# Individual Case Safety Reports and VigiBase – the vital importance of quality

## Introduction

The WHO Global Individual Case Safety Report (ICSR) database, VigiBase, is the source of worldwide post-marketing case safety reports. More than 100 countries are currently contributing to the database by submitting ICSRs collected at their national pharmacovigilance centres (NCs). VigiBase data is accessible to all NCs participating in the WHO Programme for International Drug Monitoring and is a vital source of information for countries with limited data resources.

The database is a one-stop source of global information when assessing safety issues identified at the national level, but can also be used during clinical trials and authorization of a new drug in a country, to compare with post-marketing experiences in other countries or experiences from similar drugs around the world. Pharmaceutical companies and other stakeholders may access certain VigiBase data upon request.

The purpose of this publication is to emphasize the significance of good quality data in VigiBase and other ICSR databases, by describing the scientific value of complete information from mainly a medical analysis perspective.

VigiBase is maintained by the WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre (UMC).

Periodic analysis of VigiBase data is performed, in accordance with UMC's current routine signal detection process, to find previously unrecognized adverse drug reactions (ADRs) and other patient safety issues.

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## Quality of VigiBase

UMC is constantly working on improving the quality of VigiBase, both when it comes to input of data and to output of data. A fundamental requirement for the quality of an ICSR database is that the data is up to date. As underreporting is a major problem in post-marketing reporting systems, each report is valuable. Both frequency of reporting and the numbers of reports submitted to VigiBase are quantitative measures. Just as essential is the quality of the data submitted.

- *To ascertain the availability of high quality data in VigiBase, members of the WHO Programme are expected to transmit complete ICSRs to UMC, in compliance with the World Health Assembly agreement for founding the WHO Programme.*

- *Members of the WHO Programme are expected to submit ICSRs to VigiBase at least every quarter and preferably more frequently than once a month.*

- *Members of the WHO Programme are expected to submit all post-marketing ICSRs to VigiBase, irrespective of their origin, source/reporter type, causality, and seriousness.*

*Good quality data is a world-wide patient safety concern*

Individual case safety reports constitute a key resource for the early identification of patient safety issues in relation to medicines.

The quality of data in ICSR databases is crucial; the consequence of poor quality data is the risk of drawing wrong or delayed conclusions about a patient or a safety signal, which in turn could lead to patients being harmed unnecessarily.

UMC is actively promoting the international ICSR standard exchange format; International Conference on Harmonization E2B (ICH E2B). This format includes all relevant data fields, which allows for a comprehensive medical analysis of the data.

- *UMC strongly recommends WHO Programme members to use the ICH E2B format to submit data to VigiBase.*

UMC has, together with the Swiss Agency for Therapeutic Products (Swissmedic), developed an ICSR management tool (VigiFlow) that allows for new countries entering the WHO Programme and countries with limited resources to use the ICH E2B format. This means that more and more countries have the prerequisites for managing and transmitting high quality ICSRs.

UMC recently reintroduced a tool for indicating how complete the data is given on a report; the Documentation grading – completeness score. The score is used to identify problems of missing data in reports received from NCs and aims to help countries to improve their ways of collecting, managing and transmitting complete ICSRs.

## *Minimum administrative ICSR information*

The minimum administrative information needed for the processing and identification of a report in VigiBase is:

- sender's unique case identification number
- worldwide unique case identification number,
- sender identifier, and
- date of receipt of most recent information.

The three first fields are critical to correctly identify reports, and to identify duplicate reports – this is particularly important in an international database. The date of most recent information is essential for correctly handling follow-up information; again avoiding duplication.

## *Minimum information for a valid ICSR*

The minimum information needed for a valid report according to ICH E2B is:

- one identifiable patient,
- one identifiable reporter,
- one reaction/event, and
- one suspect drug.

***The patient and reporter administrative information (name and contact details) is confidential and should NOT be sent to VigiBase, in accordance with the guidance in ICH E2B (below).***

***From ICH E2B Data Elements for Transmission of Individual Case Safety Reports***

**A.2.1.1 Reporter identifier** (name or initials)
*User Guidance:*
*The identification of the reporter may be prohibited by certain national confidentiality laws or directives. The information is only provided when it is in conformance with the confidentiality requirements and this guidance applies to all the subsections of A.2.1. Notwithstanding the above, at least one subsection should be completed to fulfill the general need of having an identifiable reporter. If only the name of the reporter is known and it is prohibited to provide it because of confidentiality requirements, initials can be used.*

**B.1.1 Patient** (name or initials)
*User Guidance:*
*The identification of the patient may be prohibited by certain national confidentiality laws or directives. The information is only provided when it is in conformance with the confidentiality requirements. This also applies to medical record number(s) (B.1.1.1).*

## *Essential information for medical assessment of ICSRs*

An inherent problem in pharmacovigilance is that most case reports concern suspected adverse drug reactions. Adverse reactions are rarely specific for the drug, diagnostic tests are usually absent and a rechallenge is rarely ethically justified.

