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REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE
**POST-APPROVAL SAFETY DATA:
DEFINITIONS AND STANDARDS FOR
MANAGEMENT AND REPORTING OF
INDIVIDUAL CASE SAFETY REPORTS**

E2D(R1)

Final version

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ICH E2D
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ICH HARMONISED GUIDELINE

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DEFINITIONS AND STANDARDS FOR MANAGEMENT
AND REPORTING OF INDIVIDUAL CASE SAFETY
REPORTS**

E2D(R1)

ICH Consensus Guideline

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1. INTRODUCTION

It is important to establish an internationally standardised 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 regional and local requirements may vary and, as such, marketing authorisation holders (MAHs) should refer to the relevant regional or local 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 exposed to a medicinal product and which does not necessarily have a causal relationship with the medicinal product. An adverse event can therefore be any unfavourable 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 causally related to this medicinal product.

2.1.2 *Adverse Drug Reaction (ADR)*

An adverse drug reaction, as defined by regional and local requirements, concerns a noxious and unintended response to a medicinal product.

The phrase “response to a medicinal product” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. A reaction, in contrast to an event, is characterised 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 AE/ADR 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 AE/ADR in which the patient was at risk of death at the time of the AE/ADR; it does not refer to an AE/ADR which hypothetically might have caused death if it were more severe);
- requires inpatient hospitalisation or results in prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is an important medical event as described below.

Important medical events that might not be immediately life-threatening or result in death or hospitalisation may also be considered serious AEs/ADRs when, based on medical and scientific judgement, they might jeopardise 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 hospitalisation, or development of dependency or substance use disorder.

2.1.4 Unexpected AE/ADR

MAHs should consider AEs/ADRs in ICSRs as unexpected if the reported AE/ADR is not included in the regional or local product labelling (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 regional or local product labelling should be considered unexpected. When an MAH is uncertain whether an AE/ADR in an ICSR should be treated as expected or unexpected for a region or country, the AE/ADR should be treated as unexpected for that region or country.

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

Product labelling 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 regional or local requirements.

NOTE: In contrast to the term “unexpected”, the term “unlisted” is not applicable to individual case safety reporting but is used to characterise 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: exposure associated with pregnancy or breastfeeding; lack of efficacy or lack of effect; 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 (see Section 5.1.3, Other Observations).

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 regional and local requirements for specifications and requirements on the reporting of AEs or ADRs to each Regulatory Authority.

2.2 Individual Case Safety Report (ICSR) including Minimum Criteria

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

Regional and local requirements determine which ICSRs should be reported (e.g., based on seriousness, expectedness, etc.). See Section 5, Standards for Reporting, for information on what should be reported. In order to be eligible for submission to any regulatory authority, ICSRs must have at least these minimum criteria:

- At least one AE/ADR – see Section 5.1.1, or other observation – see Section 5.1.3;
- At least one suspect or interacting¹ medicinal product;
- An identifiable patient² – see Section 6.1;

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, food, or other non-drug compounds. All interacting medicinal products are considered to be suspect medicinal products (See ICH E2B).

² See Section 5.1.3.2 for reporting of ICSRs of medication errors, including near miss events where a medication error occurred but did not reach a patient.

- 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 ICSR reporting; due diligence should be exercised to collect the missing criteria (see Section 6.4, Follow-up Information).

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 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). For the primary source in the case of a literature article, see Section 4.2, Literature.

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 regional or local 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). Digital platforms include but are not limited to social media, web sites, internet forums, chat rooms, mobile health technologies, and software applications (apps).

2.8 Organised Data Collection System (ODCS)

For the purposes of this document, an organised data collection system (ODCS) is an activity that gathers data relevant to an MAH's medicinal product or a medical disease area, in a planned manner, thereby enabling review to be performed.

Regional or local 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 organisation of a clinical trial or study. The term 'protocol' encompasses successive versions of the protocol and protocol modifications.

