PHARMACOVIGILANCE KEY CONCEPTS

Key words: Patient information leaflet (PIL), adverse reaction (AR), adverse event (AE), company core safety information (CCSI), summary of product characteristics (SmPC), unsolicited (spontaneous) reports (UR), solicited reports (SR), clinical trials (CT).

Pharmacovigilance is a complex system that allows all parties involved in drug circulation to ensure medicinal products safety and efficacy [1]. One of pharmacovigilance key elements is various data related to the mentioned issues (e.g. adverse reactions and events, drug interactions information).

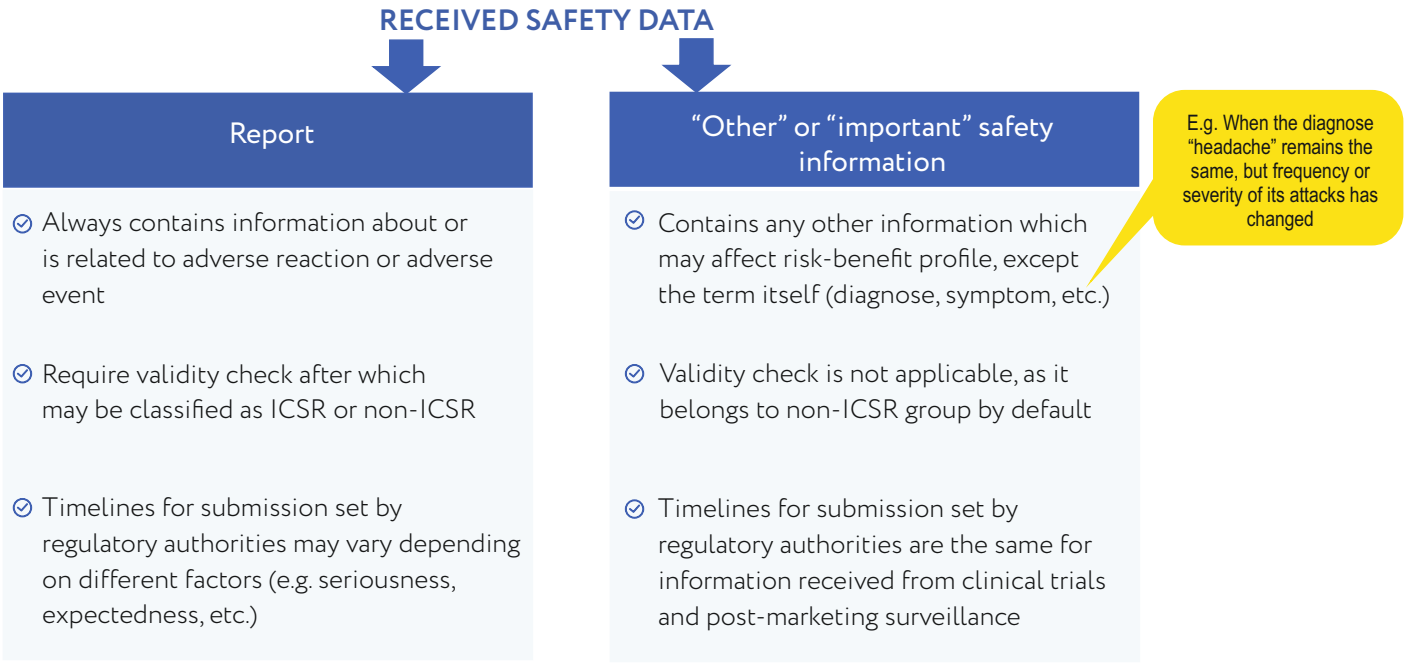
The exchange of such data is a complex and multi-stage process, the efficiency of which is largely dependent on marketing authorization holder (MAH) performance.

SAFETY INFORMATION RECEIVED BY MARKETING AUTHORIZATION HOLDER

Depending on content and validity received data may be classified either as valid or non-valid individual case safety report (ICSR).

Additionally, this data may fall under the category of information that is related to drugs safety and efficacy but is not a report (the so-called non-ICSR):

- "important safety information, which may reflect changes in drugs risk-benefit profile"[2];
- "other safety information that may impact risk-benefit assessment for investigational drug or may be used as a basis for updating its indications for use or serve as a ground for reviewing perspectives of further trial conduct" [3].



REPORT

According to information source reports are divided into unsolicited (spontaneous) and solicited [2].

