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

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

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## 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<sup>1</sup> 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, ‘statistical 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) [1].

In EudraVigilance, new SDRs are screened regularly in relation to Individual Case Safety Reports (ICSRs) originating from health care professionals and associated to authorised medicinal products. These ICSRs refer to spontaneous reports or reports from non-interventional clinical trials. SDRs are considered present when the measures of disproportionality and/or the number of individual cases exceed certain thresholds. The interpretation of SDRs is often complex and requires thorough knowledge of both the data available in the EudraVigilance Data Analysis System and the statistical methods applied.

Identified SDRs always need to be evaluated based on (i) quality controls (e.g. presence of potential duplicate reports and controls of data quality in terms of e.g. completeness or coding of data), and (ii) medical/clinical assessments. Only after such initial evaluation can SDRs be considered as ‘potential 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, the EudraVigilance Data Analysis System has been developed by the EMEA.

The EudraVigilance Data Analysis System is designed to support the pharmacovigilance activities for all types of medicinal products authorised in the Community independent of the authorisation procedure. It provides tools that facilitate the identification, evaluation and ongoing monitoring of ‘potential 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. This guideline also recognises that there are specific aspects on the use of quantitative methods for the detection of potential signals in vaccines and medicines used in children.

The term ‘signal’ in pharmacovigilance entails considerable 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 reporting tendencies, which could be a function of numerous non-causal factors (confounding, reporting artefacts, statistical noise or some combination of the above). Furthermore these results warrant investigation based on the clinical context.

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<sup>1</sup> In line with the ‘EudraVigilance Access Policies’ currently being elaborated by the EV-EWG in accordance with Community legislation.

Therefore, the concept of SDR is applied in this guideline to describe a ‘statistical signal’ that has originated from a statistical method. 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.

It needs to be emphasised that in accordance with 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 [15] 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 a priori in the context of data analysis.

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 ‘potential 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 applied to the evaluation of ICSRs originating from health care professionals and associated to authorised medicinal products i.e. spontaneous reports or non-organised methods of collection of data.

Regulatory steps that can arise following the confirmation of a SDR are described in Community legislation and related pharmacovigilance guidelines [2,3,4]. 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.

## **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 [2] 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 [3]. Further guidance is provided in Volume 9A of the Rules Governing Medicinal Products in the European Union.

## 4. GENERAL CONSIDERATIONS ON POTENTIAL SIGNALS GENERATED BY STATISTICAL 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 ‘potential signals’ that can originate from individual case analysis and formal 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 will be considered for future implementation.

### 4.2. The proportional reporting ratio (PRR)

The PRR is a statistical method used to detect SDRs in pharmacovigilance databases such as EudraVigilance. This method relies on the principle that when a SDR (involving a particular adverse event) is identified for a medicinal product (referred to 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 table based on the total number of individual cases contained in a pharmacovigilance database, as follows:

	Event (R)	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: 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<sup>2</sup>.

Following usual pharmacovigilance practices, the table takes into account the medicinal products reported as ‘suspect’ or ‘interacting’. Concomitant medication are not normally taken into account in the calculations. 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.

The general criteria to run the PRR are as follows:

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

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<sup>2</sup> In EudraVigilance 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 PRR is computed as follows<sup>3</sup>:

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

*Example 1:*

- Proportion of individual cases of nausea involving a medicinal product ‘Trade Name’ = 5% (e.g. 5 reports of nausea amongst a total of 100 reports reported with medicinal product ‘Trade Name’).
- Proportion of reports of nausea involving all the other medicinal products in a database (but medicinal product ‘Trade Name’) = 5% (e.g. 5000 reports of nausea amongst 100,000 reports reported with all other medicinal products). Therefore, the PRR is equal to 1 (0.05/0.05).

*Example 2:*

- Proportion of individual cases of nausea involving medicinal product ‘Trade Name’ = 15% (e.g. 15 reports of diarrhoea amongst a total of 100 reports reported with medicinal product ‘Trade Name’).
- Proportion of individual cases of nausea involving all other medicinal products in a database (but medicinal product ‘Trade Name’) = 5% (e.g. 5000 reports of nausea amongst 100,000 reports reported with all other medicinal products). Therefore, the PRR is equal to 3 (0.15/0.05).

