GOOD PHARMACOVIGILANCE PRACTICES (GVP) GUIDE: MODULE VII – SIGNAL MANAGEMENT

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Abbreviations: AEA: European Economic Area BGYSŞ: Bayesian Confidence Propagating Neural Network (BCPNN) BTO: Designated Medical Event (DME) BOGR: Individual Case Safety Report BÖ: Information Component (IC) HTO: Targeted Medical Event (TME) KÜB: Summary of Product Characteristics KT: Patient Information Leaflet MedDRA: Standardised medical terminology developed by the ICH (the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) for international exchange of information on medicinal products MedDRA MSSO: MedDRA Maintenance and Support Services Organization ORS: Signals of Disproportionate Reporting (SDR) ORO: Proportional Reporting Ratio (PRR) ÖTO: Important Medical Events (IME) PT: Preferred Term PYRDR: Periodic Benefit/Risk Evaluation Report RYP: Risk Management Plan

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PART I — Introduction

1.1. Introduction The purpose of this Module is to provide general advice on the structures and processes involved in signal management. In this context, signals emerging from the monitoring of data obtained from spontaneous reporting systems will be considered as the starting point of the signal management process. The same principles will also apply to data obtained from other sources. In order to better understand the signal management process, the three key elements below should be taken into consideration: 1. The starting point of signal detection is the existence of a certain degree of uncertainty, and sound judgement is always required. The likelihood of a signal may exist at different levels depending on the adequacy and strength of the data at hand. Evidence may be found in different sources, may be of varying strength, and may accumulate over time. 2. A signal is a hypothesis. It does not demonstrate a definitive causal relationship in all cases. For example, at the European Medicines Agency (EMA), 2372 potential signals were evaluated in 2015, of which only 61 were confirmed. 3. Not all signals constitute a risk, and additional regulatory action (e.g., updating the Summary of Product Characteristics (SmPC)) may not be necessary for all signals after the required reviews have been conducted. This Module will also outline the methods used in signal analysis in general terms in order to serve as guidance for marketing authorisation holders.

1.1.1. Terminology Signal Information arising from one or more multiple sources, including observations and experiments, suggesting a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action [Regulation on the Safety of Medicinal Products, Article 4(1)s]. Aspects of a known association that indicate a new dimension include changes in the frequency, duration, severity, or outcome of the adverse event. A signal usually applies to all medicinal products containing the same active substance, including combination products. Certain signals may be specific to a single medicinal product only, while some may apply to a specific indication, population, pharmaceutical form, or route of administration. Some signals may apply to all medicinal products of the same class.

Signal management process A set of activities performed to determine, based on individual case safety reports (ICSRs), aggregated data obtained from active surveillance systems or studies, literature information, and other data sources, whether there are new risks associated with the active substance or medicinal product, or whether known risks have changed, and at the same time to make recommendations, take decisions, communicate, and follow up on the risks in question. The signal management process comprises all of the following stages, from the detection of a signal to recommendations for action:

Detection of a signal Validation of a signal Confirmation of a signal Signal analysis and prioritisation

Evaluation of the signal Action recommendations

Signal detection The action of searching for and/or detecting signals using data obtained from any source.

Signal validation The process of evaluating data supporting a detected signal in order to verify that the available documentation contains sufficient evidence demonstrating a new possible causal relationship or a new aspect of a known relationship, and that the signal therefore justifies more detailed investigation. In this process, the strength of the evidence, the clinical importance, and whether there was prior awareness of the relationship should be taken into account (see 2.3.).

Signal confirmation Refers to the review and discussion of the validated signal by the competent authority. In the European Economic Area (EEA), this procedure is carried out by the EMA.

Emerging safety issue A safety alert regarding the medicinal products for which the marketing authorisation holder holds a licence, which the marketing authorisation holder considers to require urgent regulatory action and communication with healthcare professionals and patients due to its potential major impact on the benefit/risk balance of the medicinal product

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and/or on public health, and which must be promptly brought to the attention of the competent authority.

SECTION II Structures and Processes

2.1. Data and Information Sources The data sources that enable the identification of new signals are diverse. These sources encompass all scientific data relating to the use of medicinal products and the outcome of that use (e.g. quality data, non-clinical data, clinical data including pharmacovigilance and pharmacoepidemiological data). The sources commonly used in signal detection are the following: - Spontaneous reporting systems, - Active surveillance systems, - Studies including systematic reviews and meta-analyses, - Scientific literature. Signals can be obtained from spontaneous reports through: - Monitoring of ICSRs, suspected adverse reaction databases, and scientific articles, - Information obtained from marketing authorisation holders in the framework of regulatory procedures (e.g. post-authorisation commitments, variations, renewal of the marketing authorisation validity period, periodic benefit/risk evaluation reports (PBRER), Risk Management Plan (RMP) updates), - Other activities relating to the monitoring of the ongoing benefit/risk balance of medicinal products. Signal analysis is performed periodically in large databases such as the European Union Adverse Reaction Database (EudraVigilance), the US FDA Adverse Event Reporting System (FAERS), or the WHO Collaborating Centre for International Drug Monitoring database (VigiBase).

Figure 1. Information sources in the signal management steps

2.2. Signal Detection Signal detection should be based on a multidisciplinary approach. An appropriate methodology, varying according to the nature of the data and the type of medicinal product concerned, should be followed. Vaccines, orphan medicinal products, and medicinal products used in children are products that require special methodological strategies. Depending on the size of the data set, signal detection may include the review of ICSRs, statistical analyses, or a combination of both. Where the assessment of each individual case is not possible (e.g. signals detected from published studies or healthcare records data), aggregate data should be considered.