Unsolicited (spontaneous) report	Solicited report
Received without request (does not derive from trials or investigations) [2].	Received as a result of targeted data collection (investigation) [2].

- All reports are considered a priori to have causal relationship with the drug and therefore represent **adverse reaction**

  ! EXCEPTION: in case reporter specifically mentioned that the event does not have causal relationship with the drug, the report is considered to be **an adverse event.**

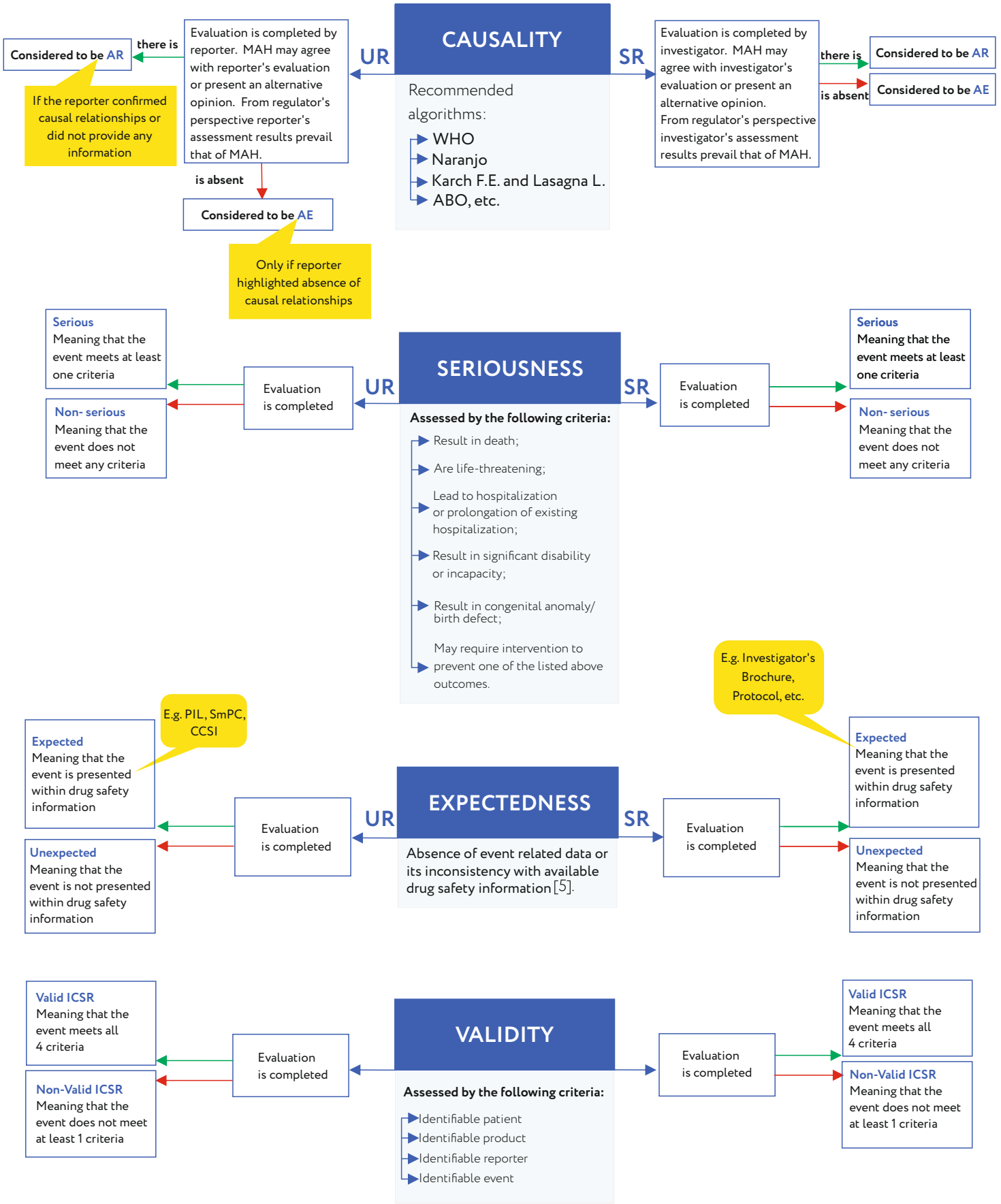
- In most cases reporters highlight causality between drug and event. If the relationship was not initially described, until it is confirmed, it is considered that causal relationship exists.