### **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 deviation of the natural logarithm of the PRR is estimated based on the following formula:

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

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

$$95\% \text{ confidence interval for PRR} = (\text{PRR} / \exp(1.96s), \text{PRR} \times \exp(1.96s))$$

### **4.4. The chi-square ( $\chi^2$ ) statistics**

The Chi-square is a statistic, which is traditionally used in disproportionality analyses. In certain standard queries of the EudraVigilance Data Analysis System, the Chi-square is used as an alternative measure of association between the medicinal product P and the adverse event R based on the following calculation:

$$\chi^2 = (AD - BC)^2 (A + B + C + D) / [(A + B)(C + D)(A + C)(B + D)]$$

### **4.5. Interpretation of signals of SDRs**

The following aspects have to be taken into account in the interpretation of the PRR results for signal detection purposes:

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<sup>3</sup> 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).

- (a) The PRR measures a reporting relationship between a medicinal product P and an adverse event R on the basis of a relative increase of the proportion of individual cases related to an adverse event. This does not necessarily imply a causal relationship between the administered medicinal product P and the occurrence of the adverse event R. Such statistical disproportionality may reflect one or more of a number of biases 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* [5,6,9,12].
- (b) The initial decision on whether a drug-event combination 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 options: either generating too many ‘false positive signals’ if the threshold is too low or missing ‘potential 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. Therefore, 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 [7]:
- The type of medicinal products included in the database
  - The medical terminology(ies) applied
  - The coding practices
  - The date of the creation of the database
  - The source of ICSRs (i.e. all unsolicited reports)
- 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. These should be taken into account regardless of whether a PRR has exceeded a pre-defined threshold. The following elements should be evaluated:
- whether the adverse event is labelled/unlabelled
  - whether the SDR has already been/is currently assessed.
- 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 and accordingly, results may not be generalizable.
- (f) The absence of a SDR does not necessarily exclude the possibility of an association between the medicinal product P and the adverse event R.
- (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 [10].

#### **4.6. Thresholds defining SDRs in EudraVigilance**

There is currently no ‘gold standard’ that establishes universal thresholds for ‘statistical signals’. Thresholds used in EudraVigilance are empirical and refer to those published by Evans et al [1]. 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 is computed on the entire EudraVigilance database, excluding interventional clinical trials. The following criteria are applied in the queries of the EudraVigilance Data Analysis System to define a SDR:

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

#### ***4.7. Subgroup analyses and stratification***

The calculations of the PRR can be performed on the whole database or on a certain subset of reports. The restriction of this domain can be carried out using several variables including age and gender (see 5.2.1 standard query (filtering) options). The functionalities of the subgrouping will be extended in the future, in particular, the computation of the static PRR will be adjusted for age and gender 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 analyses on sub-sets of individual cases using different analyses filters. This allows ad-hoc investigation of ‘potential signals’ in an exploratory and descriptive manner.

The following examples provide an illustration of the data summaries and SDR functionalities available in the EudraVigilance Data Analysis System. For detailed information on how to apply the system to data analysis, the training and user material needs to be consulted.

#### ***5.1. Standard outputs of SDRs***

The ‘Reaction Monitoring Weekly/Monthly’ Report (shown in table 2) is generated at defined intervals (weekly or monthly). The table contains the number of new individual cases (initial case or new follow-up of cases) received during the period covered by the report. The numbers displayed in the table are calculated based on ICSRs related to spontaneous reports and reports from non-interventional clinical trials. Only ‘suspect’ and ‘interacting’ medicinal products are taken into account.

The abbreviations used in the table denote the following information: ‘**PRR**’ contains the value of the PRR, ‘**PRR(-)**’ and ‘**PRR(+)**’ are respectively the lower and upper bounds of its 95% confidence interval. ‘**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**) in relation to the ICSRs received in the EudraVigilance Post-authorisation Module. As the primary source country field is not mandatory in line with the ICH E2B guideline [16], 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. Furthermore the number of new fatal cases (**New Fatal**), as well as the total number of fatal cases (**Fatal**) occurring in the period covered by the report is provided.