In practice few adverse reactions are 'certain' or 'unlikely'; most are somewhere in between these extremes, i.e. 'possible' or 'probable'. Evaluating a causal relationship between a drug and an adverse event is complex, and different approaches are used: they may be context dependent. One feature is common to all approaches: the more information the easier the assessment, and more likely to be correct. It is also common to found agreement on some essential fields of information needed.

For an example, Table 1 summarizes the minimum information needed to be able to assign a *certain, probable, possible* or *unlikely* relationship with a drug using the WHO causality assessment descriptions.

**Table 1. WHO assessment causality descriptions and corresponding information on ICSR.**

| Causality term | Assessment criteria | Information on ICSR |
|---|---|---|
| Certain | • Event or laboratory test abnormality, with plausible time relationship to drug intake<br>• Cannot be explained by disease or other drugs<br>• Response to withdrawal plausible (pharmacologically, pathologically)<br>• Rechallenge satisfactory, if necessary<br>• Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) | • **Drug(s)**<br>• **Reaction/event (or laboratory test)**<br>• **Time to onset**<br>  ○ **time interval from start of drug administration to onset of ADR**<br>  *or*<br>  ○ **dates of drug treatment and reaction/event (or laboratory test)**<br>• **Indications for use of drugs**<br>• **Dechallenge information**<br>• **Rechallenge information**<br>• **Relevant medical history**<br>• **Case narrative** |
| Probable | • Event or laboratory test abnormality, with reasonable time relationship to drug intake<br>• Unlikely to be attributed to disease or other drugs<br>• Response to withdrawal clinically reasonable<br>• Rechallenge not required | |
| Possible | • Event or laboratory test abnormality, with reasonable time relationship to drug intake<br>• Could also be explained by disease or other drugs<br>• Information on drug withdrawal may be lacking or unclear | |
| Unlikely | • Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)<br>• Disease or other drugs provide plausible explanations | |

In addition to the data fields needed for making a causality assessment, further information may be crucial for making a valid medical assessment of an ICSR. Table 2 summarizes important information that may be available on an ICSR, the reason for its importance, and the consequences of it not being available for analysis.

**Table 2. Important information for making valid medical assessments of ICSRs, and the reason for its importance.**

| Information on ICSR | Reason for importance | Consequences of missing data |
|---|---|---|
| *Administrative information* | | |
| Country | Identify the original country of the report. | Miss reports for geographical specific analyses/stratification. |
| Type of report | Important especially when type is other than spontaneous report, e.g. clinical trial report. | Risk of signalling problems based on clinical study data, since these reports are valued differently. |
| Qualification of reporter | Indicates a valid reporter and if the reporter has made a clinical assessment. | Risk of missing concerns and evidence from different reporter backgrounds. |
| Literature references | Identify published case reports which often include more information than captured in the ICSR. | Risk of incorrect conclusion about a single patient but also about a possible broader drug problem. |
| *Patient information* | | |
| Age of patient | Indicates a valid patient and possibly different risk. | Risk of incorrect conclusion about a single patient.<br>Not possible to make age specific analyses/stratification. |
| Sex of patient | Indicates a valid patient and possibly different risk. | Risk of incorrect conclusion about a single patient.<br>Not possible to make gender specific analyses/stratification. |
| Medical history and past drug history of patient | Helps characterize the individual patient.<br>Contributes with valuable information when possible confounding factors are investigated in a general overview of a drug problem. | Risk of incorrect conclusions about a single patient as well as in an overview of a drug problem. |
| Death information | Helps to characterize reaction/event.<br>Gives information on the seriousness of the case.<br>Helps to focus on the more important issues. | Risk of incorrect conclusions about a single patient but also about a possible drug problem.<br>Risk of focusing on less important issues. |
| Seriousness | Helps to characterize reaction/event.<br>Gives information on the seriousness of the case.<br>Helps to focus on the more important issues. | Risk of incorrect conclusions about a single patient but also about a possible drug problem.<br>Risk of focusing on less important issues. |
| Parent-child information | Identify parent drug exposure resulting in reaction/event in foetus/child. | Risk of missing safety issues related to parent-child exposure. |

