note: see Section 4.6, Regulatory Authority Sources, regarding cases from regulatory authorities' National or Regional AE/ADR databases available to MAHs via the regulatory authorities' digital platforms.

4.4 Patient Support Programs (PSPs)

MAHs should review all information received in a PSP for AEs/ADRs. AEs/ADRs that the MAH becomes aware of in the context of a PSP should be managed as solicited reports which includes an appropriate causality assessment (see Section 5.1.1, AEs/ADRs), or as otherwise required by local or regional requirements.

For the setup and conduct of PSPs, MAHs should have documentation in place as detailed in Section 2.8, ODCS.

PSPs vary in their nature and design. A single PSP may include a combination of activities such as nurse support, chatrooms, and delivery services. Each of the individual activities in the combined program may or may not meet the criteria of a PSP (see Section 2.9, PSP) on its own. For example, a stand-alone service delivering product to a patient's home would not meet the criteria for a PSP (see Section 2.9, PSP). However, if a program includes delivery service combined with another activity that does meet criteria of a PSP (such as a nurse helping to administer a drug), then the combined program is considered a PSP. If any one or more of the individual activities in the combined program do meet the PSP criteria, then AEs/ADRs received from any part of the program should be managed as coming from a PSP (i.e., as solicited reports).

If an AE/ADR from a PSP meets reporting requirements, the "Study Type" data element in ICH E2B should be used to reflect the origin of the report as "PSP". This enables ICSRs from PSPs to be distinguished from those originating from studies and other ODCS. MAHs may conduct a PSP using a digital platform; in this situation the ICH E2B data element value for "PSP" should be selected.

AEs/ADRs arising from MAH activities that only allow one-way interactions (e.g., delivery services, provision of vouchers or coupons) which are not part of an ODCS should be managed as spontaneous reports. Such standalone activities, which are not part of a combined multi-activity PSP, do not meet criteria for a PSP (i.e., do not have a mechanism for two-way interactions). When MAHs use third-party service providers to conduct part of or all of a PSP, the MAH should have contractual arrangements in place to ensure that those third-party service providers report AEs/ADRs to the MAH.

4.5 Market Research Programs (MRPs)

MAHs should review all information received in an MRP for AEs/ADRs. Any AEs/ADRs that the MAH becomes aware of in the context of an MRP should be managed as solicited reports, which includes an appropriate causality assessment (see Section 5.1.1, AEs/ADRs), or as otherwise required by local or regional requirements.

For the setup and conduct of MRPs, MAHs should have documentation in place as detailed in Section 2.8, ODCS.

If an AE/ADR meets reporting requirements, the "Study Type" data element in ICH E2B should be used to reflect the origin of the report as "MRP". This enables ICSRs from MRPs to be distinguished from those originating from studies and other ODCS. MAHs may conduct an MRP using a digital platform; in this situation the ICH E2B data element value for "MRP" should be selected.

4.6 Regulatory Authority Sources

Cases originating from a regulatory authority are subject to reporting to other regulatory authorities (according to local and regional requirements) by each MAH.

Cases from available National or Regional AE/ADR databases owned or operated by a regulator may be obtained by the MAH (either directly or via literature articles). MAHs should cross-reference to the source reports by including the regulator's case ID number, if available to the MAH, in the appropriate ICH E2B data element.

Re-submission of ICSRs to the originating regulatory authority is not required unless otherwise specified by local or regional requirements, or unless the MAH has obtained or received new information about the case from a primary source.

4.7 Other Sources

If an MAH becomes aware of an AE/ADR from non-medical sources, e.g., the lay press or other media, although not a direct communication to the MAH, it should be managed as a spontaneous report unless local or regional requirements indicate otherwise. Reports received by the MAH as a result of litigation should also be managed as spontaneous reports.

5 STANDARDS FOR REPORTING

5.1 What Should Be Reported?

5.1.1 AEs/ADRs

Cases of AEs/ADRs that are both serious and unexpected are subject to expedited reporting. The reporting of serious expected AEs/ADRs in an expedited manner varies according to local or regional requirements. Non-serious AEs/ADRs, whether expected or not, would normally not be subject to *expedited* reporting but may be reportable as ICSRs per local or

regional requirements and timelines.

For purposes of reporting, spontaneous reports imply a suspected causal relationship (see Section 2.1.2, ADR).

For purposes of reporting, solicited reports are classified as "report from study" in ICH E2B and should have a causality assessment; solicited reports should only be submitted if a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, as assessed by either the reporter or the MAH.

Cases that contain only an outcome (e.g., death/hospitalization) may be subject to reporting per local or regional requirements.

