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ICH guideline E19 on optimisation of safety data collection

Step 2b

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INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

Optimisation of Safety Data Collection
E19

Draft *v*ersion

Currently under public consultation

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

E19
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ICH HARMONISED GUIDELINE

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1 INTRODUCTION

1.1 Objective of the Guideline

This Guideline is intended to provide internationally harmonised guidance on an optimised approach to safety data collection in some late-stage pre-approval or post-approval studies when the safety profile of a drug is sufficiently characterised. Optimisation of safety data collection using a selective approach may improve the efficiency of clinical studies while reducing the burden to study participants. Adoption of an internationally harmonised approach to selective safety data collection may facilitate global participation in clinical studies.

1.2 Background

Regulators and industry have a shared interest in reducing the burden to study participants while facilitating the conduct of studies that could yield important new medical knowledge and advance public health. Although safety monitoring of patients during clinical studies remains critically important, unnecessary and burdensome data collection may serve as a disincentive to participation in clinical studies, e.g., frequent and time-consuming patient visits; laboratory tests; and/or physical examinations.

Knowledge about a medicinal product's safety profile continually evolves as safety data accumulates. Throughout the course of medicinal product development and subsequently while the drug is marketed, sponsors collect extensive safety-related data, including all vital signs, laboratory data, and adverse events. In the later stages of drug development, and if the safety profile is well-understood and documented, comprehensive collection of all safety data may provide only limited additional knowledge of clinical importance. In such circumstances, a more selective approach to safety data collection may be adequate and optimal, as long as the study objectives and the welfare of study participants are not compromised.

Importantly, sponsors and investigators should ensure that routine patient care is not compromised by the selective safety data collection approach outlined in this Guideline. It is recognised that safety monitoring serves to protect individual study participants and will continue to be performed as per standard of care.

1.3 Scope of the Guideline

This guidance is intended to apply to collection of safety data during the late-stage development of medicinal products in interventional and non-interventional studies, in the post-approval setting and, for specific cases, in the pre-approval setting.

In the pre-approval setting, comprehensive safety data collection is expected in order to elucidate frequency, severity, seriousness, and dose-response of adverse events, including potential differences across subsets, e.g., demographic; concomitant illnesses; and/or concomitant therapy. However, even before approval of a new medicinal product, if there is agreement with regulatory authorities that sufficient safety data are available or are being collected in ongoing late-stage studies, selective safety data collection may be appropriate in certain studies.

Selective safety data collection following the principles of this Guideline does not alter local/regional safety reporting requirements.

2 GENERAL PRINCIPLES

2.1 Types of Data for Which Selective Safety Data Collection May be Appropriate

2.1.1 Types of Safety Data Where It May be Appropriate to Limit or Stop Collection

1. Non-serious adverse events
2. Routine laboratory tests
3. Information on concomitant medications
4. Physical examinations (including vital signs)
5. Electrocardiograms

2.1.2 Types of Safety Data That Should Generally be Collected under All Circumstances

For the following types of events/data, comprehensive details should generally be provided to allow adequate assessment of the event/data, e.g., history; associated adverse events; relevant laboratory values; concomitant medications; vital signs; and/or follow-up outcome.

1. Deaths
2. Serious adverse events
3. Significant adverse events that led to an intervention, including withdrawal or dose reduction of investigational medicinal product or addition of concomitant therapy
4. Marked laboratory abnormalities (other than those meeting the definition of serious)
5. Overdose
6. Pregnancies
7. Adverse events of special interest (if defined). These adverse events may warrant collection of additional information across the entire study population to better characterise these events (e.g., particular laboratory parameters; vital signs; risk factors; concomitant therapies; and/or concomitant illnesses). For example, if gastrointestinal haemorrhage was an adverse event of special interest, one might want to proactively collect concomitant antithrombotic therapy across the entire study population
8. Laboratory data, vital signs, electrocardiograms of special interest (if defined)

2.1.3 Baseline Data

Use of a selective safety data collection approach does not change considerations for baseline data collection. Baseline data are needed to ensure that subjects meet inclusion and exclusion criteria for study enrolment and are important in the assessment of safety. For example, particular serious adverse events may occur more frequently in subgroups defined on the basis of

demographics, baseline disease characteristics, coexisting illnesses, or concomitant therapies; analyses of such information can be important in considering the benefit-risk profile of the drug.

2.2 When May Selective Safety Data Collection Be Considered?

When sponsors choose to implement selective safety data collection for a clinical study, a scientific justification should be provided. Factors that contribute to a determination that selective safety data collection would be appropriate include:

1. The medicinal product has received marketing authorisation from a regulatory authority for the indication under investigation
2. Availability of post-approval safety data and findings
3. The dose, dosing regimen, dosage form, route of administration and treatment duration used in the previously conducted studies are comparable to the planned use of the drug in the proposed study
4. The patient population from previously conducted studies is representative of subjects in the planned study regarding demographic characteristics, underlying medical conditions, concomitant drugs, and other important factors (e.g., Cytochrome P450 enzymes (CYP) metabolizer status)
5. Exposure in previously conducted (or ongoing, if applicable) studies that contribute to the overall safety database, i.e., number exposure to drug, treatment duration
6. Consistency of the safety profile across previous studies
7. Characteristics of previous studies, e.g., study design; study conduct; adequacy of safety monitoring/safety data collection; availability of protocols; statistical analysis plan; and/or access to data
8. Knowledge of the mechanism of action of the medicinal product under study
9. Knowledge of the safety profile of approved drugs in the same pharmacologic class

The above factors should be considered in determining whether the safety of the medicinal product has been sufficiently characterised to provide justification for selective safety data collection in the proposed study.

