



**EUDRAVIGILANCE EXPERT WORKING GROUP
(EV-EWG)**

**GUIDELINE ON THE USE OF STATISTICAL SIGNAL DETECTION METHODS IN THE
EUDRAVIGILANCE DATA ANALYSIS SYSTEM**

DRAFT AGREED BY EUDRAVIGILANCE EXPERT WORKING GROUP	23 May 2006
AGREED BY EUDRAVIGILANCE STEERING COMMITTEE	12 June 2006
AGREED BY CHMP-PHARMACOVIGILANCE WORKING PARTY	20 September 2006
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	16 November 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	16 May 2007
AGREED BY EUDRAVIGILANCE EXPERT WORKING GROUP	18 December 2007
AGREED BY EUDRAVIGILANCE STEERING COMMITTEE (written procedure)	6 May 2008
AGREED BY CHMP-PHARMACOVIGILANCE WORKING PARTY	18 March 2008
ADOPTION BY CHMP	26 June 2008
DATE FOR COMING INTO EFFECT	26 December 2008

KEYWORDS	<i>EudraVigilance, Signal detection, Quantitative signal detection methods, Proportional reporting ratio, Risk management</i>
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LIST OF ABBREVIATIONS

CHI² or χ^2 : Chi-square statistics

DME: Designated Medical Event

EU-RMP: EU Risk Management Plan

EV-DAS: EudraVigilance Data Analysis System

EV-PM: EudraVigilance post-authorisation module

HLGT: MedDRA High Level Group Term

HLT: MedDRA High Level Term

ICSR: Individual Case Safety Report

LLT: MedDRA Lowest Level Term

PRR: Proportional Reporting Ratio. PRR(+) and PRR(-) denote respectively the upper and lower bounds of the 95% confidence interval of the PRR

PSUR: Periodic Safety Update Report

PT: MedDRA Preferred term

SDR: Signal of Disproportionate Reporting

SMQs: Standard MedDRA query

SOC: MedDRA System Organ Class

SUSAR: Suspected Serious Unexpected Adverse Reaction

TME: Targeted Medical Event

EXECUTIVE SUMMARY

The EudraVigilance Data Analysis System has been developed by the EMEA to support the EU pharmacovigilance activities and the implementation of the EU risk management strategy. The EudraVigilance Data Analysis System allows stakeholders to analyse adverse event data or subsets of data based on statistical methods to identify potential safety issues related to medicinal products. In this guidance, signals originating from statistical methods measuring disproportionality of reporting of drug-event pairs are referred to as “Signals of Disproportionate Reporting (SDR)”. The specific disproportionality measure implemented in the EudraVigilance Data Analysis System is the proportional reporting ratio (PRR).

In EudraVigilance post-authorisation module (EV PM), a regular screening process is carried out for new SDRs. The screening is based on Individual Case Safety Reports (ICSRs) originating from health care professionals and involving authorised medicinal products. SDRs are considered present when the measures of disproportionality together with the number of individual cases exceed predefined thresholds. The interpretation of SDRs is complex and requires thorough knowledge of the data available in the EudraVigilance Data Analysis System, the statistical methods applied as well as the medical knowledge of the medicinal product and the medical condition (indication) or underlying disease of the patients treated with this medicinal product.

Once the SDRs are identified, they need to be evaluated taking into consideration (i) quality controls such as the presence of potential duplicate reports, completeness of the information contained in the ICSRs and coding practices, and (ii) medical/clinical assessments of the adverse events including causality assessment. Only after such initial evaluation can SDRs be considered as signals related to the safety of medicinal products, which require further steps of analysis.

1. INTRODUCTION (background)

On 20 November 2005, in the European Economic Area (EEA), electronic reporting of individual case safety reports (ICSRs) became mandatory, save in exceptional circumstances. In order to support the analysis of these ICSRs in EudraVigilance database, the EudraVigilance Data Analysis System has been developed by the EMEA.

The EudraVigilance Data Analysis System has been designed to support the pharmacovigilance activities for medicinal products authorised in the Community, regardless of the authorisation procedure. It provides tools that facilitate the detection, evaluation and ongoing monitoring of signals related to the safety of medicinal products and the implementation of the EU risk management strategy.

In this context, the EudraVigilance Data Analysis System integrates statistical methods with traditional methods used in pharmacovigilance. The quantitative methods of signal detection have originally been designed to screen large spontaneous reporting system databases. They represent a systematic, automated and practical means of screening large databases such as EudraVigilance. These methods contribute to the protection of public health by detecting signals on databases which cannot easily be screened using conventional methods of pharmacovigilance. These methods also provide a safety net for human error.

This guideline acknowledges that the use of quantitative methods for the detection of signals in special situations needs to be evaluated. This is the case when the data from spontaneous reporting are sparse, inconclusive or difficult to assess clinically because of the complexity of the confounding or the underlying diseases. This is also the case when the nature of the risk is difficult to identify, for example when the increased risk is very small compared to the background incidence in the population. In such cases, the detection of new signals also involves other, often active, methods of surveillance. Examples include but are not limited to vaccines, orphan drugs or medicines used in children. Signal detection is also complicated by the fact that some classes of medicinal products are

often given in combination (e.g. vaccines or anticancer agents). Additional guidance will be given as further work is made available in these different fields.

The term ‘signal’ in pharmacovigilance entails ambiguity. The potential for confusion about the meaning of signal may be amplified with increased use of statistical algorithms in signal detection, each of which has its own model assumptions, metrics and *ad hoc* thresholds. Therefore, when referring to statistical calculations, devoid of any clinical context, the term ‘Signal of Disproportionate Reporting’ (SDR) should be used rather than ‘signal’. This is to emphasise that results from such approaches may merely reflect a disproportionality of reporting, which could be a function of numerous non-causal factors such as confounding, reporting artefacts, different coding practices or combination of the above. Furthermore these results always warrant investigation taking into consideration the clinical context.

The disproportionality analysis is not an inferential exercise (i.e. the exercise is not aimed at drawing conclusions about a parent population on the basis of evidence obtained from a random sample from this population). The concept of SDR is used in this guideline to describe a ‘statistical signal’ that has originated from the use of an analysis of disproportionality of reporting. The underlying principle of this method is that a drug –event pair is reported more often than expected relative to an independence model, based on the frequency of ICSRs on the reported drug and the frequency of ICSRs of a specific adverse event. **This statistical association does not imply any kind of causal relationship between the administration of the drug and the occurrence of the adverse event.**

In accordance with the Community legislation the reporting requirements are based on ‘suspected adverse reactions’ related to medicinal products. However, this guideline refers to adverse events as defined in the ICH E2A guideline [1] i.e. *‘any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product’*. This is to stress that a potential causal relationship between a drug and an adverse event cannot be established based on data analysis alone.