5.1.2 Important Safety Findings

Safety findings which do not qualify for ICSR reporting and which may lead to changes in the known risk-benefit balance of a medicinal product and/or impact on public health should be communicated as soon as possible to the regulatory authorities in accordance with local or regional requirements. Examples include any significant unanticipated safety findings from an in vitro, animal, epidemiological, or clinical study that suggest a significant human risk, such as evidence of mutagenicity, teratogenicity, carcinogenicity, or immunogenicity or increased mortality.

5.1.3 Other Observations

It is recognized that an MAH may become aware of certain observations as detailed below related to the use of a product that may or may not be associated with an AE/ADR. These cases should be recorded by the MAH and followed up to obtain information needed for evaluation of the case.

Such observations in the absence of an AE/ADR should only be reported as an ICSR if required by local or regional regulations, guidelines, or other regulatory authority conditions and should be discussed in the periodic report according to the ICH E2C guidelines where applicable.

5.1.3.1 Lack of Efficacy

Reports of lack of efficacy occurring independently (i.e., with no associated AE/ADR) should only be reported as ICSRs if required by local or regional regulations, guidelines, or

other regulatory authority conditions. Note that in some countries lack of efficacy may be considered an AE/ADR itself, depending on local or regional requirements. Products used in critical conditions or for the treatment of life-threatening diseases, vaccines, and contraceptives are examples of classes of medicinal products where lack of efficacy with no AE/ADR may be subject to ICSR reporting according to local or regional requirements. MAHs should apply judgment when determining if a case report represents a lack of efficacy with consideration of the local product labeling. Reports associated with AEs/ADRs are subject to ICSR reporting requirements.

5.1.3.2 Overdose, Abuse, Misuse, Medication Error, and Occupational Exposure

Reports associated with overdose, abuse, misuse, medication error, or occupational exposure, with no associated AE/ADR should only be reported as ICSRs if required by local or regional regulations, guidelines, or other regulatory authority conditions. MAHs should apply judgment when determining if a case represents overdose, abuse, misuse, medication error or occupational exposure with consideration of the local product labeling and indication. Reports associated with AEs/ADRs *are* subject to ICSR reporting requirements.

5.1.3.3 Use of Medicinal Products in Pregnancy/Lactation

Reports of exposure through a parent, such as the use of medicinal products in pregnancy or breastfeeding, with no associated AE/ADR in either the parent or the child should only be reported as ICSRs if required by local or regional regulations, guidelines, or other regulatory authority conditions. AEs/ADRs, such as abnormal outcome following parental exposure, including congenital anomalies, potential epigenetic responses, developmental disorders in the fetus or child, fetal death/spontaneous abortion, or AEs/ADRs in the mother or new-born, are subject to ICSR reporting requirements.

5.1.3.4 Off-label Use

Reports of intentional use of a product not in accordance with the terms of the marketing authorization with no associated AE/ADR should only be reported as ICSRs if required by local or regional regulations, guidelines, or other regulatory authority conditions. MAH should apply judgment when determining if a case report represents off-label use with consideration of the local product labeling. Reports associated with AEs/ADRs are subject to ICSR reporting requirements.

5.2 Reporting Timeframes

In general, ICSRs that fulfill local or regional criteria for expedited reporting (see Section 5.1, What Should Be Reported?) should be submitted as soon as possible, but not later than 15 calendar days after day zero (see below). Timeframes for reporting AEs/ADRs that are reportable as ICSRs, but which do not meet local criteria for expedited reporting, including non-serious AEs/ADRs, may vary according to local or regional requirements and may be subject to non-expedited (greater than 15 calendar days) timelines.

The regulatory reporting time clock is considered to start on the date when any personnel of the MAH (including third parties, such as service providers and contractual partners, acting on behalf of the MAH) obtains sufficient information to determine that a case report fulfills the minimum criteria for reporting (see Section 2.2, ICSR). This date should be considered day zero unless otherwise specified by local or regional requirements. Refer to Sections 4.2 and 4.3 for specific information regarding day zero for case reports from literature and digital platforms.

When additional medically relevant information is received for a previously reported case, the reporting time clock is considered to begin again for submission of the follow-up report, as such day zero for follow-up information is the date the MAH receives the additional information. In addition, a case initially classified as a non-expedited report, would qualify for expedited reporting upon receipt of follow-up information that indicates the case should be re-classified (e.g., from non-serious to serious), and day zero is the date of receipt of the follow-up information.

When submitting an amendment to a previously submitted report (i.e., a correction based on MAH internal quality review) with no receipt of additional information, a new clock start date (day zero) should not be assigned.

6 GOOD CASE MANAGEMENT PRACTICES

Accurate, complete, and authentic information is important for MAHs and regulatory agencies identifying and assessing AE/ADR reports. Both are faced with the task of acquiring sufficient information to help ensure that the reports are authentic, accurate, as complete as possible, and non-duplicative.