2.3. Evaluation of Evidence Supporting a Signal When evaluating the evidence supporting a detected signal, the following factors should be taken into account: - The strength of the evidence obtained from ICSRs o The total number of cases after removal of duplicate cases, the number of supporting cases among them, e.g. compatible temporal relationship, positive dechallenge or positive rechallenge, the absence of plausible alternative causes, assessment of the causal relationship as possible by the reporting healthcare professional, supportive findings from similar/related studies, o Additional cases reported with related terms (e.g. other MedDRA terms indicating different stages or clinical complications of the same reaction), o The consistency of the evidence across cases (e.g. repeated observation of the relationship), o The quality of the data and documentation, o Where applicable, the existence of cases meeting internationally accepted case definitions, o The plausibility of a possible mechanism of biological and pharmacological relationship, o The number of cases in the context of patient exposure, o If applicable, measures of disproportionality. - Clinical importance, e.g.: o The seriousness and severity of the reaction, o Reactions occurring in the context of drug-drug interactions, o Reactions occurring in susceptible populations (e.g. pregnant women, children or the elderly, or patients with underlying risk factors), o Reactions occurring with different patterns of use (e.g. overdose, misuse of the medicinal product, off-label use, medication errors), o Whether the signal provides additional understanding of the expected reaction, for example in terms of severity, outcome, incidence, or management. - Previous awareness, for example: o The extent to which the information is included in the product information (e.g. SmPC, PL or packaging information), o Whether the reaction is included in the SmPCs of other medicinal products containing the same active substance (some signals may be specific to a particular medicinal product only), o Whether the relationship has been evaluated in the initial application for marketing authorisation, the RMP, the PBRER, or any other regulatory procedure. Example: It is not always easy to check whether the adverse event is included in section 4.8 of the SmPC. - The event may have been expressed with a similar but different PT (e.g.

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anaphylactic shock, anaphylaxis; vertigo, dizziness; swelling of the tongue may appear as angioedema). - The event may be included in the SmPC, but the signal may provide new information (e.g. anatomical features, severity, or duration). - The term included in the SmPC may not reflect the event (e.g. rash includes morbilliform rash, but does not include Stevens-Johnson syndrome; the inclusion of liver damage in the SmPC does not indicate that it also covers fulminant hepatitis). - Additional information sources may provide further evidence regarding the relationship between the medicinal product and the adverse reaction. E.g.: o Clinical trial data, o Findings on similar cases, including information on active substances of medicinal products of the same class in the scientific literature, o Experimental or non-clinical findings, o Databases containing broader data sets where the signal has been obtained from a national or company-based database, o Healthcare databases providing information on the characteristics of exposed patients and patterns of medicinal product use, o Information obtained from other regulatory authorities. The evaluation of the evidence supporting a signal may require discussions by expert groups and decision-making at various levels. As a result, various decisions may be taken: - Closure of the signal: The signal is closed if the available data do not support a causal relationship between the medicinal product and the adverse reaction, or if sufficient information on the relationship is available in the product information. The signal may be reopened at a later stage should new evidence emerge. - Monitoring of the signal: Whether new data support the causal relationship

new information from ICSRs or from the scientific literature shall be reviewed at appropriate intervals in order to monitor the signal. Recommendation of action: Where there is sufficient evidence of a causal relationship, actions such as varying the product information to modify it are recommended.

2.4. Prioritisation of Signals The fundamental and continuously maintained consideration in the signal management process is to promptly identify signals that may have a significant impact on public and/or patient health and/or on the benefit/risk balance of the medicinal product. When assessing this impact, the following aspects should be examined: the severity, seriousness, outcome and reversibility of the adverse reaction, and the possibility of its prevention, patient exposure and the expected frequency of the adverse reaction, where appropriate, exposure of patients in a susceptible population and/or in populations with different patterns of use, the consequences of discontinuing treatment and the availability of other therapeutic options, the expected magnitude of regulatory intervention (e.g. additions to contraindications, warnings, adverse reactions, the introduction of additional risk minimisation measures, or the suspension or withdrawal of the marketing authorisation of the medicinal product), whether the signal may also apply to other medicinal products of the same class.

Special attention should be paid to signals that cause problems in large populations, such as adverse events occurring after intensive vaccination programmes. How the signal will subsequently be managed, including timelines, depends on the prioritisation. Since prioritisation is a continuous process, appropriate measures should be taken at each step where information exists requiring the timely prevention or minimisation of a risk. Such measures may also be needed before the formal assessment of the signal has concluded. Professional judgement and flexibility should be applied throughout the process.

2.5. Quality Requirements Signal management is a critical process. The signal management system should be clearly documented to ensure that system functions operate appropriately and effectively; that roles, responsibilities and tasks are standardised; that these tasks are carried out by individuals with the relevant expertise and clearly explained to all parties involved; and, where deemed necessary, that the system is further developed and appropriate control is ensured. This also includes the justification of the methodology and frequency of repetition of signal review activities. Therefore, a quality assurance and quality control system consistent with quality system standards should be in place and applied to the entire signal management process (see Module IV). Detailed procedures for the quality system should be developed, documented and

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implemented. The performance of the system should be checked and, where used, performance indicators should be presented in the pharmacovigilance system master file. For continuity of documentation, organisational duties and responsibilities for the activities, including quality control and review and verification and preventive action, must be assigned and recorded. As a critical process, signal management activities, including processes carried out by service providers and contracted pharmacovigilance service providers, should be audited at regular intervals. The accuracy of data and documents, including their confidentiality, security and integrity during transfer between organisations, must be ensured.