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| ***Reaction information*** | | |
| Reaction/event | As precise and correct description of the reaction/event as possible is of utmost importance for evaluation. Applies to both the reaction/event as originally reported and the coded reaction/event. | Risk of incorrect conclusions about a single patient but also about a possible drug problem. |
| Date of onset of reaction/event | Needed to calculate time to onset, in order to evaluate the time relationship between drug and reaction/event. | Unable to confirm the time relationship between drug and reaction/event; cannot do complete causality assessment. |
| Outcome of reaction/event | Indicates the seriousness of the reaction/event and further characterizes a clinical event.<br>Needed to determine outcome of dechallenge when drug was withdrawn. | Unable to confirm a relationship between drug and reaction/event and assess impact.<br>Risk of focusing on less important issues. |
| Laboratory findings | Helps verifying and characterizing the reaction/event. | Lead to incorrect conclusion about a single patient but also about a possible drug problem. |
| ***Drug information*** | | |
| Drug | As precise and correct description as possible of the medical product, including trade name and drug characterization (suspected/interacting/concomitant), is of utmost importance for evaluation. | Risk of incorrect conclusion about a single patient but also about a possible drug problem. |
| Drug start- and stop dates | Needed to calculate time to onset and duration of treatment.<br>Stop date might be an indication that the reaction prompted cessation of treatment. | Unable to confirm time relationship between drug and reaction/event; cannot do complete causality assessment. |
| Time to onset | Time to onset reported as the time interval between start of drug and reaction onset is important if drug start- and reaction start dates are missing.<br>Needed to evaluate the time relationship between drug and reaction/event. | Unable to confirm time relationship between drug and reaction/event; cannot do complete causality assessment. |
| Drug administration data | Identify problems related to form, strength or route of administration of a medicinal product. | Unable to investigate certain hypothesis based on influence of form, strength or route of administration on a reaction/event. |
| Dose | Important from a pharmacological point of view.<br>Identify non-optimal use of drug, resulting in reaction/event. | Lead to incorrect conclusion about a single patient but also about a possible drug problem. |
| Indication | The reaction/event may be influenced by the indication; i.e. the patient's underlying disease. Especially important if the drug may be used for very different indications.<br>May give hint on route of administration, of importance if the route of administration data is missing.<br>May identify off label use. | Risk of incorrect conclusions if drug is used for very different indications; confounding by indication should always be considered. |

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|---|---|---|
| Dechallenge | Crucial as a positive dechallenge indicates association between drug and reaction/event – especially important when information on time to onset is missing. | Unable to confirm drug-adverse reaction relationship. |
| Rechallenge | Crucial as a positive rechallenge strongly indicates association between drug and reaction/event. | Risk of missing very important drug problems reported very rarely but with strong evidence of causality. |
| *Further information* | | |
| National PV Centres' Causality assessment | Valuable additional information since the NC's judgement is often based on more information available locally.<br>Helps to focus on the more likely associated issues. | UMC assessment different from the NCs': NCs may add information not known by others.<br>Risk of focusing on less likely associated issues. |
| Comments from NC/reporter | Valuable additional information since the NCs'/reporters' comments on the case are often based on more information than what is available in VigiBase. | Missing valuable information from source with more knowledge about the case. |
| Case narrative | A medical report of the case that often includes additional valuable information that cannot be captured in the structured fields.<br>The information is of utmost importance. | Unable to confirm drug-adverse reaction relationship.<br>Risk of wrong conclusion about a single patient but also about a possible drug problem. |

## Data Quality versus Data Protection

UMC is subject to, and complies with the EU data protection law, and adheres to the guidance in ICH E2B for protecting patient and reporter confidentiality.

High quality data and completeness of information are critical factors for UMC's ability to live up to its core mission of assessing new patient safety issues on behalf of the WHO Programme. All ICSR information has its purpose, either administratively or medically. With the exception of confidential patient and reporter details, preferably no information should be left out if available on the original report.

- *UMC does not make free-text information from medical history and case narrative available to third parties. Instead, the national pharmacovigilance centre from which the information originated is referred to when that information is requested.*

- *UMC only publishes anonymised data in Signal and other scientific publications.*