Finally, the guideline puts the signal detection activities using the quantitative methods in the context of other pharmacovigilance activities namely signal evaluation, communication between stakeholders and risk management activities.

SDRs require thorough evaluation taking into account all available clinical information at individual case level and, if considered necessary, further assessment including e.g. comparison with other relevant medicinal products using epidemiologic methods. In general the use of statistical methods in detecting signals is useful but requires a profound knowledge of the available data in EudraVigilance to interpret correctly the results originating from calculations. Therefore, special attention has been paid by the EMEA to develop stakeholder training, focusing on the functionalities of the EudraVigilance Data Analysis System as well as the statistical methods and the nature of the data available that can affect results and their interpretation.

2. SCOPE

This guideline describes quantitative methods implemented in the EudraVigilance Data Analysis System together with the elements for their interpretation and their potential limitations in the frame of pharmacovigilance. It encompasses the use of quantitative methods in EudraVigilance applied to the evaluation of ICSRs originating from health care professionals and involving authorised medicinal products i.e. spontaneous reports and/or non-organised methods of data collection depending on the user choice [2]. This guideline is not a discussion paper on the use of quantitative methods in pharmacovigilance in general.

Regulatory steps following the confirmation of a SDR are described in Community legislation and related pharmacovigilance guidelines [3, 4, 5]. The use of quantitative methods for the analysis of the data related to solicited reports (as defined in ICH E2D) is out of the scope of this document [2].

3. LEGAL BASIS

The legal framework for the conduct of pharmacovigilance of medicinal products is provided in Council Directive 2001/83/EC on the Community code relating to medicinal products for human use [3] and in Regulation (EC) No 726/2004 laying down the Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency [4]. Further guidance is provided in Volume 9A of the Rules Governing Medicinal Products in the European Union¹.

4. SIGNALS DETECTED BY THE QUANTITATIVE METHODS

4.1 Signals of disproportionate reporting (SDRs)

SDRs refer to statistical associations between medicinal products and adverse events i.e. drug-event pairs. They should be distinguished from signals that can originate from individual case analysis and epidemiological studies. Different statistical methods to generate SDRs are in use. In the EudraVigilance Data Analysis System, the Proportional Reporting Ratio (PRR) has been implemented in the first release. Other methods (incl. Bayesian methods) will be considered for future implementation.

4.2 The proportional reporting ratio (PRR)

The PRR is a measure of disproportionality of reporting used to detect SDRs in pharmacovigilance databases such as EudraVigilance. This method makes the assumption that when a SDR (involving a particular adverse event) is identified for a medicinal product (P), this adverse event is reported relatively more frequently in association with this medicinal product P than with other medicinal products. This relative increase in the adverse event reporting for the medicinal product P is reflected in a 2x2 contingency table (Table 1) based on the total number of individual cases contained in a pharmacovigilance database, as follows:

	Event (E)	All other events	Total
Medicinal Product (P)	A	B	A + B
All other medicinal products	C	D	C + D
Total	A + C	B + D	N = A+B+C+D

Table 1: 2x2 contingency table for the computation of the PRR

In this table the elements counted are the individual cases available in the database. Thus, a given individual case may contribute to only one of the cells of the table, even if the individual case refers to multiple medicinal products or multiple adverse events. The approach of performing the computations of the PRR on the individual case counts instead of number of ADRs has been chosen to keep the independence between the variables used to compute the PRR so that the variance of the PRR will not be underestimated.

The general criteria to calculate the PRR are as follows:

- The value **A** indicates the number of individual cases with the suspect medicinal product P involving an adverse event E.
- The value **B** indicates the number of individual cases related to the suspect medicinal product P, involving any other adverse events but E.
- The value **C** indicates the number of individual cases involving event E in relation to any other medicinal products but P.

¹ In accordance with the Community legislation, 'EudraVigilance Access Policies' are currently elaborated by the EV-EWG and EV-SC. The guideline will be updated once the "EudraVigilance Access Policies" will be finalized and implemented in EudraVigilance.

- The value **D** indicates the number of individual cases involving any other adverse events but E and any other medicinal products but P.

The PRR is computed as follows²:

$$PRR = \frac{A/(A+B)}{C/(C+D)}$$

Example 1:

- The proportion of individual cases of nausea amongst all the reports involving a particular medicinal product P is equal to 5% (e.g. 5 reports of nausea amongst a total of 100 reports reported with this medicinal product P; in that case A = 5, B = 95, A+B = 100).
- The proportion of reports of nausea amongst all the reports involving all the other medicinal products of the database (but not the medicinal product P) is also equal to 5% (e.g. 5,000 reports of nausea amongst 100,000 reports reported with all other medicinal products; similarly in this case C = 5000, D = 95,000, C+D = 100,000). In that example, the PRR is equal to 1 (i.e. 0.05/0.05).

Example 2:

- The proportion of individual cases of nausea amongst all the reports involving medicinal product P is equal to 15% (e.g. there are 15 reports of nausea amongst a total of 100 reports reported with this medicinal product P; in this case A = 15, B = 85 and A+B = 100).
- The proportion of individual cases of nausea amongst all the reports involving all the other medicinal products of the database (but not medicinal product P) is equal to 5% (e.g. 5000 reports of nausea amongst 100,000 reports reported with all other medicinal products; similarly in that case C = 5000, D = 95,000, C+D = 100,000). In this second example, the PRR is equal to 3 (i.e. 0.15/0.05).

A query implemented in the EudraVigilance provides the details of the computation of a PRR to the users for a selected drug-event combination (see section 5.2.2).

Following usual pharmacovigilance practices, the table takes into account the medicinal products reported as ‘suspect’ or ‘interacting’ (in the context of a drug-drug interaction). For specific ad hoc analyses i.e. drug-drug interactions, the concomitant medication can be added to the calculation. Other additional criteria can be added to further refine the analysis (see section 5.2.1).

4.3 The 95% confidence interval of the PRR

The EudraVigilance Data Analysis System also computes the 95% confidence interval of the PRR. The standard error of the natural logarithm of the PRR is estimated based on the following formula [15, 17]:

$$se = \sqrt{(1/A + 1/C - 1/(A+B)) - 1/(C+D)}$$

The 95% confidence interval for ln(PRR) is then estimated as ln(PRR)±1.96se and, taking the exponential, the following result is obtained:

95% confidence interval for PRR = (PRR / exp(1.96se), PRR x exp(1.96se))

² When C=0, the PRR cannot be computed. In EudraVigilance, the value of the PRR is arbitrarily set at 99.9 to reflect the presence of a possible SDR. The PRR can be computed at all the levels of the MedDRA hierarchy and the main levels of the medicinal product dictionary (i.e. international non-proprietary name, invented name (recoded or not when applicable) or even formulation level).