With a tracking system, all parties should maintain a record (audit trail) of signal management activities, including how signals were detected, validated, confirmed and assessed, together with the associated queries and outcomes. The audit trail will allow retrospective traceability of how signals were detected and how validated and confirmed signals were assessed. The Agency may request, before and after authorisation, that marketing authorisation holders submit documentation containing the rationale/evidence for the processes carried out and decisions taken, for review, in order to demonstrate their compliance with the requirements concerned. Relevant personnel should receive specific training on signal management activities in accordance with their assigned roles and responsibilities. The training system and the location details of training records should be documented, and staff curricula vitae and job descriptions should be archived.

MODULE III Methods for Signal Analysis

3.1. Methods Used in Signal Detection 3.1.1. Traditional Methods In spontaneous reporting systems, signal detection is carried out in two ways: qualitative and quantitative. From a historical perspective, a general classification can be made into traditional and advanced quantitative, statistical or automated signal detection methods. Traditional methods include both qualitative approaches (e.g. review of individual cases or case series) and simple quantitative approaches (e.g. frequency/reporting rate, grouping, cross-tabulation, etc.). The renaissance that has occurred in statistical approaches, together with the increase in the number of spontaneous reports and the growth in the size of databases, has created a need for the development of more complex quantitative methods. In quantitative signal detection, the analysis should be performed at the MedDRA (Medical Dictionary for Regulatory Activities) "preferred term (PT)" level.

3.1.1.1. Review of cases and case series One of the most commonly used techniques in traditional pharmacovigilance is the "index case" or "striking case" method. The trained pharmacovigilance professional usually detects the signal upon the first review conducted when ICSRs (spontaneous adverse reaction reports, systematic data collection systems or cases published in the literature) arrive, or during the routine review of incoming data. While the identification of a single, unusually striking and well-documented ICSR may occasionally be interpreted as a signal, in practice strong suspicions about possible drug-event relationships are most often based on series of cases with similar characteristics (clustering). In addition, the elimination of positive challenge/de-rechallenge is also among the important criteria used in defining a signal. Undoubtedly, such reviews are subjective. For this reason, the reviewing expert must possess sufficient knowledge of the pharmacology of the medicinal product, the indications for its use, and the patient population exposed to it. One of the key steps in the review of case reports is the "designated medical events" (DMEs). DMEs are adverse events that are rare, serious and carry a high risk of being attributable to the medicinal product. For events of this type, one to three reports may be considered a potential signal. Typical examples include aplastic anaemia, toxic epidermal necrolysis, Stevens-Johnson syndrome, Torsade de pointes and hepatic failure. However, the definition is not absolute, and there are also events that should be considered DMEs even though they do not meet the above criteria. E.g. Pancreatitis (in most adults, the risk is attributable to alcohol use and gallbladder disease). This

therefore, any event decided to require special interest may also be defined as an MTI. There is no universally accepted correct list of MTIs. This list may always be subject to changes.

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Each organization has its own specific list. The EMA list dated 17 August 2016 is provided in Annex 2.

Special interest areas associated with a particular drug and/or patient population, concerning other events, are termed "targeted medical events" (TMEs). These events are similar to MTIs, but their classification depends on the drug. In this case, pharmacovigilance logic and scientific knowledge about the drug, the therapeutic indication, and/or the patient populations facilitate making predictions about potential problems that may arise.

A selected group of events considered serious is also termed important medical events (IMEs). This list has been developed by the organization that maintains MedDRA (MedDRA MSSO) and is coordinated by the EMA.

Special attention may need to be paid to other clinical features. For example, hyperacute (needle-tip) events require careful evaluation. These are events that, while the condition is otherwise stable, emerge within an extremely short time during parenteral administration of the drug and are biologically plausible. The clinical features of the event indicate that the drug at least contributed to its occurrence. E.g., kidney stones or gallstones composed of pure drug...

In signal detection, in addition to MTI and TME classification, other criteria exist that are part of the clinical triage of cases. For example; if a hypothetical drug is known to cause moderate respiratory depression, but the incoming reports are in the form of apnea/respiratory arrest, a biological justification must be made for this event, which is defined but occurs more severely.

For the safety of newly authorized drugs, the preparation and analysis of periodic assessments is a very important traditional signal detection method in pharmacovigilance. PSURs may be given as an example of reports made by collecting such data periodically. Such reports also allow a comprehensive look at the data over a specific period of time.

In the examination of individual reports and case series, the scientific review and experience of experts are of utmost importance.

3.1.1.2. Simple Analysis of Larger Data Sets For an adverse event or a group of adverse events, if the observed value is greater than the expected value for any of the following situations, this indicates that a signal has been detected: - The number of a specific adverse event (absolute number) - The number of a specific adverse event / the total number of reports related to the drug (ratio), or; - The number of a specific adverse event / the estimated exposure to the drug (rate).

The ICH E2E Pharmacovigilance Planning Guideline lists post-marketing pharmacovigilance data collection methods. Among these are passive surveillance (spontaneous reports, case series), active surveillance (Prescription Event Monitoring, Registries, etc.), comparative observational studies (case-control studies, cross-sectional studies, cohort studies), targeted clinical investigations (genetic testing, studies to be conducted in special populations, large simple trial), and descriptive studies (natural history of disease, drug utilization study).