MAHs should follow local and regional requirements for the protection of personal data privacy

including patients, reporters, HCPs, and others, when transmitting or re-transmitting information in ICSRs.

The ICSR should include the verbatim terms as used by the reporter, or an accurate translation. Any MAH personnel receiving information about a case should provide an unbiased and unfiltered report of the information from the reporter. While the recipient of the information is encouraged to actively query the reporter to elicit the most complete account possible, inferences and imputations should be avoided in report submission. However, clearly identified evaluations by the MAH are considered appropriate and are required by some regulatory authorities, and they should be recorded in the relevant ICH E2B data elements.

When information is received from a consumer, their description of the event should be retained. The MAH should request and include follow-up information from the consumer or relevant HCPs as needed, seeking consent where necessary.

6.1 Assessing Patient and Reporter Identifiability

Patient and reporter identifiability is important to avoid case duplication, ensure authenticity, and facilitate follow-up of appropriate cases. The term identifiable in this context refers to the verification of the existence of a patient and a reporter (i.e., a primary source; see Section 2.4, Primary Source). Second-hand reports (i.e., situations where an individual notifies the MAH of an AE/ADR but does not have first-hand knowledge about the event), are considered incomplete and, where permissible and feasible, attempts should be made to verify the existence of an identifiable patient and reporter.

One or more of the following should automatically qualify a patient as identifiable: age (or age category, e.g., adolescent, adult, elderly), gestational age, sex, initials, date of birth, name, or patient identification number.

Examples of characteristics that qualify a reporter as identifiable include but are not limited to: name, initials, or address (e.g., reporter's organization, department, street, city, state or province, postcode, country, email, phone number), qualification (e.g., healthcare professional, lawyer, consumer or other non-healthcare professional). For cases where the reporter wishes to remain anonymous, the ICSR should still be reported, as long as the existence of an individual as the reporter is known.

In the absence of qualifying descriptors, a report referring to a definite number of patients should not be regarded as a case until the four minimum criteria for reporting are met. For example, "Twenty patients experienced…" or "a few patients experienced" should be followed up for patient-identifiable information before creating an ICSR. To qualify for ICSR reporting it should be possible to associate an AE/ADR or AEs/ADRs with a specific identifiable patient.

In relation to cases from digital platforms, the identifiability of the reporter/patient refers to the existence of a real person (i.e., where permissible and feasible, attempts can be made to verify that the patient and the reporter exist). The presence of a digital platform username or identifier (i.e., "handle") in the absence of qualifying identifiers is insufficient to confirm that there is a real patient and/or reporter. In addition, MAHs should only consider the person providing the information to qualify as a reporter if the person experienced the event or has first-hand information about it. Where follow-up is feasible, MAHs should attempt to obtain evidence of the existence of a real patient and reporter (e.g., via requesting at least one identifiable characteristic such as sex, age, or age category).

6.2 The Role of Narratives

The objective of the narrative is to summarize all relevant clinical and related information, including patient characteristics, therapy details, medical history, concurrent conditions, clinical course of the event(s), AE(s)/ADR(s) including the outcome, diagnosis, laboratory evidence (including normal ranges), and any other information that supports or refutes an AE/ADR. The narrative should serve as a comprehensive, stand-alone "medical story". The information should be presented in a logical time sequence; ideally this should be presented in the chronology of the patient's experience, rather than in the chronology in which the information was received. In follow-up reports, new information should be clearly identified.

Abbreviations and acronyms should be avoided, with the possible exception of laboratory parameters and units. Key information from supplementary records should be included in the report, and its availability should be mentioned in the narrative and appropriate ICH E2B data element and supplied on request. Any relevant autopsy or pathologic findings should also be summarized in the narrative and related documents should be provided according to local or regional requirements and where permitted by local data privacy laws.

Terms (e.g., AEs/ADRs, indication, and medical conditions) in the narrative should be accurately

reflected in appropriate ICH E2B data elements.

6.3 Clinical Case Evaluation

The purpose of careful medical review is to ensure correct interpretation of medical information. If possible, information about the case should be collected from the HCPs who are directly involved in the patient's care. Regardless of the source of an AE/ADR report, the initial recipient should carefully review the report for the accuracy and completeness of the medical information. The review should include, but is not limited to, the following considerations:

- Are the AE(s)/ADR(s) serious (according to the criteria in Section 2.1.3, Serious AE/ADR)?
- Is a diagnosis possible from the AE(s)/ADR(s) and is it supported by evidence?
- Have the relevant diagnostic procedures been performed?
- Were alternative causes and/or confounding factors for the AE(s)/ADR(s) considered?
- Is there information regarding a temporal association between the medicinal product and the AE(s)/ADR(s), and information on the outcome?
- What additional information is needed?