4.4 The chi-square (X^2) statistic

The Chi-square is a test the independence of categorical variables³. In certain standard queries of the EudraVigilance Data Analysis System, the Chi-square is used as an alternative measure of heterogeneity in the contingency table built with the medicinal product P and the adverse event E.

A query implemented in the EudraVigilance provides the details of the computation of a chi-square for a selected drug-event combination to the users (see section 5.2.2).

4.5 Interpretation of SDRs

The disproportionality analysis is not an inferential exercise. There are obviously significant problems in utilising inferential statistical methods in an exploratory analysis, particularly the possibility that statistical validity may wrongly be implied for purely speculative analyses. Caution should be exercised to avoid the fitting of an analysis that fulfils pre-existing expectations. Statistical analysis, if carried out in an undisciplined manner in a database, can entail subjective decisions in the selection, deployment, and interpretation of data mining procedures and outputs. Finally, none of the choices made available for these exploratory analyses have been convincingly validated for designing a data mining analysis.

The results of quantitative methods should be interpreted with caution and bearing in mind the limitations of the spontaneous reporting system databases. Therefore, the following aspects should be taken into account in the interpretation of the PRR results for signal detection purposes:

- (a) The PRR measures a reporting relationship between a medicinal product P and an adverse event E on the basis of a relative increase of the proportion of individual cases related to an adverse event. This does not imply any kind of causal relationship between the administered medicinal product P and the occurrence of the adverse event E. Such statistical disproportionality may reflect one or more of a number of biases (including a bias due to the underlying disease of the patients) and artefacts inherent in pharmacovigilance data as well as “statistical noise”. *Consequently, there is a scientific consensus that SDRs identified with quantitative methods should always be medically assessed* [6, 7, 8, 9].
- (b) The initial decision on whether a drug-event pair should be further investigated is based on thresholds applied to the estimates of the PRR and other statistics (e.g. the estimated lower bound of the confidence interval). There is no gold standard on the thresholds that should be adopted for SDRs.
- (c) The thresholds commonly used to detect SDRs are a trade-off between two conflicting options: either generating too many false positive signals if the threshold is too low or missing true signals if this threshold is too high.
- (d) The PRR involves the comparison of a reporting relationship for a specific medicinal product P with all other medicinal products in a database. The value of the PRR and consequently the SDRs identified with this method depend on the data in the database on which the PRR is computed. Therefore, the PRR interpretation should take the following elements into account [10]:
 - The type of medicinal products included in the database
 - The medical terminologies which have been used in the reports populating the database
 - The coding practices
 - The date of the creation of the database
 - The source of ICSRs (i.e. all unsolicited reports)

³ The Chi-square statistic is an inexact test which results from the normal approximation of the Poisson distribution. In certain situations particularly when the cell counts are low, an exact test should be performed (Fisher exact test). This test is based on the use of hypergeometric distribution. More details concerning the formulae, statistical aspects and assumptions underlying these tests may be found in statistical textbooks [11, 12]. However, such distributional assumptions cannot be reliably adopted and checked in the context of SRS data. The only reliable way of validating methods relying on disproportionality analysis is through empirical approach.

These elements influence the value of the PRR and may induce masking effects. Alternatively they may exaggerate the importance of a medicinal product-adverse event statistical association.

- (e) In addition to quantitative aspects it is also important to consider other elements in the selection and prioritisation of SDRs identified in a database. In particular, the following elements should be considered:
- The potential impact of the SDR in terms of Public Health,
 - The terms of the marketing authorisation and in particular whether the adverse event is expected/unexpected (in particular if there is evidence of a change in the frequency of reporting or seriousness of a known adverse drug reaction),
 - Whether the potential risk associated with the SDR has already been/is currently confirmed.

These should be evaluated regardless of whether a PRR has exceeded a pre-defined threshold.

- (f) The absence of a SDR does not necessarily exclude the possibility of an association between the medicinal product P and the adverse event E.
- (g) The PRR may be refined using similar techniques to other SDRs (e.g. combining multiple medicinal products and/or adverse events, stratification by age and sex of the patient). The possibility of masking of medicinal product-adverse event relationships by other medicinal products should also be kept in mind when assessing SDRs based on the PRR [13].

4.6 Thresholds defining SDRs in EudraVigilance

There is currently no 'gold standard' that establishes universal thresholds for signals of disproportionate reporting. Thresholds used in EudraVigilance are empirical and refer to those published [1]. The PRR is a very sensitive method which may generate a high number of false-positive signals particularly when the number of reports is low. Therefore case count thresholds (number of reports ≥ 3) are also used in association with the PRR and Chi-square statistics to reduce the number of false positives. Further practical experience as well as formal validation studies are necessary to assess which thresholds should be applied routinely in the EudraVigilance Data Analysis System.

However, defining SDRs in terms of absolute values of a PRR or other statistics may prove to be almost impossible. Therefore these statistics have to be considered as one of many elements that may be taken into account to prioritise potential drug-event associations for further evaluation.

As per standard pharmacovigilance practices, the value of the PRR can be computed on the entire EudraVigilance PM module or on the spontaneous reports only, in any case excluding interventional clinical trials [15]. The following criteria are applied in the queries of the EudraVigilance Data Analysis System to define a SDR (for a given drug-event combination):

- a) When the PRR is displayed with its 95% confidence interval:**
- **The lower bound of the 95% confidence interval greater or equal to one**
 - **The number of individual cases greater or equal to 3**

These criteria are used in the main weekly/monthly signal monitoring report.

The chi-square statistic has also been used in association with the PRR [14]. In such case the following criteria, using the Chi-square statistic, have been implemented in the queries:

- b) When the PRR is displayed with the χ^2 statistic:**
- **The PRR ≥ 2**
 - **The $\chi^2 \geq 4$**
 - **The number of individual cases greater or equal to 3.**

4.7 Subgroup analyses and stratification

Stratification is a statistical procedure aimed at mitigating the effects of confounding by adjusting for associations between a drug and a confounding variable and the event of interest and the same confounding variable [6]. The calculations of the PRR can be performed on the whole database or on a subset of reports. The restriction of this domain can be carried out using several variables including age and gender (see 5.2.1). The functionalities of the grouping will be extended in the future. The computation of the static PRR will be adjusted for age, gender and year of reporting by stratification. The subgroup analyses will also be possible on product or class of products basis.

5. DESCRIPTION OF THE EUDRAVIGILANCE DATA ANALYSIS QUERIES

The EudraVigilance Data Analysis System is currently used in two ways:

- To periodically generate data summaries and SDRs for reported medicinal products. These standard listings provide an objective basis for routine signal detection activities.
- To conduct dedicated analysis on sub-sets of individual cases using different analysis filters. This allows ad-hoc scientific evaluation of signals.

The following examples provide an illustration of the data summaries and functionalities available in the EudraVigilance Data Analysis System. Reference is made to the training and user material for detailed information on how to use the system for data analysis.