In the pre-approval setting, selective safety data collection may be justifiable if sufficient safety data are available from completed studies. Moreover, when sufficient safety data will be forthcoming from one or more ongoing late-stage study(ies), selective safety data collection may be appropriate for a concurrently conducted study-initiated pre-approval.

2.2.1 Benefit-Risk Considerations for Selective Safety Data Collection

It should be recognised that the contribution of non-serious adverse events to the benefit-risk profile of a drug may differ depending on the indication of use and patient characteristics (e.g., age and/or cardiovascular risk factors). These factors should be considered when accepting the comparability of patient populations and the applicability of selective safety data collection. For example, even when safety of a drug is sufficiently characterised in a patient population with advanced disease, comprehensive safety data collection in a patient population with less

advanced disease may be appropriate to ensure that the benefits outweigh the risks in the less severely affected population.

2.2.2 Extent of Exposure

Selective safety data collection could be considered for studies using lower doses and/or shorter durations than in previous studies. Conversely, selective safety data collection would generally not be acceptable if higher doses and/or longer treatment durations than previously studied are planned. Nonetheless, even when exposure is greater in the planned study, there may be circumstances where selective safety data collection is still appropriate, e.g., a study designed to characterise infrequent serious adverse events (e.g., renal toxicity; myocardial infarction; and/or stroke) associated with longer term use of the medicinal product within the labelled indication; a planned five-year study when a one-year study has been completed.

2.3 Examples Where Selective Safety Data Collection May be Considered

Selective safety data collection may be appropriate in studies used to evaluate some of the following objectives. These are not the only circumstances where selective safety data collection may be appropriate.

1. New indications of approved drugs
2. To study additional endpoints, e.g., patient-reported outcome for symptomatic improvement; quality of life; and/or outcome studies (e.g., mortality; morbidity; and/or specific safety issues)
3. To study comparative effectiveness/efficacy
4. Demonstration of superiority when non-inferiority has been demonstrated
5. Characterisation of adverse events of special interest
6. Fulfilment of post-approval requirements, post-authorisation safety studies based on data collection from registries or electronic health records
7. Late-stage premarketing outcome study in a large population

Additional examples and situations for applying selective safety data collection may be found in Section 3, Methods of Implementation.

2.4 Ensuring Patient Safety within Studies

Patient safety monitoring serves two purposes: 1) to protect the welfare of individual study participants; and 2) to accumulate safety information to be used in the assessment of benefit-risk for the proposed indication. The recommendations in this Guideline do not obviate the need for monitoring to protect individual patient welfare. Although certain safety data, e.g., non-serious adverse events, would not need to be recorded in the case report form (CRF) when selective safety data collection is determined to be appropriate, the protocol should stipulate that patients are monitored per standard of care. For example, for a medicinal product known to cause hyperglycaemia, where routine blood glucose monitoring is recommended in labeling, glucose should be monitored in patients participating in a study. If hyperglycaemia is well-characterised with this medicinal product, the glucose data do not need to be recorded in the CRF or reported to the sponsor in studies using selective safety data collection. Glucose levels would be recorded

in the CRF and reported to the sponsor if stipulated in the protocol, e.g., as an adverse event of special interest, associated with a serious adverse event.

2.5 Changes in Approach to Safety Data Collection

When an unexpected safety issue arises during the course of a study, e.g., a postmarketing safety signal; a finding from a nonclinical study; higher than expected withdrawals; and/or concern from a data monitoring committee; a change in the selective safety data collection approach may be warranted, e.g., denoting a new adverse event of special interest; and/or reverting to comprehensive safety data collection.

2.6 Early Consultation with Regulatory Authorities

Studies must be conducted according to local and regional laws and regulatory requirements. When sponsors are considering selective safety data collection in interventional studies, they should discuss their scientific rationale and planned methods with regulatory authorities prior to initiating the study(ies). The same applies to non-interventional studies that are being conducted to address requests from regulatory authorities.

It is possible to conduct a multi-regional clinical study using a single protocol with selective safety data collection if the safety profile of the product is considered to be sufficiently characterised, and all regulatory authorities agree with the proposed approach. A well-designed multi-regional clinical study that takes this Guideline into account will help the sponsor reach agreement with regulatory authorities in multiple regions (See ICH E17 – General Principles for Planning and Design of Multi-Regional Clinical Trials).