For MAH ODCS activities that are not conducted according to a protocol (e.g., a market research program, a patient support program, or accessing data on a digital platform in the context of an ODCS), the MAH should have documentation in place that at least 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 look-back period and/or duration of the data collection;
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 or other observations 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 MAHs' routine pharmacovigilance operations for spontaneous reports), see Section 4, Sources of ICSRs.

Specific examples of ODCS in the context of this Guideline include clinical trials, non-interventional studies (e.g., pharmacoepidemiologic, drug utilisation 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. In addition, an activity where an MAH monitors and analyzes user communications on a social media site, often referred to as social listening or digital listening, is an example of an ODCS.

2.9 Patient Support Program (PSP)

PSPs are ODCSs initiated by an MAH, in which patients enrol 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 4.5 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-authorisation 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 collection of healthcare professional and/or consumer insights by an MAH (or a third party acting on the MAH's behalf), 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 organisation (e.g., Regional Pharmacovigilance Centre) that describes one or more AE(s)/ADR(s) in a patient who was exposed to one or more medicinal products and that was not gathered as part of an ODCS (see Section 2.8, 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.

There are certain AEs/ADRs that, although not direct communications to the MAH, if required to be reported as ICSRs, should be managed as spontaneous reports: see Section 4.2 Literature, Section 4.3.2 Digital Platforms Not Under the Responsibility of the MAH, and Section 4.8 Other Sources.

Regional or local 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 organisation (e.g., Regional Pharmacovigilance Centre) 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 refer to regional and local 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 regional and local requirements.

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. If AEs/ADRs are suspected by the article’s author to be associated with one or more medicinal products in a literature article, then the MAH should report the case as an ICSR if it otherwise meets reporting requirements. If multiple products are mentioned in an article, an ICSR should be reported 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). Where the author’s suspicion is not stated or not available, MAHs should consider the relationship

between products and events in this context to determine if AEs/ADRs from literature should be reported. 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 report it as an ICSR.

Once a determination is made to submit an ICSR from literature, 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”. 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. Conversely, if a case in the literature arises from a study, “Type of Report” in ICH E2B format should be classified as “report from study”. 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.

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 ICSR³, 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 an ICSR and/or to obtain additional medically relevant information (see Sections 2.2, ICSR Including Minimum Criteria, 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 are met (refer to Section 2.2, ICSR Including Minimum Criteria, and 5.2, Reporting Timeframes). This date should be considered day zero unless otherwise specified by regional or local requirements. If follow-up is required to determine that the criteria for ICSR reporting are met, then day zero is the date the MAH

³ 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.

receives sufficient follow-up information to determine that these criteria are met.

In some literature articles, a suspect medicinal product is identified by its active substance, and the product source, brand, or trade name are not specified. Unless otherwise specified by regional or local requirements, the MAH is not required to collect or submit ICSRs from literature if the MAH can determine, based on the region or country, product name, active substance name, pharmaceutical form, batch number, marketing status, or other characteristics, that the product is not the MAH's product; and 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 the narrative of their ICSRs that the specific brand was not identified.

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 (see Section 2.2, ICSR Including Minimum Criteria), 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 (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 4.7, Regulatory Authorities, 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 regional and local 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 guidance 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, web sites, internet forums, chat rooms, mobile health technologies, 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 organisation 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). The regulatory time clock for reporting starts (day zero) as soon as sufficient information to determine that the criteria for an ICSR (i.e., the minimum criteria as defined in Section 2.2, ICSR Including Minimum Criteria) was posted on the digital platform. 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 organised 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 and assessed for reporting as required by regional or local 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 Including Minimum Criteria) are met; day zero is not necessarily the date the digital platform data was accessed. If follow-up information is received or obtained, 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, it should be managed as a solicited report which includes an appropriate causality assessment (see Section 5.1.1, AEs/ADRs). For these ICSRs, the “Study Type Where reaction(s) / event(s) Were Observed” data element in ICH E2B should be used to reflect the origin of the report as from a digital platform in the context of an ODCS. This designation enables these ICSRs to be distinguished from ICSRs originating from studies and other ODCS.