5.1 Standard outputs

The ‘Reaction Monitoring Intensive/Routine’ Report (Table 2) is generated at defined intervals (two-weeks or monthly). This report is generated automatically, sent to pre-defined users and cannot be changed. A similar report can be accessed via the Data Analysis System for which the settings can be customised by the users (see 5.2). The table contains the number of new individual case reports, whether initial or follow-up, received during the period covered by the report. The PRR is calculated based on the total number of ICSRs. Only ‘suspect’ and ‘interacting’ (in the context of a drug-drug interaction) medicinal products are included.

Reaction SOC	Reaction PT	Metrics	PRR (-)	PRR	PRR (+)	New	Total	New EEA	EEA	New Non EEA	Non EEA	New Fatal	Fatal
Blood and lymphatic system disorders													
	Agranulocytosis		0.14	0.44	1.35	1	3	0	2	1	1	0	0
	Anaemia		1.94	2.31	2.77	7	64	0	10	7	54	1	6
	Anaemia megaloblastic		1.05	7.56	54.51	1	1	0	0	1	1	0	0
	Aplasia pure red cell		2.44	4.42	8.00	1	10	0	3	1	7	0	1
	Bone marrow depression		2.09	3.07	4.52	5	17	0	2	5	14	0	2
	Granulocytopenia		0.42	1.32	4.09	1	2	0	1	1	1	0	1
	Haemolytic anaemia		1.19	2.15	3.89	1	9	1	3	0	6	0	2
	Histiocytosis haematophagic		0.88	3.53	14.18	1	2	0	0	1	2	0	1
	Hypoplastic anaemia		1.97	14.43	105.53	1	1	0	0	1	1	1	1
	Idiopathic thrombocytopenic purpura		0.08	0.56	3.98	1	1	0	0	1	1	0	0
	Leukocytosis		0.32	0.85	2.26	1	4	0	1	1	3	0	0
	Leukopenia		1.57	2.12	2.85	2	33	0	7	2	26	0	3
	Lymphadenopathy		0.81	1.62	3.24	1	8	0	1	1	6	0	0
	Macrocytosis		0.60	4.33	31.01	1	1	0	0	1	1	0	0
	Neutropenia		0.75	1.12	1.69	4	20	1	3	3	17	0	1
	Normochromic normocytic anaemia		0.32	1.30	5.19	2	2	2	2	0	0	0	0
	Pancytopenia		1.31	1.81	2.51	6	30	0	7	6	23	2	7
	Red blood cell abnormality		0.89	6.44	46.30	1	1	0	0	1	1	1	1
	Thrombocytopenia		0.60	0.88	1.28	5	23	1	7	4	16	0	5
	Thrombotic thrombocytopenic purpura		5.17	9.39	17.05	1	10	0	2	1	8	1	3
Cardiac disorders													

Table 2: ‘Reaction Monitoring Weekly/Monthly’ Report (see paragraph 5.1 for list of abbreviations).

The abbreviations used in the table denote the following information: '**PRR**' contains the value of the PRR, '**PRR(-)**' and '**PRR(+)**' are the lower and upper bounds of its 95% confidence interval respectively. The cells corresponding to the PRR is highlighted in red when all the criteria a) (section 4.6) are satisfied (lower bound of the 95% confidence interval of the PRR is ≥ 1 and the number of individual cases is ≥ 3). '**New EEA**' is the number of new cases occurring in the EEA received in the period covered by the report. '**New Non-EEA**' is the number of new individual cases occurring outside the EEA and received in the period covered by the report. The report displays the total number of spontaneous cases ('**Total**'), the number of individual cases originating from the EEA ('**EEA**') and the number of spontaneous cases originating from outside the EEA ('**Non EEA**') received in the EudraVigilance Post-authorisation Module. As the primary source country field is not always provided, the number of EEA cases and the number of non-EEA cases may not sum up to the total. The total includes all relevant cases reported to EudraVigilance.

The number of new fatal cases ('**New Fatal**') is the total number of fatal cases ('**Fatal**') occurring in the period covered by the report is provided. The PRR is computed on the total number of reports.

5.2 Exploratory analyses

The EudraVigilance Data Analysis System provides tools to perform exploratory analyses, which can be defined by the user on subsets of individual cases. These subsets can be generated using different variables such as age, gender, primary source country and concomitant medication, and other variables which are indicative of the medical condition of the patients. Examples of these queries are described below.

5.2.1 Filtering options for the standard queries

In the filters of the standard queries, the user can select the appropriate levels of the hierarchy in the EudraVigilance Medicinal Product Dictionary as well as in MedDRA. Results are calculated on the basis of the specified level e.g. if the MedDRA level of the Preferred Term (PT) is selected in the filtering options of the queries, then all statistics will be calculated at PT level.

The user can also choose the criteria to filter the output, which will be produced by the query. For example, a filter can be applied at any level of the MedDRA hierarchy from System Organ Class (SOC) to PT level as well as Standard MedDRA Queries (SMQs). The query can also be customised to select specific MedDRA terms and medicinal products.

Other filters are available to the user:

- The type of ICSRs (spontaneous reports, study reports)
- The time periods and dates when ICSRs were received in EudraVigilance
- The medicinal product characterisation (suspect, interacting [in the context of a drug-drug interaction] or concomitant)
- Primary source country
- Occurrence country
- Reporting organisation
- Age of the patient
- Sex of the patient
- Seriousness of the adverse event
- Sponsor study number
- EudraCT Number
- Only parent child reports
- Only pregnancy reports

The thresholds used to define SDRs can be set up by the user. The thresholds of the PRR, the 95% confidence interval of the PRR, the χ^2 or the number of individual cases received in EudraVigilance can be chosen.

The exploratory data analysis can also be applied after the execution of the query, through “drilling (up or down)” functionalities. This possibility allows the user to move from different levels of the medicinal product and of the MedDRA hierarchies. For example, if the user has initially chosen to calculate the PRR at PT level, the drilling allows performing the calculation also at a higher level (e.g. HLT) without repeating the query.

Finally, it is also possible to perform a query on a query result. This is important when the user wants to further assess ICSRs related to SDRs. For instance, depending on the access rights, the user can perform a drilling from the PRR result to the individual case listing linked to this SDR and retrieve the cases in CIOMS/E2B(M) format.

5.2.2 Static PRR Table

The static PRR table is a query which provides the details of the calculations described under section 4.2.