In cases where the data collection method is passive surveillance, i.e., spontaneous reports are routinely collected (e.g., MedWatch in the USA, the Yellow Card System in the United Kingdom, EudraVigilance in the European Economic Area), or where certain types of reports are collected in a targeted manner and during extended follow-up (such as the Varicella Vaccine Pregnancy Registry), noteworthy reports with positive rechallenge involving MTIs or TMEs, cumulative reports in which spontaneous reports are periodically reviewed, automatic scanning of the adverse event database, or data mining methods may be used in signal detection.

In cases where the data collection method is active surveillance (such as Prescription Event Monitoring), signal searching is performed using more advanced methods.

Disproportionate reporting signals require careful, detailed case and literature review, including preclinical and pharmacological data, and the assessment of pharmacoepidemiological and/or clinical studies.

3.1.2. More Complex Quantitative Methods Quantitative methods have been developed to detect signals in large spontaneous reporting system databases. These methods allow systematic, automated, and practical scanning of data that cannot be easily scanned by conventional means,

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while also minimizing human error.

Advanced quantitative methods include computer-assisted statistical methodologies and data mining algorithms. These methods are based on disproportionality analysis relying on 2x2 contingency tables.

3.1.2.1. Disproportionality Analyses Disproportionality analysis (DA) refers to the scanning of ADR databases to detect reporting rates higher than expected, and its main purpose is to identify statistically significant reporting relationships between drug-event pairs contained in the spontaneous reporting system.

A disproportionate reporting signal (DRS) refers to the numerical outputs of these analyses made without clinical context, and is used instead of the term signal in statistical calculations.

The key feature of data mining algorithms supporting disproportionality analysis is to summarize very complex safety data sets into a 2x2 contingency table for each drug-event pair. The statistical 2x2 table is widely used in drug safety and forms the basis of the calculations to be made for measuring association.

For drug-adverse reaction pairs, as common measures of disproportionality: - Proportional reporting ratio, - Reporting odds ratio, - Information component, - Empirical Geometric Mean are used.

There are also disproportionality measures for drug-drug-adverse reaction triplets. One of these is Omega (Ω), which is used by the WHO Collaborating Centre for Drug Monitoring.

3.1.2.1.1. Proportional Reporting Ratio (PRR) The reporting disproportionality measure used to obtain DRSs in pharmacovigilance databases is the PRR. It shows how common an adverse event is relative to all events in the database for a particular drug. In this method, if a DRS (containing a specific adverse event) has been identified for a drug (P), an assumption is made that this adverse event is reported relatively more frequently for drug (P) compared to other drugs. The relative increase in the adverse events reported for drug P is expressed, as in the table below, based on the total number of individual cases contained in the pharmacovigilance database in a 2x2 contingency table:

Table 1: 2x2 contingency table used for the calculation of the ROR Event (E) All other events Total Drug (P) A B A+B All other drugs C D C+D Total A+C B+D N=A+B+C+D

The elements in this table are the individual cases contained in the database. The basic criteria in the calculation of the ROR are as follows: The value A is the number of individual cases in which the adverse event E was observed in association with drug P, The value B is the number of individual cases in which all adverse events other than E were observed in association with P, The value C is the number of individual cases in which event E was observed in association with all drugs other than P The value D is the number of individual cases in which events other than E were observed in association with all drugs other than P.

The ROR is calculated as follows:

ROR = A/(A+B) C/(C+D)

Example 1: - Among all reports associated with drug P, the proportion of individual nausea cases is 5% (5 out of a total of 100 reports for drug P are nausea cases. A=5, B=95, A+B=100). - The proportion of nausea reports among all reports associated with all other drugs in the database (other than drug P) is also equal to 5% (e.g., among 100,000 reports associated with all other drugs there are 5,000 nausea cases; similarly, in this case C=5,000, D=95,000, C+D=100,000). In this example, the ROR is equal to 1 (e.g., 0.05/0.05).

Example 2: - Among all reports associated with drug P, the proportion of individual nausea cases is 15% (15 out of a total of 100 reports for drug P are nausea cases. A=15, B=85, A+B=100). - The proportion of nausea reports among all reports associated with all other drugs in the database (other than drug P) is also equal to 5% (e.g., among 100,000 reports associated with all other drugs there are 5,000 nausea cases; similarly, in this case C=5,000, D=95,000, C+D=100,000). In this example, the ROR is equal to 3 (e.g., 0.15/0.05).

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3.1.2.1.1.1. 95% confidence interval of the ROR The data analysis system to be established must also calculate the confidence interval of the ROR. The standard error of the natural logarithm of the ROR is calculated according to the following formula:

?????????????= √(1 A + 1 C − 1 A+B − 1 C+D)

The 95% confidence interval for ln(ROR) is calculated as ln(ROR)-/+1.96SE. Taking the exponential, the following result is obtained:

95% confidence interval for ROR = (ROR / exp(1.96SE), ROR x exp(1.96SE))