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

## 5.2. Exploratory functionalities

The EudraVigilance Data Analysis System provides a way 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, which are indicative of the medical condition of the patients. Examples of these queries are described below.

### 5.2.1. Standard query (filtering) options

All standard queries can be customised. A set of standard options "Standard query template" is available in the EudraVigilance Data Analysis Query Library.

The user can select as query parameter the appropriate medicinal product hierarchy level (EudraVigilance Medicinal Product Dictionary) and the MedDRA hierarchy level. Results are calculated on the basis of the specified level e.g. if the Preferred Term (PT) is selected, then all statistics are calculated at PT level.

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

Other filters available to the user are as follows:

- 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 or concomitant)
- Primary source country
- Reporting organisation
- Age of the patient
- Sex of the patient
- Seriousness of the adverse event
- Sponsor study number

Finally it is possible to choose the thresholds of the PRR, the 95% confidence interval of the PRR,  $\chi^2$  combined with the number of individual cases received in EudraVigilance, which will define SDRs.

The exploratory data analysis can also be applied after the execution of the query, through “drilling” 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 to perform the calculation also at a higher level (e.g. HLT) without repeating the query.

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 an option to further examine details of the intermediate steps in the calculations described in section 4.2.

Table 3 shows an example for a Static PRR Table report. The abbreviations used in this table are the same as the abbreviations used in table 1 . The use of upper case letters in this table simply reflects the standard output from EudraVigilance.

$\text{CHI}^2(\text{A})$ ,  $\text{CHI}^2(\text{B})$ ,  $\text{CHI}^2(\text{C})$  and  $\text{CHI}^2(\text{D})$  are the individual components of the  $\chi^2$  statistics (denoted by  $\text{CHI}^2$ ) contributed by each cell (A, B, C, D).

$$\chi^2 = (AD - BC)^2 (A + B + C + D) / [(A + B)(C + D)(A + C)(B + D)] \text{ or equivalently}$$

$$\chi^2 = (\text{ExpA} - \text{ObsA})^2 / N + (\text{ExpB} - \text{ObsB})^2 / N + (\text{ExpC} - \text{ObsC})^2 / N + (\text{ExpD} - \text{ObsD})^2 / N$$

Where the expected values of A, B, C and D (ExpA, ExpB, ExpC and ExpD) denote the expected value of each cell of the Static PRR Table based on the hypothesis that the PRR is equal to one<sup>4</sup>.

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 obtained by differencing the values displayed in the table ‘A’, ‘A+B’, ‘A+C’, ‘A+B+C+D’.

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<sup>4</sup> The formula of the Chi-square statistics is given in paragraph 4.4. Each individual component of the Chi-square statistics is computed as follows:  $\text{CHI}^2(\text{A}) = (\text{Expected value for A} - \text{Observed value for A})^2 / \text{Expected value for A}$ . The Expected value of the cell A is computed by the product of each marginal value divided by the total number of reports. Expected value for A is  $(A + B)(A + C)/N$ , Expected value for B is  $(A + B)(B + D)/N$ , Expected value for C is  $(A + C)(C + D)/N$  and Expected value for D is  $(C + D)(B + D)/N$  (see Table 1: Table for the computation of the PRR).

Metrics*	
A	3
A + B	2,430
A + C	254
A + B + C + D	163,417
CHI <sup>2</sup> (A)	0.1598
CHI <sup>2</sup> (B)	0.0002
CHI <sup>2</sup> (C)	0.0024
CHI <sup>2</sup> (D)	0.0000
CHI <sup>2</sup>	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 Report

In the Static PRR Report, the same calculations as explained in section 5.2.2. are performed on selected medicinal products and the MedDRA level/terms chosen by the user. Standard rules are applied to highlight SDRs. The report marks (in red) the calculation of the PRR, the  $\chi^2$  and the number of individual cases where the PRR  $\geq 2$ , the  $\chi^2 \geq 4$  and the number of individual cases  $\geq 3$ . When the lower confidence limit of the PRR is  $\geq 1$  the cell is also highlighted.