Table 3 shows an example of computation of a PRR based on the contingency table displayed in Table 1 (the letters used in Table 3 refer exactly to the same cells of Table 1). $\text{CHI}^2(\text{A})$, $\text{CHI}^2(\text{B})$, $\text{CHI}^2(\text{C})$ and $\text{CHI}^2(\text{D})$ are the individual components of the χ^2 statistics (denoted by CHI^2) contributed by each cell (A, B, C, D) based on the expected values of each cell (Expected A, B, C and D). PRR(-) and PRR(+) denote respectively the lower and upper bounds of the 95% confidence interval of the PRR computed on the cell A, B, C, D. The values of A, B, C, D can be easily obtained by subtracting the values displayed in the table ‘A’, ‘A+B’, ‘A+C’, ‘A+B+C+D’. The computation of the expected values of A, B, C and D under the assumption of independence can be found in statistical textbooks [11, 12].

Metrics	
A	3
A + B	2,430
A + C	254
A + B + C + D	163,417
$\text{CHI}^2(\text{A})$	0.1598
$\text{CHI}^2(\text{B})$	0.0002
$\text{CHI}^2(\text{C})$	0.0024
$\text{CHI}^2(\text{D})$	0.0000
CHI^2	0.1625
Expected A	3.7770
Expected B	2,426.2230
Expected C	250.2230
Expected D	160,736.7770
PRR (-)	0.26
PRR	0.79
PRR (+)	2.46

Table 3: ‘Static PRR Table’ Report

5.2.3 Static PRR Monitor

The Static PRR Monitor Report provides a tabular presentation of PRR statistics performed simultaneously at all levels of the MedDRA hierarchy (SOC, HLT, HLT, PT). Although numerical values of association (95% confidence interval of the PRR) are not presented, the report highlights (in red) the results of the calculations of the PRR. The cell is highlighted in red when all the criteria a)

(section 4.6) are satisfied (the lower bound of the 95% confidence interval of the PRR ≥ 1 and number of ICSRs ≥ 3).

An example of results of a Static PRR Monitor Report for a selected medicinal product is given in Table 4.

Reaction SOC	Reaction HLGT	Reaction HLT	Reaction PT	Metrics	PRR (SOC)	PRR (HLGT)	PRR (HLT)	PRR (PT)
Eye disorders (Maximum)					0.93	2.51	2.97	66.34
	Ocular structural change, deposit and degeneration NEC (Maximum)				0.93	0.44	2.29	4.74
		Retinal structural change, deposit and degeneration (Maximum)			0.93	0.44	0.65	4.74
			Macular degeneration		0.93	0.44	0.65	0.79
			Macular hole		0.93	0.44	0.65	4.74
			Maculopathy		0.93	0.44	0.65	2.21
		Structural change, deposit and degeneration of eye NEC (Maximum)			0.93	0.44	2.29	2.76
			Exophthalmos		0.93	0.44	2.29	2.76
	Retina, choroid and vitreous haemorrhages and vascular disorders (Maximum)				0.93	0.52	0.95	1.14
		Retinal bleeding and vascular disorders (excl retinopathy) (Maximum)			0.93	0.52	0.38	0.69
			Retinal haemorrhage		0.93	0.52	0.38	0.69
		Retinopathies NEC (Maximum)			0.93	0.52	0.95	1.14
			Diabetic retinopathy		0.93	0.52	0.95	1.14
			Retinal exudates		0.93	0.52	0.95	0.68
			Retinopathy		0.93	0.52	0.95	1.14
	Vision disorders (Maximum)				0.93	1.07	2.88	66.34
		Blindness (excl colour blindness) (Maximum)			0.93	1.07	0.71	66.34
			Blindness		0.93	1.07	0.71	0.51
			Blindness hysterical		0.93	1.07	0.71	66.34
			Blindness transient		0.93	1.07	0.71	3.11
			Blindness unilateral		0.93	1.07	0.71	0.50
		Partial vision loss (Maximum)			0.93	1.07	0.68	0.68
			Visual acuity reduced		0.93	1.07	0.68	0.68
		Refractive and accommodative disorders (Maximum)			0.93	1.07	1.62	11.06
			Accommodation disorder		0.93	1.07	1.62	2.65
			Presbyopia		0.93	1.07	1.62	11.06

Table 4: Static PRR Monitor Report

5.2.4 Static PRR Report

In the Static PRR Report, the calculations detailed in sections 4.2 to 4.4 are performed on selected medicinal products and the MedDRA level/terms chosen by the user. The standard rules given in section 4.6 are applied to highlight SDRs:

- The cells corresponding to the PRR (PRR and lower bound of the 95CI) are highlighted in **orange** when all the criteria a) are satisfied: lower bound of the 95CI of the PRR is ≥ 1 and the number of individual cases is ≥ 3 .
- The cell corresponding to the chi-square is highlighted in **red** when all the criteria b) are satisfied: $PRR \geq 2$, the $\chi^2 \geq 4$ and the number of individual cases ≥ 3 .

An example of results of a Static PRR Report for a selected medicinal product is given in Table 5.

Reaction PT	PRR (-)	PRR	PRR (+)	CHI ²	# Cases
Accommodation disorder	0.37	2.65	18.84	0.9911	1
Angle closure glaucoma	0.87	3.49	13.96	3.3792	2
Blepharospasm	4.53	12.06	32.14	34.3431	4
Blindness	0.16	0.51	1.57	1.4469	3
Blindness hysterical	9.34	66.34	470.98	32.1792	1
Blindness transient	1.00	3.11	9.64	4.1036	3
Blindness unilateral	0.07	0.50	3.57	0.4890	1
Cataract	0.10	0.39	1.56	1.8983	2
Conjunctival hyperaemia	0.09	0.66	4.66	0.1776	1
Conjunctivitis	0.03	0.24	1.68	2.4530	1
Corneal lesion	2.34	16.59	117.75	11.7171	1
Diabetic retinopathy	0.16	1.14	8.12	0.0178	1
Diplopia	0.72	1.43	2.86	1.0172	8
Dry eye	0.08	0.54	3.80	0.4012	1
Exophthalmos	0.39	2.76	19.62	1.0812	1
Eye discharge	0.20	1.41	10.02	0.1175	1
Eye disorder	0.05	0.38	2.72	0.9865	1
Eye movement disorder	0.08	0.57	4.03	0.3280	1
Eye pain	0.13	0.52	2.08	0.8789	2
Eye rolling	0.09	0.66	4.71	0.1692	1
Eye swelling	0.04	0.28	2.01	1.8056	1
Eyelid oedema	0.28	0.85	2.65	0.0738	3
Eyelid ptosis	0.08	0.56	3.96	0.3486	1
Foreign body sensation in eyes	1.56	11.06	78.50	7.8411	1

Table 5: Static PRR Report

5.2.5 Graphic PRR Monitor (PRR Confidence Interval): the PRR is displayed with its 95% confidence interval

The Graphic PRR Monitor (PRR Confidence Interval) report displays the results of the static PRR calculation as described in section 5.2.2. The graph displays the value of the PRR as well as the lower and upper bounds of the 95%CI of the PRR on a logarithmic scale (see Figure 1). The bold line represents the threshold for the PRR equal to 1. The number of individual cases for each drug-event combination is not displayed; however it is possible to perform a filtering on the results of the report.