3.1.2.1.1.2. Interpretation of safety signals Disproportionality analysis is not an inferential exercise. The use of inferential statistical methods in such exploratory analyses can lead to major problems. If statistical analyses of the database are carried out in an undisciplined manner, it is possible for subjective decisions to arise in the selection, distribution and interpretation of data mining processes and their outputs. The results of quantitative methods should be interpreted with care and the limitations of the spontaneous reporting system database should be taken into account. When interpreting ROR results in analyses performed for signal detection purposes, the following points should be considered: a) The ROR measures the reporting relationship between drug P and adverse event E on the basis of the relative increase in the rate of individual cases associated with the adverse event. It does not indicate any causal relationship between the administration of drug P and the occurrence of adverse event E. Such statistical disproportionality may reflect one or more biases (e.g., bias due to the patient's underlying disease), artefacts naturally present in the pharmacovigilance system, and also statistical noise. For this reason, safety signals identified by quantitative methods must necessarily be medically evaluated. b) When making the initial decision as to whether further analysis of a drug-event pair is necessary, the threshold value of the applied ROR and other statistical estimates (e.g., the estimated lower limit of the confidence interval) is examined. There is no threshold value accepted as the gold standard for safety signals. c) The threshold values commonly used to detect safety signals represent a choice between two conflicting options: if the threshold value is too low, false positive signals may be generated, or if the threshold value is too high, true signals may be missed. d) The ROR also allows comparison of the reporting relationship for drug P with that for all other drugs in the database. The ROR value and, consequently, the safety signals identified by this method depend on the data in the database from which the ROR was calculated. Therefore, the interpretation of the ROR should be made taking into account the following elements: I. The type of drugs contained in the database II. The medical terminology used in the reports constituting the database III. Coding IV. The date on which the database was created V. The source of the ICSRs (e.g., all unsolicited reports)

These elements may affect the ROR value and may create a masking effect. Conversely, they may lead to an overestimation of the significance of the statistical relationship between the drug and the adverse event. e) In addition to the quantitative aspect, it is important to also consider other elements in the selection and prioritisation of safety signals identified in the database: I. The potential impact of safety signals on public health II. Licensing conditions and, in particular, whether the adverse event is expected/unexpected (in particular whether or not there is evidence of a change in reporting frequency or in the severity of the known adverse drug reaction) III. Whether the potential risk associated with the safety signal has previously been or is currently being confirmed

These should be assessed independently of whether the ROR exceeds a previously defined threshold value.

f) The absence of an ROR does not imply the exclusion of the possibility of a relationship between drug P and adverse event E. g) The ROR can be refined using techniques similar to those used for other RORs (e.g., combining a large number of drugs and/or adverse events, stratifying by patient age and sex). When analyzing RORs on the basis of the PRR, the possibility that the drug–adverse event relationship is masked by other drugs should be kept in mind.

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3.1.2.1.1.3. Threshold values identifying RORs in the EudraVigilance database At present, there is no gold standard for establishing a universal threshold value for a signal of disproportionate reporting. The threshold values used in EudraVigilance are empirical. The PRR is a highly sensitive method that may lead to the emergence of a large number of false positive signals, particularly when the number of reports is low. For this reason, in association with the PRR, a case count threshold value (number of reports ≥ 3) and the chi-square statistic are used to reduce the number of false positive results. The following criteria are used in the query performed to identify the ROR (drug–event combination) in the EudraVigilance Data Analysis System.

a) When the PRR is expressed with a 95% confidence interval: - The lower limit of the 95% confidence interval is equal to or greater than one - The number of individual cases is equal to or greater than three These criteria are used in weekly/monthly signal monitoring. The chi-square statistic is also used in association with the PRR. In such cases, the following criteria are used in the query: b) When the PRR is expressed with the $\chi 2$ statistic: - PRR ≥ 2 - $\chi 2 \geq 4$ - The number of individual cases is three or more.

3.1.2.1.1.4. Subgroup analyses and stratification Stratification is a statistical process that aims to reduce confounding effects by making adjustments according to the relationship between the drug and a confounding variable, and between the event and the same confounding variable. The calculations of the PRR can be performed on the entire database as well as on a subset of the reports. Restriction of the field can be done using many variables such as age and sex. The calculation of the unadjusted PRR can be adjusted by stratification according to age, sex, or date of reporting. It is also possible to conduct subgroup analyses on the basis of the drug or the drug class.

3.1.2.1.1.5. Validation The large number of methodological issues makes it difficult to systematically and comprehensively evaluate the performance of quantitative methods used in signal detection. The absence of a gold standard to be used in signal detection makes this evaluation difficult. The following conclusions can be drawn from validation studies: a) The high sensitivity calculated in these studies is based on a simple definition of the signal (e.g., a drug–event pair). This definition of the signal may not reflect the true causal relationship between the drug–event pair in the context of clinical assessment in pharmacovigilance. b) The low specificity of the statistical methods emphasized in the aforementioned validation studies is an indication that a large number of false positive signals may arise.