Note: the value for digital platform in the context of an ODCS should only be used for the “Study Type Where reaction(s)/event(s) Were Observed” data element if the AE/ADR was collected from a digital platform and none of the other study types apply. For example, if the AE/ADR was collected in the context of a PSP, then the PSP study type should be selected, instead of digital platform (see Sections 4.5, PSP, and 4.6, 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 or solutions to a business question and sees an AE/ADR mentioned), the MAH is expected to review the safety information and collect AEs/ADRs in accordance with regional and local requirements. Although these cases are not direct communications to the MAH, if

an AE/ADR collected from a digital platform outside the context of an ODCS meets reporting requirements, then it should be managed as a spontaneous report (see Section 5, Standards for Reporting, for information on standards and timeline for reporting).

Note: see Section 4.7, Regulatory Authorities, regarding cases from regulatory authorities' National or Regional AE/ADR databases available to MAHs via the regulatory authorities' digital platforms.

4.4 Non-interventional Studies

Non-interventional studies (also known as observational studies) are a type of study in which participants receive an approved medicinal product during routine medical practice and are not assigned, according to a study protocol, to a specific intervention or treatment. For non-interventional studies conducted by, or on behalf of, an MAH, MAHs should have a protocol in place as detailed in Section 2.8, ODCS.

Non-interventional studies can involve primary data collection and/or secondary use of data:

- Primary data collection: Data collected specifically for the present study to address the study objectives by collecting data directly from participants, caregivers, healthcare professionals or other persons involved in the participant's care. Primary data in the context of non-interventional studies may be collected, for example, via case report forms, laboratory measurements, electronic patient reported outcomes, or mobile health technologies (See ICH E8).
- Secondary use of data: Use of existing data for a different purpose than the one for which they were originally collected. Examples of existing data sources that can be used in non-interventional studies include publicly available databases on death or poisoning, or on AEs/ADRs, disease and drug registries, administrative claims data, and medical and administrative records from routine medical practice (See ICH E8 and ICH M14).

The guidance provided hereafter applies for the management of AEs/ADRs or other observations for non-interventional studies, unless regional or local requirements indicate otherwise in relation to whether the data are from primary data collection and/or secondary use of data.

4.4.1 Non-interventional studies with primary data collection

MAHs should review for AEs/ADRs or other observations all information received in non-interventional studies with primary data collection. When permitted by regional or local requirements and supported by adequate justification, a selective approach to safety data collection (see ICH E19) may be considered.

AEs/ADRs that the MAH collects in the context of primary data collection should be

managed as solicited reports which includes an appropriate causality assessment to determine reporting (see Section 5.1.1, AEs/ADRs). For these ICSRs, the “Study Type Where reaction(s) / event(s) Were Observed” data element in ICH E2B should be used to reflect the origin of the report as ‘Other studies’.

If required by regional or local requirements, AEs/ADRs should be summarised in the final study report.

4.4.2 Non-interventional studies with secondary use of data

The design of non-interventional studies with secondary use of data is characterised by the utilization of existing data for a different purpose than the one for which they were originally collected.

AEs/ADRs that the MAH identifies in the context of secondary use of data should not be reported as ICSRs, unless regional or local requirements indicate otherwise.

If required by regional or local requirements, AEs/ADRs should be summarised in the final study report.

4.5 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 recorded, managed and assessed for reporting as required by regional or local 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, it should be managed as a solicited report which includes an appropriate causality assessment (see Section 5.1.1, AEs/ADRs). For these ICSRs, the “Study Type Where reaction(s)/event(s) Were Observed” 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 agreements in place to ensure that those third-party service providers report AEs/ADRs to the MAH (see Section 6.5, Contractual Agreements).