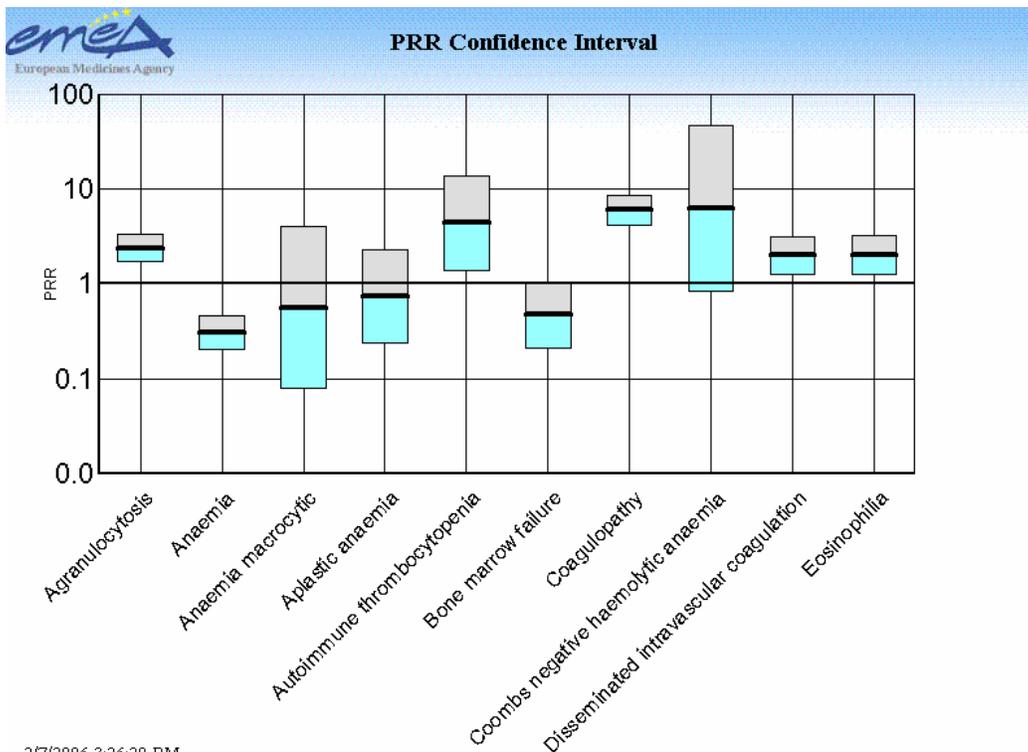


Figure 1: Graphic PRR Monitor report displaying the PRR Confidence Interval (y-axis is in logarithmic scale)

5.2.6 Graphic PRR Monitor (CHI²): the PRR is displayed with the CHI² statistics

The Graphic PRR Monitor (CHI²) report displays the results of the static PRR calculation as described in section 5.2.2. in the format of a graph. The graph displays the following values PRR, χ^2 and the numbers of individual cases involved in the drug-event combination.

A typical output is shown in Figure 2. The bold lines represent the thresholds of PRR = 2 and $\chi^2 = 4$ both on logarithmic scales. The number of the individual cases is displayed on the top of the bubbles. The size of the bubbles is proportionate to the number of reports involved in the drug-event combination.

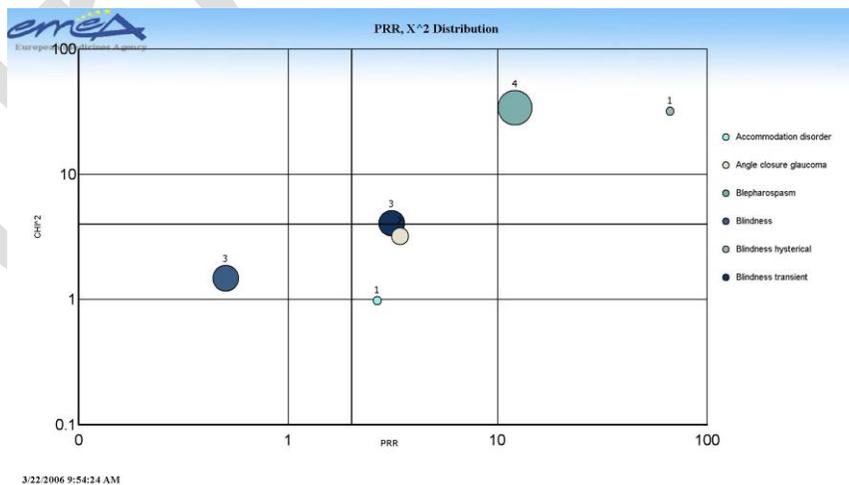


Figure 2: Graphic PRR Monitor (CHI²) report (axes are in logarithmic scales)

5.2.7 Dynamic PRR Report

The Dynamic PRR Report shows the evolution of the PRR over time. The report calculates the PRR (cumulative) and the PRR 95% confidence interval at a specific level of the MedDRA hierarchy (default PT Level) and at a specific level of the product hierarchy (default Scientific Product of the EudraVigilance Medicinal Product Dictionary) selected by the user. An example of results of a Dynamic PRR Report for a selected medicinal product is shown in Figure 3.

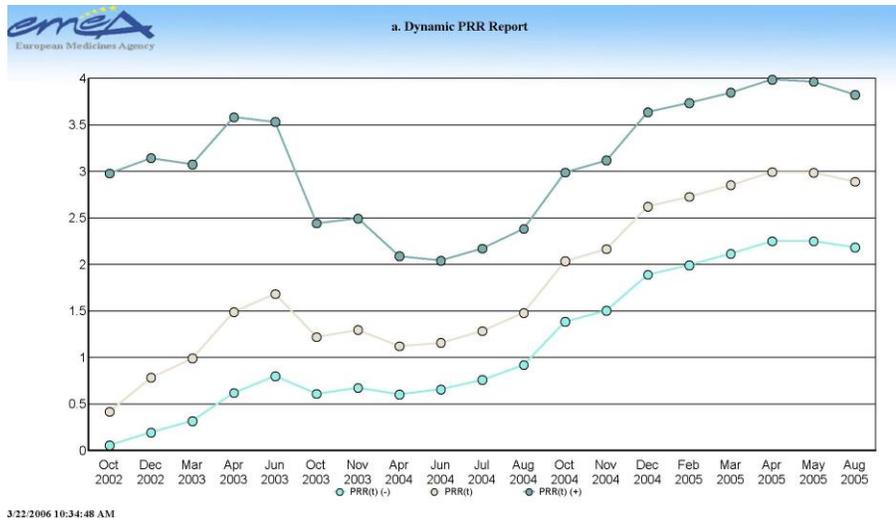


Figure 3: Dynamic PRR Report

The graph above gives an example of the evolution of a PRR for a drug-event pair over a period of time (e.g. between October 2002 and August 2005, the time points correspond to the receipt of a new report for this drug-event pair). The PRR is indicated by the dotted line in the middle of the graph. The two other dotted lines displayed in the graph represent respectively the lower bound of the 95% confidence interval of the PRR (lower line of the graph) and the upper bound of the 95% confidence interval of the PRR (upper line of the graph).