3.1.2.1.2. Information Component The Information Component, introduced through the Bayesian Confidence Propagation Neural Network (BCPNN) Method developed by the WHO Programme for International Drug Monitoring to detect signals from adverse drug reactions contained in VigiBase, is a measure of the disproportionality between the observed and expected reporting of a drug–adverse reaction pair. A positive IC value indicates that a particular drug–adverse reaction combination is reported more frequently than expected relative to the remaining reports in the database. An IC value of 0 indicates that there is no quantitative dependence, whereas a negative IC value indicates that the combination occurs less frequently than statistically expected in the database. The IC value is calculated on the basis of the following information: - The total number of case reports related to drug X (Cx) - The total number of case reports related to adverse reaction term Y (Cy) - The total number of reports related to a particular drug–reaction pair (Cxy) - The total number of reports in the database (C) New reports may cause the IC value to increase or decrease. If the IC value is calculated from large figures, a new report cannot lead to a large fluctuation in the IC value. The standard deviation of each IC value is a measure of the robustness of the value. The higher the values of Cx, Cy and Cxy, the narrower the confidence interval. The lower limit value of the 95% confidence interval for the IC value is the IC025. The IC value does not provide information about the qualitative causality of the drug–adverse reaction combination. The IC indicates the quantitative dependence between the adverse reaction and the drug based on the reports in VigiBase. If the IC value increases over time and the IC025 value is positive, the likelihood of a positive quantitative relationship between the

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drug and the adverse reaction is high, but clinical assessment is still mandatory. As of 30 September 2016, the database of the WHO Collaborating Centre (UMC) (VigiBase) contained 14 million ICSRs. The data contained in VigiBase are periodically analyzed within the scope of the UMC's routine signal search process, and previously unidentified adverse drug reactions are detected. After drug–adverse reaction combinations are automatically identified, clinical assessment is performed. By means of the triage ranking method, using the measure of disproportionality (IC) between the observed and expected reporting of drug–adverse reaction combinations and other statistics, the number of drug–adverse reaction combinations is reduced, thereby increasing the likelihood of finding the most important signal. The predictive capability of the UMC's data mining method has been investigated; the positive predictive value is 44% and the negative predictive value is 85%. In the signal detection process, in order to identify the signal, the following procedure is followed for the drug–adverse reaction combination: 1. Relative reporting rates are calculated for all drug–adverse reaction combinations reported to VigiBase. The IC value indicates that the drug–adverse reaction combination is reported more frequently than expected relative to the history of the database. 2. For the more frequently reported drug–adverse reaction combination, the triage algorithm selects combinations containing ICSRs originating from at least two countries, and these combinations must meet at least one of the following criteria: a. New drug and serious reaction (the drug having entered the database within the last five years and the adverse reaction being one of the critical terms of WHO-ART (the WHO adverse reaction terminology)) b. The IC value having risen significantly since the previous quarter 3. The drug–adverse reaction combinations screened by the triage algorithm are then reviewed by UMC staff to determine whether they are included in the Summary of Product Characteristics of the drug or in the literature

checked for the reaction. If the reaction cannot be found or is not sufficiently well defined, individual case reports are obtained from VigiBase. 4. ICSRs are evaluated by UMC staff or members of the UMC signal review panel. Consequently, signal detection is carried out through a combination of data mining methods and expert clinical assessment.

Clinical evaluation of the potential signal by experts: - Quantitative strength of the association o Number of ICSRs o Statistical disproportionality - Consistency of the data (pattern) - Exposure–response relationship o Region, timing, dose, reversibility - Biological plausibility of the hypothesis o Pharmacological, pathological - Experimental findings o e.g., dechallenge, rechallenge, blood levels, metabolites, drug-dependent antibodies - Nature and quality of the data o Unbiasedness, documentation, causality assessment

During the evaluation, further detail of the reports is also requested from National Centres.

3.1.3. Integration of Statistical Methods with Classical Methods The quantitative methods used in signal detection in pharmacovigilance should be used in conjunction with other traditional methods. Traditional methods may enable the detection of safety signals that cannot be detected by data mining methods. If a medicinal product has recently been placed on the market and only a limited number of ICSRs have been received, it is more reasonable to assess those ICSRs individually rather than on the basis of a statistical method. One reason for this is that the reliability of statistical screening is more limited for small numbers of ICSRs. Moreover, in the early period following the marketing of a medicinal product, knowledge about its safety profile is essentially based on clinical experience. Therefore, the screening of individual cases adds further value to the monitoring process. The regular and systematic evaluation of all new ICSRs still remains one of the fundamental mainstays of pharmacovigilance. Statistical methods allow the prioritisation of ICSRs and the consideration of additional factors. For example, the PRR method does not routinely examine concomitant drug–event pairs for drug–drug interactions. These must be subjected to assessment by experts examining this situation. Knowledge about the nature of the data is also of vital importance, because the indications of the same medicinal product may differ between countries.

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3.1.3.1. Systematic Evaluation of Observed-to-Expected Ratios The critical point in the integration of the classical methods used in signal detection in pharmacovigilance with statistical methods is the systematic evaluation of observed-to-expected ratios. There is a scientific consensus that disproportionality reporting signals identified by statistical methods should be considered together with medical judgement. Signals of Disproportionate Reporting (SDRs) requiring further evaluation should be systematically subjected to medical review.

The review process for SDRs should include the following steps: - Identifying possible duplications: - Checking the quality of the data: Reviewing information such as whether the information provided is complete and the accuracy of the codes - Providing additional information where possible: If the information obtained is insufficient for the assessment of the case, requesting new information - Checking the licensing conditions: Reviewing the SmPC and Package Leaflet of the medicinal product to obtain further information (e.g., whether the adverse event was expected, possible drug–drug interactions) - Checking relevant additional information: In the evaluation of observed-to-expected ratios, support may be drawn from the dossier, PSUR, Suspected Unexpected Serious Adverse Reactions (SUSARs), PASS, post-marketing commitments and post-marketing studies.

3.1.3.2. Special Considerations in the Use of Quantitative Methods for Vaccines and Medicinal Products Used in Children There are specific requirements for analyses to be conducted for vaccines and medicinal products used in children. The detection of new signals concerning such products or this population should be evaluated separately with appropriate scientific expertise.