4.6 Market Research Programs (MRPs)

MAHs should review all information received in an MRP for AEs/ADRs. AEs/ADRs that the MAH becomes aware of in the context of an MRP should be recorded, managed and assessed for reporting as required by regional or local requirements.

For the setup and conduct of MRPs, MAHs should have documentation in place as detailed in Section 2.8, ODCS. When MAHs use third-party service providers to conduct part of or all of an MRP, the MAH should have contractual agreements in place to ensure that those third-party service providers report AEs/ADRs to the MAH (see Section 6.5, Contractual Agreements).

If an AE/ADR from an MRP meets reporting requirements, it should be managed as a solicited report which includes an appropriate causality assessment (see Section 5.1.1, AEs/ADRs). For these ICSRs, the “Study Type Where reaction(s)/event(s) Were Observed” 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.

4.7 Regulatory Authorities

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

Cases from 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.

When an MAH obtains a case from a regulatory authority, the MAH is not required to re-submit the case as an ICSR to the same regulatory authority unless the MAH has received or obtained

new information about the case from a primary source, or unless otherwise specified by regional or local requirements.

4.8 Other Sources

If an MAH becomes aware of an AE/ADR from non-medical sources, e.g., the lay press or other media, it should be recorded, managed and assessed for reporting as required by regional and local requirements. Although not a direct communication to the MAH, if an AE/ADR collected from a non-medical source meets reporting requirements, then it should be managed as a spontaneous report (see Section 5, Standards for Reporting, for information on standards and timeline for reporting). 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 regional and local requirements. Non-serious AEs/ADRs, whether expected or not, would normally not be subject to *expedited* reporting but may be reportable as ICSRs per regional or local 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) should only be reported as an ICSR if required by regional or local 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 regional or local 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, 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. The MAH should record these cases, and, as applicable, conduct follow-up (see Section 6.4, Follow-up Information).

Such observations in the absence of an AE/ADR should only be reported as an ICSR if required by regional or local requirements or other regulatory authority conditions and should be discussed in the periodic report according to the ICH E2C guidelines where applicable. If such observations are required to be reported as ICSRs, then they should be managed as spontaneous or solicited depending on the context in which the MAH received the report, in the same way that ICSRs for AEs/ADRs are managed (see Section 3, Types of Report).

5.1.3.1 Lack of Efficacy or Lack of Effect

Reports of lack of efficacy or lack of effect occurring independently (i.e., with no associated AE/ADR) should only be reported as ICSRs if required by regional or local requirements or other regulatory authority conditions. Note that in some regions or countries lack of efficacy and lack of effect may be considered AEs/ADRs, depending on regional or local 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 or lack of effect with no associated AE/ADR may be subject to ICSR reporting according to regional or local requirements. MAHs should apply judgement when determining if a case report represents a lack of efficacy or lack of effect with consideration of the local product labelling. 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 regional or local requirements or other regulatory authority conditions. MAHs should apply judgement when determining if a case represents overdose, abuse, misuse, medication error or occupational exposure with consideration of the local product labelling. Reports associated with AEs/ADRs are subject to ICSR reporting requirements.

Medication errors where no associated AE/ADR has occurred may, in some instances, not involve a patient (e.g., near miss events or intercepted medication errors where a medication error occurred but did not reach a patient) and may also be required to be reported as an ICSR per regional and local requirements; in this instance, the ICSR should include the minimum criteria (see Section 2.2, ICSR Including Minimum Criteria) except for the identifiable patient.