Uses of the dynamic PRR are described in the scientific literature [14, 16].

6. VALIDATION STUDIES ON STATISTICAL METHODS FOR SIGNAL DETECTION

Many methodological issues complicate the systematic and comprehensive assessment of the performances of the quantitative methods of signal detection. The lack of gold standard in signal detection is one important obstacle which makes this evaluation difficult to perform [6, 17].

The following conclusions can be drawn from these validation studies:

- The high sensitivity calculated in these studies relies on a simplistic definition of a signal (i.e. a drug-event pair). This definition of a signal may not reflect a real causal relationship between the drug-event pairs in terms of the clinical assessment in pharmacovigilance.
- The low specificity of statistical methods highlighted in the aforementioned validation studies indicates that many false positive signals may be generated.

7. INTEGRATION OF STATISTICAL METHODS WITH THE CLASSICAL METHODS OF SIGNAL DETECTION IN PHARMACOVIGILANCE

Currently only a limited number of publications have discussed the integration of statistical methods with the classical methods of signal detection in pharmacovigilance [6, 13, 17]. The quantitative methods of signal detection in pharmacovigilance should be used in addition to the other 'traditional' pharmacovigilance methods. It should also be noted that traditional methods can reveal safety signals that are not otherwise detected by data mining methods. Therefore data mining should not be relied upon as a substitute for traditional methods, particularly with rare events or designated medical events [6].

One of the first steps in the review of case reports is to focus on **designated medical events** (DMEs), e.g. adverse events, which are rare, serious and which are more likely to be associated with a high drug-attributable risk [13]. Typical examples include Lyell or Stevens-Johnson syndrome or aplastic anaemia.

Other events of specific interest, also referred to as **targeted medical events** (TMEs), are associated with particular medicinal products and/or patient populations [13] (see section 8).

Statistical methods are used to support the analysis of large volume of ICSRs to identify the signals. There is scientific consensus that SDRs require a careful and detailed case and literature review including an assessment of preclinical and pharmacological data, pharmacoepidemiological and/or clinical studies (depending on the context). As such the use of statistical methods (such as the PRR) provides additional tools to support standard pharmacovigilance practices. The statistical methods may also be used to investigate a signal detected by traditional methods, although such an approach would not be determinative in itself [13].

When a medicinal product is new to the market and only a small number of ICSRs have been received, it is feasible and probably more appropriate to assess these ICSRs individually than to rely on statistical methods. This is partly due to the fact that the reliability of the statistical screening is limited by the small numbers of ICSRs. Furthermore, the knowledge about the safety profile of a medicinal product at early marketing stages is mainly based on the clinical experience and therefore the screening of individual cases may add further value to the monitoring process.

The mainstay of pharmacovigilance still remains, however, the regular and systematic review of all new ICSRs. Statistical methods, as currently implemented in EudraVigilance, mainly provide tools to prioritise the review of ICSRs and additional factors need to be taken into account. For example, the PRR method does not examine routinely concomitant drug-event pairs for drug-drug interactions, which have to be assessed by the reviewer. Knowledge of the nature of the data available is also vital. This refers for instance to the origin of the ICSRs (EEA or third countries), since the indications for the same medicinal product may vary across countries.

The current statistical methods only take into account a limited number of data fields focusing mainly on the drug-event pair and the patient's characteristics. However, further experience needs to be gained with regard to the sophisticated ICH E2B(M) and M2 data structure and the extensive data fields, thus providing further opportunities to potentially improve the statistical data analysis [18].

7.1 *Systematic evaluation of SDRs*

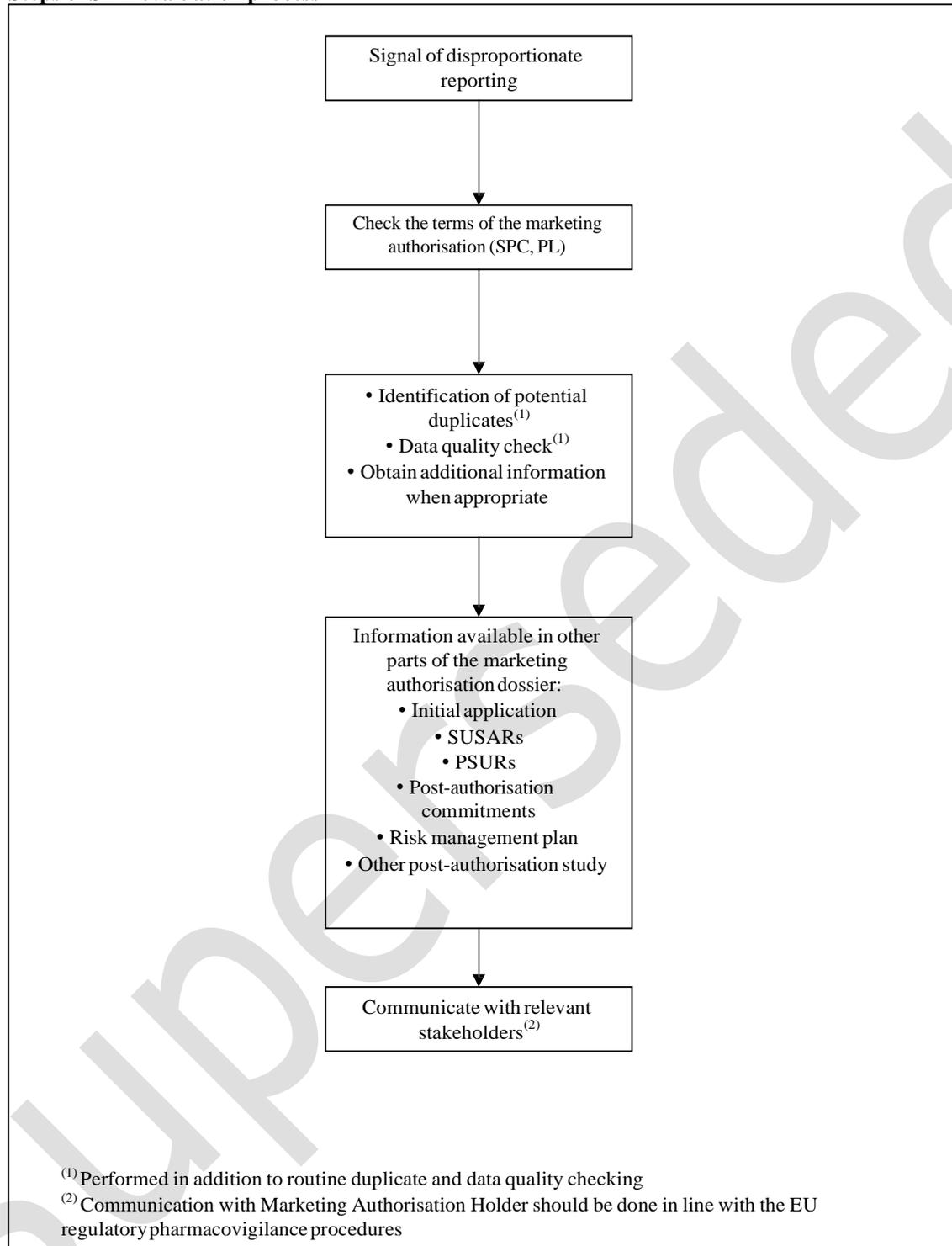
The critical aspect of the integration of statistical methods with the classical methods of 'signal detection' in pharmacovigilance is the systematic evaluation of the SDRs. *There is scientific consensus that signals of disproportionate reporting identified with statistical methods must be considered with a medical judgement. The SDRs which are considered to warrant further evaluation should always be systematically medically assessed* [6].