3 METHODS OF IMPLEMENTATION

Having considered the principles outlined in Section 2, General Principles, with respect to when it may be appropriate to limit or stop collection of certain types of safety data, a number of approaches for selective safety data collection may be considered.

Use of selective safety data collection can introduce important complexities in study conduct and safety analysis. The specific approaches should be carefully planned and clearly delineated within the relevant study documents, e.g., protocol; monitoring plan; and/or statistical analysis plan, with a reference to this Guideline.

Regardless of the method chosen, it is essential to ensure patient safety and adhere to local and regional laws and regulations. When the selective safety data collection approach is used for a clinical study, the approach should be described in the appropriate document(s) when safety findings are presented, e.g., the Clinical Study Report (CSR); Development Safety Update Report (DSUR); Periodic Benefit-Risk Evaluation Report (PBRER); Periodic Safety Update Report (PSUR); and/or Common Technical Document (CTD).

The following examples of methods of implementation are not meant to be all-inclusive. These approaches can be applied in both the pre- and post-approval settings and require a scientific rationale and justification. The data supporting these approaches are more likely to be available in the post-approval setting than in the pre-approval setting.

3.1 Selective Safety Data Collection for All Patients in the Study

For all patients in the study, parameters listed in Section 2.1.2, General Principles, are collected throughout the study, e.g., serious adverse events; adverse events of special interest; and/or deaths. Conversely, the parameters listed in Section 2.1.1, General Principles, are not collected, e.g., non-serious adverse events; routine laboratory values; concomitant medications; physical examination data; vital signs; and/or electrocardiograms.

In the post-approval setting, this approach may be useful to address a specific safety concern, for example, to meet a post-authorisation commitment, when safety in other regards has been sufficiently characterised.

In the pre-approval setting, this approach may be also used. For example, consider a development programme for a lipid-lowering drug, where a decrease in low-density lipoprotein (LDL) cholesterol will serve as the basis of approval, but the impact on cardiovascular risk is being investigated. In addition to the completed Phase 2 programme, two Phase 3 studies are ongoing with LDL cholesterol as the primary endpoint, which will provide adequate exposure to assess safety sufficiently. The sponsor wishes to initiate a third study with major adverse cardiovascular events as the primary endpoint. For the third study, a selective safety data collection approach could be justified considering the data available in light of the principles above.

3.2 Comprehensive Safety Data Collection for a Specific Subset(s) of the Population, with Selective Safety Data Collection for Other Patients

Comprehensive safety data are collected for specific subset(s) of the patient population where additional information is deemed important, whereas selective safety data are collected for other patients. For example, if the patient population in previous studies included few patients over the age of 65, it could be of value to collect full data on this population in a new study in the same indication or in a related indication. Other examples of specific subsets include those based on geographic location; ethnicity; sex; baseline disease status (renal/hepatic impairment), CYP status; or genetics.

3.3 Comprehensive Safety Data Collection in a Representative Subset of the Population, with Selective Safety Data Collection for Other Patients

In some cases, efficacy studies must enrol many thousands of patients in order to achieve adequate statistical power. In such settings, such as a large clinical outcomes study, the number of patients planned for enrolment may greatly exceed the number needed to assess the non-serious adverse events adequately. In this setting, comprehensive safety data could be collected for only a representative subset of patients, for example, full data collection could be undertaken at randomly selected sites.

3.4 Comprehensive Safety Data Collection for the Initial Portion of the Study, with Selective Data Collection Thereafter

Comprehensive safety data are collected from baseline through some pre-determined interval of the study, with selective safety data collection thereafter. A data monitoring committee could

consider the safety data and provide agreement with selective safety data collection for the subsequent portion of the study. These approaches can be useful for studies designed to assess important long-term drug effects, where safety would be adequately characterised in the early part of the study, e.g., one year, through comprehensive safety data collection. For example, consider a study to prevent an important outcome such as dementia, end-stage kidney disease, and/or hepatic failure. Assuming it would take three years to collect adequate events to have adequate statistical power for efficacy, it may be appropriate to utilize a selective approach to safety data collection once data have been analysed for all patients followed through one year and non-serious adverse events have been deemed to be adequately characterised. The selective approach would discontinue collection of non-serious adverse events, vital signs, laboratory tests, etc., and utilize less frequent study visit intervals. The protocol should include a prospective plan for concurrence of a data monitoring committee prior to the change to selective safety data collection.

4 RELATIONSHIP WITH OTHER GUIDELINES/REGULATIONS

This guideline should be considered in conjunction with other ICH guidelines relevant to the conduct of clinical studies and clinical safety data management, e.g., E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting); E2F (Development Safety Update Report); E3 (Structure and Content of Clinical Study Reports); E6(R2) (Good Clinical Practice: Integrated Addendum to ICH E6(R1)); E8 (General Considerations for Clinical Trials); and/or E17 (General Principles for Planning and Design of Multi-Regional Clinical Trials). Evaluation of the information generated through post-approval pharmacovigilance activities is also important for all products to ensure their safe use, e.g. E2E (Pharmacovigilance Planning); E2D (Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting); and E2C(R2) (Periodic Benefit-Risk Evaluation Report).