5.1.3.3 *Exposure to Medicinal Products Associated with Pregnancy or Breastfeeding*

Reports of exposure through a parent, such as the use of medicinal products in pregnancy or breastfeeding or paternal exposure, with no associated AE/ADR in either the parent or the child should only be reported as ICSRs if required by regional or local requirements or other regulatory authority conditions. The MAH is not expected to record exposures during pregnancy for products specifically indicated for use during pregnancy, if not associated with an AE/ADR. AEs/ADRs, such as abnormal outcome following parental exposure, including congenital anomalies, potential epigenetic responses, developmental disorders in the foetus or child, foetal 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 off-label use with no associated AE/ADR should only be reported as ICSRs if required by regional or local requirements or other regulatory authority conditions. MAHs should apply judgement when determining if a case report represents off-label use with consideration of the local product labelling. Reports associated with AEs/ADRs are subject to ICSR reporting requirements.

5.2 Reporting Timeframes

In general, ICSRs that fulfil regional or local 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 regional or local criteria for expedited reporting, including non-serious AEs/ADRs, may vary according to regional or local 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 other contractual partners, acting on behalf of the MAH) obtains sufficient information to determine that a case report fulfils the minimum criteria for reporting (see Section 2.2, ICSR Including Minimum Criteria). This date should be considered day zero unless otherwise specified by regional or local 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 (e.g., 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 refer to regional and local requirements for the protection of personal data privacy including patients, reporters, HCPs, and others, when gathering, transmitting or re-transmitting information in ICSRs.

When information is received from a primary source, the primary source's description of the event should be retained. 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. While the recipient of the information is encouraged to actively query the primary source 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.

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.

To have an identifiable patient, there should be enough information to indicate the existence of a specific patient. 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, patient identification number, or other identifiers specified by regional or local requirements.

Examples of characteristics that qualify a reporter as identifiable include but are not limited to: name, initials, or address (e.g., reporter's organisation, department, street, city, state or province, postcode, region or 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 and the case otherwise meets reporting requirements.

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 or patient refers to the existence of a real person; 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).

6.2 The Role of Narratives

The objective of the narrative is to summarise 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 an assessment of a causal relationship between a medicinal product and 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 summarised in the narrative and related documents should be provided according to regional or local 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 description of 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?

6.4 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 AEs/ADRs 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). 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 regional or local data privacy laws.

To optimise the value of follow-up, the first consideration should be prioritisation 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. 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) should be prioritised.

All requests and 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 optimising the collection of missing information to allow meaningful case evaluation.

To facilitate the capture of clinically relevant and complete information, use of a targeted questionnaire or 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.

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 regional and local privacy regulations.

6.4.1 Other Observations

For some other observations without an AE/ADR, there are specific considerations for follow up as outlined below:

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 Exposure to Medicinal Products Associated with Pregnancy or Breastfeeding

MAHs are expected to follow up all pregnancy reports from HCPs or consumers where the embryo or foetus could have been exposed (through maternal or paternal exposure) to one of its medicinal products. For certain types of medicinal products, potential for embryo-foetal exposure may need to be considered even if the medicinal product was taken before the gestational period commenced. MAHs should collect information on the outcome of the pregnancy, health of the newborn, and, where appropriate, development of the child. This follow up is not expected for cases of exposure during pregnancy for products specifically indicated for use during pregnancy if not associated with an AE/ADR.

6.5 Contractual Agreements

Contractual agreements may take place between MAHs and third parties (e.g., service providers) who perform activities for the MAH in which they would foreseeably receive or otherwise obtain safety information associated with the MAH's medicinal product. Further, the marketing of medicines may take place through contractual agreements between MAHs and other companies, which may market one or more products with the same active substance name in the same or different regions or countries.

It is important that these 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 regional and local requirements. Processes should be in place to identify responsibilities, as applicable, and avoid duplicate reporting to regulatory authorities.

Whatever the nature of the agreements, the MAH is ultimately responsible for reporting within

the required timelines; therefore, the contractual partners should minimise 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 observation by multiple MAHs.

MAHs may utilise 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 or 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 regions or countries where ICH E2B has yet to be implemented, other formats (e.g., CIOMS I) may be utilised. ICH E2B uses the Medical Dictionary for Regulatory Activities (MedDRA, ICH M1) for coding medical information.