The steps outlined in the diagram below provide general guidance on the reviewing process of SDRs, which relies on medical judgment. These steps should include the following aspects:

- *Identification of potential duplicates:* Review of the individual case reports related to the SDR in the light of potential duplicates; although EudraVigilance is screened regularly for potential duplicates, there may be situations when an individual report is reported more than once in the database and may not appear initially as a potential duplicate.
- *Data quality check:* Review of the individual cases related to the SDR with regard to the completeness of the information provided, the coding practices and other factors that could impact on the assessment of the individual case.
- *Obtaining additional information when appropriate:* Taking into account the information available on the individual case, there may be the need to obtain further information from the sender to allow for the assessment of the individual case (e.g. translation of case narrative if not available in English).
- *Checking the terms of the marketing authorisation:* In particular, the summary of product characteristics (SPC) and the Package Leaflet should be checked to obtain further information e.g. on the expectedness of the adverse event, potential known drug-drug interactions.
- *Checking additional relevant information:* Further information such as the application dossier, the Risk Management Plan, data on Suspected Unexpected Serious Adverse Reactions (SUSARs), Periodic Safety Update Reports (PSURs), post-authorisation commitments and data on post-authorisation studies should be taken into account to assist the evaluation of the SDRs.

The different steps of the SDR review process as outlined in the diagram below should be fully documented and performed in accordance with internationally agreed quality standards to ensure that decisions are made on the principles of a sound medical approach and regulatory decision making [19].

Steps of SDR evaluation process



7.2 Specific aspects of the use of quantitative methods for vaccines and medicines used in children

This guideline acknowledges the specific requirements for the analysis of vaccines and medicines used in children [20, 21, 22]. The detection of new signals for these products or this population must be conducted separately with an appropriate scientific expertise [21, 22]. These aspects are discussed in specific EU guidelines which have been published or which are under preparation [20].

Additional guidance will be given as further work is made available in these different fields.

8. TARGETED MONITORING AND RISK MANAGEMENT

The detection, monitoring and evaluation of potential risks are addressed in the risk management plan submitted by Applicants or Marketing Authorisation Holders [23]. The adoption of the risk management plan should include specific aspects on the monitoring of identified and potential risks.

Targeted Medical Events (TMEs) correspond to the important identified and potential risks that require further characterisation or evaluation which are identified in the safety specification and listed in the Risk Management Plan [24] and in the corresponding interface between the European Risk Management Plan (EU-RMP) and EudraVigilance [25]. These TMEs are a list of MedDRA terms that can either be HLGT, HLT, PT or SMQs. These TMEs will be associated with the corresponding medicinal product in EudraVigilance. All new ICSRs received in EudraVigilance will be screened against these TMEs.

Additional TMEs may be set up to focus on the following aspects of the EU risk management plan [23]:

- The potential for overdose, the transmission of infectious agents and the potential for misuse for illegal purposes.
- The potential for off-label use; queries targeting the indications and the patients characteristics will be performed on the ICSRs to check whether the medicinal product was given in accordance with the approved indications.
- Special populations not studied in the pre-authorisation phase such as children, elderly, pregnant or lactating women.
- Drug-drug interactions or other forms of interactions (e.g. with food) will also be specifically monitored in EudraVigilance. The detection of these interactions requires an adequate MedDRA coding by selecting the appropriate PT or LLT term to identify the agent interacting with the medicinal product. The interaction could involve agents such as food, alcohol, tobacco, device or radiation for example.

9. IMPORTANCE OF DATA QUALITY IN SIGNAL DETECTION

Adherence to quality principles is a pre-requisite for successful implementation of statistical methods in pharmacovigilance. Quality principles refer to:

- The completeness of the case information available to the sender and provided in structured format in line with the principles of ICH E2B
- The coding practises in line with ICH M1 [26]
- The adherence to general pharmacovigilance practices as outlined in ICH E2D [27] and Community guidance.

The reporting of medicinal product information in the absence of an international standard is an additional challenge to meeting the data quality standards necessary for data analysis.

The need to adhere to the data quality principles has been included in Volume 9A of the 'Rules governing the medicinal products in the EU'. These quality standards include the provision of the complete information for an individual case, including case narratives, compliance with the reporting timeframes and adherence to the international and Community standards on the electronic reporting of

ICSRs. The use of different Community languages has been identified as a limiting factor in the evaluation of SDRs and has also been addressed in Volume 9A [5].

10. DEFINITIONS OF TERMS

The definitions of the terms used in this guideline (in particular *individual case safety report and suspected*) can be found in the Volume 9A of the Rules Governing Medicinal Products in the European Union. Guidelines on Pharmacovigilance for Medicinal Products for Human Use [5].

Drug-event pair: A drug-event pair is a combination of a medical product and an adverse event term (or another medical term linked to it in the medical terminology dictionary) reported in an individual case safety report.

Proportional reporting ratio: Measure of disproportionality of reporting used to detect signals of disproportionate reporting in pharmacovigilance databases such as EudraVigilance (see section 4.2).

Signal of disproportionate reporting: Statistical associations between medicinal products and adverse events i.e. drug-event pairs identified by data mining algorithms using disproportionality analyses. The presence of this statistical association does not imply any kind of causal relationship between the administration of the medicinal product and the occurrence of the reaction (see section 4.1).

Statistical association or statistical signal: see signal of disproportionate reporting.

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