6.1 Follow-up Information

Initial AE/ADR reports may not have sufficient information for clinical case evaluation, and efforts should be made to seek additional information on reports, including AE(s)/ADR(s) that were reported second-hand (i.e., cases where the reporter is aware of an AE/ADR, but does not have first-hand knowledge of relevant information about the event).

To optimize the value of follow-up, the first consideration should be prioritization of case reports by importance. Highest priority for follow-up are cases which are both serious and unexpected. At a slightly lower priority are serious, expected, and non-serious, unexpected cases. However, in addition to seriousness and expectedness as criteria, cases ‘‘of special interest’’ (e.g., AEs/ADRs under enhanced monitoring at the request of regulatory authorities) also deserve extra attention.

All requests/attempts for follow-up information should be documented. The MAH should provide specific questions it would like to have answered. Follow-up methods should be tailored

towards optimizing the collection of missing information.

To facilitate the capture of clinically relevant and complete information, use of a targeted questionnaire/specific form is encouraged, preferably at the time of the initial report. Individuals with the appropriate level of pharmacovigilance training and therapeutic expertise should be involved in the follow-up of received cases. For serious AEs/ADRs, it is important to continue follow-up and report new information until the outcome has been established or the patient's condition is stabilized.

It is important that at the time of the original report, sufficient details about the patient and reporter be collected and retained to enable follow-up, within the constraints imposed by local data privacy laws. In relation to cases from digital platform not under the responsibility of the MAH, MAHs should exercise caution prior to conducting follow-up of any message marked as private, as this may constitute a breach of consent depending on local and regional privacy regulations.

6.4.1 Other Observations

As per Section 5.1.3, Other Observations, reports of other observations (without an AE), should also be followed up to obtain complete information, and to ascertain if an AE/ADR has occurred.

6.4.1.1 Overdose, Abuse, Misuse, Medication Error and Occupational Exposure

Reports should be followed up to ensure that the information is as complete as possible with regard to suspected drug(s) and the context of occurrence.

6.4.1.2 Use of Medicinal Products in Pregnancy/Lactation

MAHs are expected to follow-up all pregnancy reports from HCPs or consumers where the embryo/fetus could have been exposed (through maternal or paternal exposure) to one of its medicinal products. When an active substance, or one of its metabolites, has a long half-life, this should be taken into account when considering whether a fetus could have been exposed (e.g., if medicinal products taken before the gestational period commenced should be considered). MAHs should collect information on the outcome of the pregnancy, health of the new-born, and, where appropriate (for example, per a regulatory authority condition), development of the child. Consideration should be given as to whether the product is

specifically indicated for use during pregnancy.

6.5 Contractual Agreements

The marketing of many medicines takes place through contractual agreements between two or more companies, which may market one or more products with the same active substance name in the same or different countries/regions. Pharmacovigilance arrangements vary considerably with respect to inter-company information exchange and regulatory responsibilities.

It is important that agreements specify the management and reporting of ICSRs (i.e., processes for exchange of safety information, including timelines and regulatory reporting responsibilities) in accordance with local and regional requirements. Processes should be in place to identify responsibilities, as applicable, and avoid duplicate reporting to regulatory authorities (e.g., clearly assigning responsibility for literature monitoring and ICSR reporting (including from regulatory authority sources)).

Whatever the nature of the arrangement, the MAH is ultimately responsible for reporting within the required timelines; therefore the contractual partners should minimize the data exchange period to enable compliance with MAH responsibilities (see Section 5.2, Reporting Timeframes).

6.6 Duplicate Management

Detection and handling of duplicate reports is an important element of good case management. Regulatory Authorities and MAHs should consider and manage duplicates when reviewing pharmacovigilance data, as duplicates negatively impact signal detection.

Examples of common causes of duplicate reports are:

- A consumer and HCP reporting the same AE/ADR or other observation;
- Multiple HCPs treating the same patient reporting the same AE/ADR or other observation;
- An AE/ADR or other observation being reported by the original reporter to both the MAH and the regulator;
- Literature reporting of the same AE/ADR or other observations by multiple MAHs.

MAHs may use duplicate management strategies that are most suitable for their individual situation. ICH E2B supports specific actions to be taken upon detection of duplicates (i.e., population of ICH E2B data elements with other case identification numbers by which the case is known and submission of nullification/amendment reports as applicable).

Duplicate detection relies on good quality data and is generally based on similarities but should take into account that information in ICSRs may differ between reporters.

6.7 How to Report

ICSRs should be transmitted electronically using the ICH E2B format, according to the ICH E2B guidelines. In countries/regions where ICH E2B has yet to be implemented, other formats (e.g., CIOMS I) may be used. ICH E2B uses the Medical Dictionary for Regulatory Activities (MedDRA, ICH M1) for coding medical information.