PART IV — Tasks and Responsibilities

4.1. Tasks and Responsibilities of the Marketing Authorisation Holder with Regard to Signal Management Monitoring the safety of medicinal products throughout their time on the market is of vital importance. To this end, marketing authorisation holders must ensure that all sources of information are screened in order to detect any potential signal, that appropriate action is taken to respond to any new evidence affecting the benefit/risk balance of the medicinal product, and that the Agency, healthcare professionals and patients are informed of any change in the benefit/risk balance. There are numerous methods that can be used for signal detection. The method to be used should be selected based on the product portfolio and the number of suspected adverse reaction reports. However, all marketing authorisation holders must have systems and methods in place for systematic signal detection. All marketing authorisation holders should have formal written procedural documents, such as standard operating procedures, that define and describe the signal detection method they use. These documents should provide detailed information on the roles and responsibilities of all personnel involved in signal detection, the sources of information included in the analysis, and the methods used in signal detection. The pharmacovigilance system master file must also contain written procedures related to signal generation, detection and evaluation (see Module V). In addition, the marketing authorisation holder should also have written procedures regarding the actions to be taken based on the results of the signal detection activity. These procedures should also cover further analyses to be conducted after the identification of a potential signal. The marketing authorisation holder should adequately document the signal detection activities, including the decisions taken and outcomes during these activities. Procedures related to signal analysis should be arranged so as to include, as a minimum, the following: 1. An increase occurring in the frequency and severity of adverse reaction reports and in the mortality rate

if this occurs: How adverse drug reaction reports are to be managed is described in Module I. In the situations mentioned above, the marketing authorisation holder must immediately inform TÜFAM and, in view of the possibility that the situation arises from the quality of the medicinal product, must review which processes in the manufacture of the medicinal product have been changed, closely monitor the processes that have been changed, and carry out the necessary analyses and inform the Agency of the result. 2. Periodic signal detection in cumulative data:

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PSURs constitute an important part of the signal detection system in that they allow the review of all data from the reporting period. However, especially in cases where a report is required to be prepared once every three years, this interval may be too long for signal detection. Continuous monitoring of the safety of medicinal products is the duty of all marketing authorisation holders, irrespective of their product portfolio. Therefore, if the marketing authorisation holder analyses safety data only in the course of producing PSURs, it should bear in mind that this will be questioned during pharmacovigilance inspections. 3. Taking the necessary actions in line with the recommendations by following the signals published every month under the heading "Recommendations of the Pharmacovigilance Risk Assessment Committee on safety signals" on EMA's official website at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000375.jsp: a. If the recommendation requires an addition to the SmPC/PIL, the marketing authorisation holder of the reference medicinal product must submit a variation application to the Agency. b. If additional information has been requested from the marketing authorisation holder, the additional information must be submitted to the Agency at the same time as it is submitted to EMA, upon notifying the Agency of the matter. c. Other recommendations for which it is stated that no action is required at this stage, such as monitoring of PSURs or the conduct of routine pharmacovigilance, must also be taken into consideration. The documents evidencing this situation must be archived and submitted to the Agency immediately upon request. 4. Taking the necessary actions in line with the recommendations by following the signals published quarterly under the heading "Potential signals of serious risks/new safety information identified from the FDA Adverse Event Reporting System (FAERS)" on FDA's official website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/UCM082196 5. Monitoring the outcome of the assessments made in PSURs in EU procedures and taking the necessary actions: Taking the necessary actions by following the list published under the heading "Assessment reports of periodic safety update reports" on EMA's official website at http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/psusa_search.jsp&mid=WC0b01ac0580902b8d: a. If the regulatory outcome is "maintain", no action is required. b. If the regulatory outcome is "variation", the marketing authorisation holder of the reference medicinal product must submit a variation application to the Agency for the matter to be added to the SmPC/PIL. When informing the Agency regarding signal detection, an explanation must be provided of the actions planned and taken in EU procedures and of the actions contemplated to be taken in our country. After evaluating the signal in question, the Agency may decide on one or more of the following actions:

No action other than routine pharmacovigilance is required. Additional information must be submitted by the marketing authorisation holder within a specified time period. A RMP must be submitted or updated. A variation must be made to the marketing authorisation. Additional risk minimisation measures must be implemented. The marketing authorisation holder must sponsor a post-authorisation study in accordance with an agreed protocol and must submit the results of the study to the Agency. An urgent safety restriction must be applied. The marketing authorisation must be suspended. An inspection must be conducted to confirm whether the marketing authorisation holder complies with the pharmacovigilance requirements. The Agency may also decide to take any other appropriate action not listed above.

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ANNEXES

ANNEX 1 Signal Validation and Evaluation Checklist Signal validation Key sources: SmPC, PSUR, RMP, TİTCK website and other regulatory processes 1. Does the event appear in the SmPC of the medicinal product for the active substance? i. Review the SmPC of the medicinal product. For active substances with generics, first check the SmPC of the innovator medicinal product. Check sections 4.3, 4.4, 4.5, 4.6, 4.8 and 4.9 of the SmPC in relation to the adverse event. Check whether the adverse event appears in the SmPC using a similar term or a higher-level term. Check whether the adverse event appears in the SmPC of another medicinal product containing the same active substance. Check whether the adverse event appears in the SmPC of another medicinal product in the same class. In the case of an interaction, check whether there is information regarding the interaction in the SmPCs of the other medicinal products. 2. Does the adverse event represent a new dimension of a known association? Increase in incidence Change in duration or time to onset of the adverse reaction Change in severity Change in the pattern of occurrence (e.g., affecting a special population) Change in previously reported outcome (e.g., new fatal cases) 3. Has the association previously been described within regulatory processes? Check the PSUR of the medicinal product. Check the RMP of the medicinal product. Check the EMA and FDA websites. Check whether a variation application has been submitted in relation to the same safety alert.