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

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

Table 4: Static PRR Report

#### 5.2.4. Graphic PRR Monitor (CHI^2)

The Graphic PRR Monitor (CHI^2) report displays the results of the static PRR calculation as described in section 5.2.2. in the format of a graph. The graph shows the following values:

- PRR
- $\chi^2$
- Numbers of individual cases

A typical output is shown in Table 5. The bold lines represent  $PRR = 2$  and  $\chi^2 = 4$ . The number of the individual cases is reported on the top of the bubbles. The following graph shows the data from the first six lines of Table 4:

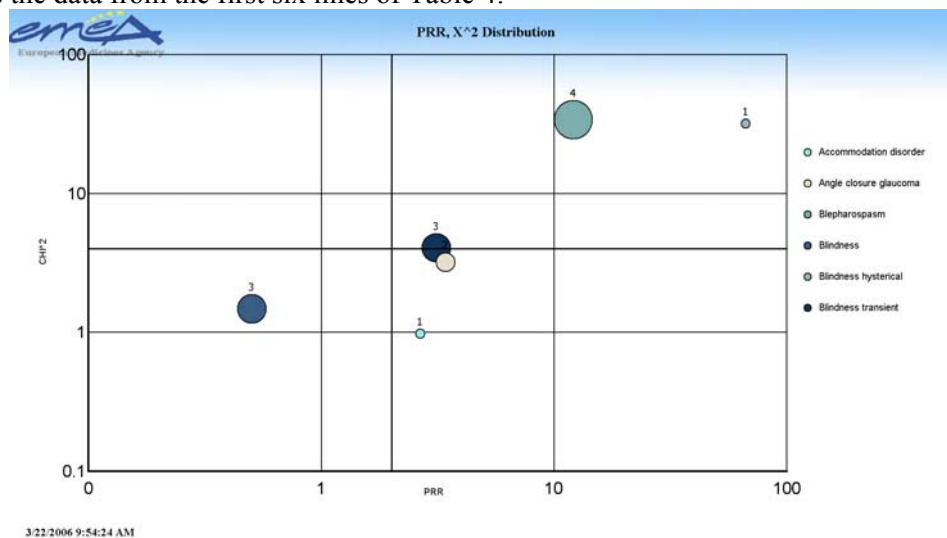


Table 5: Graphic PRR Monitor (CHI^2) report

### 5.2.5. Static PRR Monitor

The Static PRR Monitor Report gives a tabular presentation of PRR statistics performed simultaneously at all levels of the MedDRA hierarchy (SOC, HLGT, HLT, PT). Although numerical values of association (95% confidence interval of the PRR) are not presented, the report highlights (in red) the calculation of the PRR, if the PRR  $\geq 2$  and lower bound of the 95% confidence interval of the PRR  $\geq 1$  and number of ICSRs  $\geq 3$ .

An example of results of a Static PRR Monitor Report for a selected medicinal product is shown in Table 6.

Reaction SOC	Reaction HLGT	Reaction HLT	Reaction PT	Metrics	PRR (SOC)	PRR (HLGT)	PRR (HLT)	PRR (PT)
Eye disorders (Maximum)					<b>0.93</b>	<b>2.51</b>	<b>2.97</b>	<b>66.34</b>
	Ocular structural change, deposit and degeneration NEC (Maximum)				<b>0.93</b>	<b>0.44</b>	<b>2.29</b>	<b>4.74</b>
		Retinal structural change, deposit and degeneration (Maximum)			<b>0.93</b>	<b>0.44</b>	<b>0.65</b>	<b>4.74</b>
			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)			<b>0.93</b>	<b>0.44</b>	<b>2.29</b>	<b>2.76</b>
			Exophthalmos		0.93	0.44	2.29	2.76
	Retina, choroid and vitreous haemorrhages and vascular disorders (Maximum)				<b>0.93</b>	<b>0.52</b>	<b>0.95</b>	<b>1.14</b>
		Retinal bleeding and vascular disorders (excl retinopathy) (Maximum)			<b>0.93</b>	<b>0.52</b>	<b>0.38</b>	<b>0.69</b>
			Retinal haemorrhage		0.93	0.52	0.38	0.69
		Retinopathies NEC (Maximum)			<b>0.93</b>	<b>0.52</b>	<b>0.95</b>	<b>1.14</b>
			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)				<b>0.93</b>	<b>1.07</b>	<b>2.88</b>	<b>66.34</b>
		Blindness (excl colour blindness) (Maximum)			<b>0.93</b>	<b>1.07</b>	<b>0.71</b>	<b>66.34</b>
			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	<b>3.11</b>
			Blindness unilateral		0.93	1.07	0.71	0.50
		Partial vision loss (Maximum)			<b>0.93</b>	<b>1.07</b>	<b>0.68</b>	<b>0.68</b>
			Visual acuity reduced		0.93	1.07	0.68	0.68
		Refractive and accommodative disorders (Maximum)			<b>0.93</b>	<b>1.07</b>	<b>1.62</b>	<b>11.06</b>
			Accommodation disorder		0.93	1.07	1.62	2.65
			Presbyopia		0.93	1.07	1.62	11.06