INFORMATION SOURCES

- **Patients and consumers (regardless of medical confirmation)**
- **Healthcare professionals**
- **Regulatory authorities (Federal and Regional centers)**
- **Specialized and non-professional literature**
- **Results of spontaneous healthcare professionals interview by MAH representatives (not within the context of any study)**
- **Responses to "Address to healthcare professionals"**
- **Law suits against drug classes**
- **Internet and other media sources (e.g. television, radio, etc.)**
- **Pre- (phases I-III) and post-marketing non-interventional and interventional studies and trials**
- **Registries**
- **Personalized programs for non-registered drug administration**
- **Collection of information related to safety and patients' adherence**
- **Results of patients and healthcare professionals interview conducted as a part of study**
- **Other programs for administration of non-registered drugs due to exceptional circumstances for compassion and disease monitoring reasons**

To evaluate if the case is the subject for express reporting to regulatory authorities, it is evaluated by the following parameters:

SR - Solicited report
UR - Unsolicited (spontaneous) report



In case event is classified as non-valid ICSR all possible efforts should be made to obtain missing information.

As per current legislation, following cases are subject to expedited reporting:

DEADLINES FOR SUBMISSION	SUBJECT OF REPORTING	
	UNSOLICITED (SPONTANEOUS) REPORT (VALID)	SOLICITED REPORTS
7 calendar days	---	Life-threatening serious unexpected adverse reactions or those resulting in death
15 calendar days	Serious AR identified on territory of countries-EAEU members Unexpected AR identified on territory of outside EAEU countries	Other serious unexpected adverse reactions

INDIVIDUAL CASE SAFETY REPORTS

Individual case safety reports (ICSR) undermine not only certain report content, but specific format of submission as well. Most frequently the information included in the report may be transferred via at least two forms.

The first form is exploited by MAH to receive information from reports (such form is developed by each company separately – in frames of certain studies for solicited report and within pharmacovigilance system in general for spontaneous reports). Regardless of its application sphere, such forms must be straightforward, minimalistic, comprehensive and available in electronic and paper-based forms. The second form type is utilized by MAH to submit reports to regulatory authorities. In this situation form for submitting spontaneous reports to Russian regulatory authorities is defined by routes of submission – either via Automated Information System (AIS) or via e-mail (pharm@roszdravNadzor.ru). Each of them has specific features:

AIS	ROSZDRAVNADZOR E-MAIL
• Allows to enter data in predefined form.	• Allows to submit information in initially received format (including CIOMS or internal MAH reporting forms)
• Supports information exchange in .xml form per ICH E2B standard	• Enables forwarding information in fuller volume
• Form does not always enable submission of source information in initial volume	• When submitting cases initially provided in foreign language, the translation to Russian should be provided as well

In case of solicited reports forms for submission to regulatory authorities serious unexpected AR are recommended to be submitted via “Report on serious unexpected AR to investigational drug” form provided in Appendix 2 of 1071 Order.

«OTHER» OR «IMPORTANT» SAFETY INFORMATION

Apart from ICSR terms like "other safety information" or "important safety information" are mentioned in everyday pharmacovigilance related communication. This data most frequently may not be classified per described above parameters but affects drugs benefit-risk ratio. These terms do not have exact definition within Russian legislation, however are actively used among drug market participants.

Good pharmacovigilance and Good clinical practices contain only comprehensive list of certain pieces of information that require expedite submission without comments regarding other data types. Decision to collet "other" or "important" information which is not provided in the mentioned list should be based on possibility to include it in periodic reports. Additionally, while planning activities towards such information drug features as well as marketing strategy should also be considered. For example, if it is planned to update PIL after registration with information about drug administration in pregnant and lactating women, data collection during all drug lifecycle stages should be organized in such a manner that this information won't get lost.

"Other" and "important" information is submitted mainly via e-mail in initially received form, as AIS does not allow entering such data.

Timelines for expedite reporting to regulatory authorities of any information regardless of its source and requiring such submission is 15 calendar days.

CONCLUSION

- Given classification branching for the safety data, it is necessary for each MAH to determine, verify and confirm the exchange strategy for this information in advance and reflect this process in pharmacovigilance system master file as well as in the safety management plan for individual clinical trials.

- Key role in the successful implementation of the message processing scheme is played by a person who directly process information received (qualified for pharmacovigilance person, medical monitor, drug safety physician, etc.). Therefore, special attention should be paid to the issue of appropriate training for employees holding this position, or their functions full or partial outsourcing.