Signal evaluation Key sources: ICSRs, national databases, literature, EudraVigilance database, WHO database 1. Review of the cases supporting the signal Number of cases supporting the association (after exclusion of duplicate cases and cases without an appropriate temporal relationship) Number of cases appropriately documented with sufficient information (e.g., suspect medicinal product, reported event, age and sex, indication, outcome, concomitantly used medicinal products) Consistency of evidence across cases (e.g., patterns) Route of administration and formulation of the medicinal product Clustering of reports, e.g., multiple reports may be submitted by the same reporter. Cases meeting the diagnostic criteria of the event 2. Strengths Biological and pharmacological plausibility (possible mechanism) Dose relationship Number of cases with a positive dechallenge

- Number of positive dechallenge cases - Low background incidence of the event - Time to onset 3. Clinical importance - Seriousness/severity of the event - Whether the event is reversible - Events affecting special populations (e.g., pregnant women, children, the elderly) or patients with underlying risk factors - Events occurring in different patterns of use (e.g., off-label use, misuse, overdose, medication errors) - Relationship applicable to other active substances in the same class - Potential for prevention 4. Other considerations - Possible class effect - Possible drug-drug interaction - Possible medication error - Possible quality defect - Possible off-label use - Possible dependence, abuse, misuse 5. Weaknesses - Poor data quality of case reports - High number of cases with confounding factors/alternative explanations - Signs of stimulated reporting (e.g., increased media attention) - Abnormal reporting pattern - Presence of other risk factors related to the event: underlying disease, co-morbidities, co-medications

Additional Sources of Information Important sources: Literature, other adverse reaction databases, clinical trial data, registries, drug utilisation data, studies 1. Additional data - National databases (e.g., signals identified in the literature) - Databases containing larger data sets such as EudraVigilance or VigiBase - Information on active substances in the same class - Literature findings on similar case reports, pharmacoepidemiological studies or studies on the possible mechanism of action - Clinical trials - Pre-clinical data 2. Information on exposure - Drug utilisation data obtained from the DSUR or national drug utilisation records (national exposure, patterns of use) - Health databases 3. Additional information - The RMP of the medicinal product (information on ongoing or planned studies that may provide evidence of causality) - Registries

ANNEX 2 List of Designated Medical Events

Acute hepatic failure Acute kidney injury Agranulocytosis Anaphylactic reaction Anaphylactic shock Anaphylactoid reaction Anaphylactoid shock Angioedema Aplasia pure red cell Aplastic anaemia Autoimmune haemolytic anaemia Autoimmune hepatitis Autoimmune pancreatitis

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Azotaemia Blindness Bone marrow failure Deafness Deafness neurosensory Deafness permanent Deafness transitory Dermatitis exfoliative Dermatitis exfoliative generalised Drug reaction with eosinophilia and systemic symptoms Drug-induced liver injury Erythema multiforme Febrile neutropenia Granulocytopenia Haemolysis Haemolytic anaemia Hepatic failure Hepatic infarction Hepatic necrosis Hepatitis fulminant Immune thrombocytopenic purpura Intestinal perforation Ischaemic pancreatitis Neutropenic colitis Neutropenic infection Neutropenic sepsis Oedematous pancreatitis Optic ischaemic neuropathy

Pancreatitis Pancreatitis acute Pancytopenia Product contamination microbial Progressive multifocal leukoencephalopathy Pulmonary arterial hypertension Pulmonary fibrosis Pulmonary hypertension Renal failure Reye's syndrome Rhabdomyolysis Stevens-Johnson syndrome Sudden cardiac death Sudden hearing loss Sudden visual loss Thrombotic thrombocytopenic purpura Torsade de pointes Toxic epidermal necrolysis Toxic optic neuropathy Transmission of an infectious agent via product Ventricular fibrillation

References: 1. Eudravigilance Expert Working Group (EV-EWG), Guideline on the use of statistical signal detection methods in the Eudravigilance data analysis system. 26 June 2008, EMEA/106464/2006 rev. 1. 2. Council for International Organizations of Medical Sciences (CIOMS). Report of CIOMS Working Group VIII on Practical Aspects of Signal Detection in Pharmacovigilance. Geneva:CIOMS; 2010. 3. Guideline on good pharmacovigilance practices (GVP) Module IX – Signal Management, 22 June 2012, EMA/827661/2011. 4. Guideline on good pharmacovigilance practices (GVP) Module IX – Signal Management (Rev 1), 4 August 2016, EMA/827661/2011 Rev 1 Draft for Public Consultation. 5. Guideline on good pharmacovigilance practices (GVP) Module IX Addendum I: Methodological Aspects of Signal Detection from Spontaneous Reports of Suspected Adverse Reactions, 4 August 2016, EMA/209012/2015 Draft for Public Consultation. 6. http://who-umc.org/DynPage.aspx?id=115096&mn1=7347&mn2=7252&mn3=7613&mn4=761 (accessed 31 October 2016). 7. http://who-umc.org/graphics/28463.pdf (accessed 31 October 2016).

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