Table 6: Static PRR Monitor Report

### 5.2.6. Dynamic PRR Report

The Dynamic PRR Report shows how the PRR changes over time. The report calculates the PRR 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 Table 7.

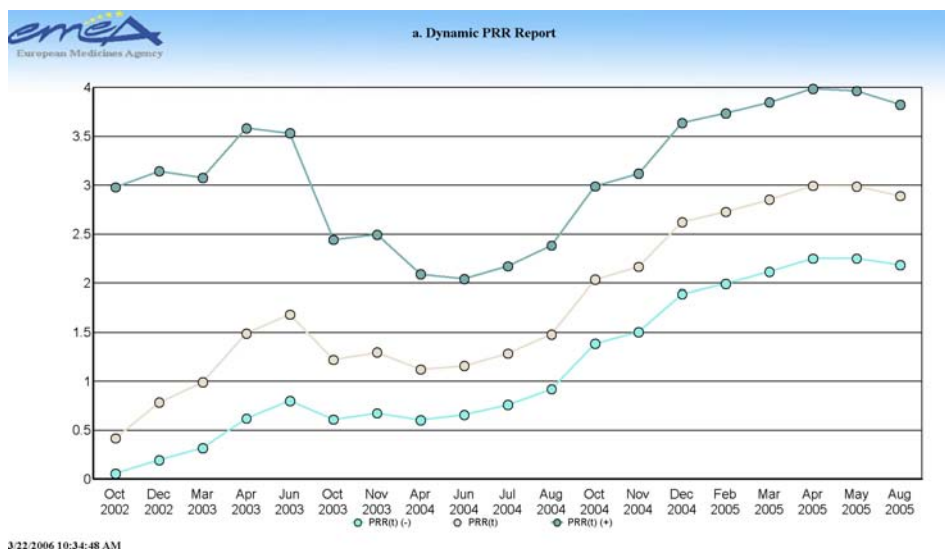


Table 7: Dynamic PRR Report

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 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).

Initial results on the use of the dynamic PRR are described in the scientific literature [14].

## 6. VALIDATION STUDIES ON STATISTICAL METHODS FOR SIGNAL DETECTION

It is important to emphasise that currently no statistical method for signal detection in pharmacovigilance (including the traditional pharmacovigilance methods) has been convincingly validated. However, some methodological considerations on the assessment of the performance of the various methods have been discussed [5, 8].

The following conclusions can be drawn from these validation studies:

- The high sensitivity calculated for certain metrics in these studies relies on a simplistic definition of a 'potential signal' (i.e. a drug-event pair). This definition of a 'potential 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 [5,8, 10]. Traditional pharmacovigilance methods (i.e. the manual screening of individual cases) are generally satisfactory when the number of reports in a database is small [5].

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 [10]. 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 [10].

Statistical methods are used to support the analysis of large volume of ICSRs to identify the ‘potential 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 ‘potential signal’ detected by traditional methods, although such approach would not be determinative in itself [10].

When a medicinal product is new to the market and only a small number of ICSRs has been received, it is feasible and probably more appropriate to review these ICSRs individually than to rely on statistical methods. This is partly due to the fact that the power of the statistical screening are likely to be limited with low 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 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 improve the statistical data analysis.

### 7.1. Systematic evaluation of SDRs:

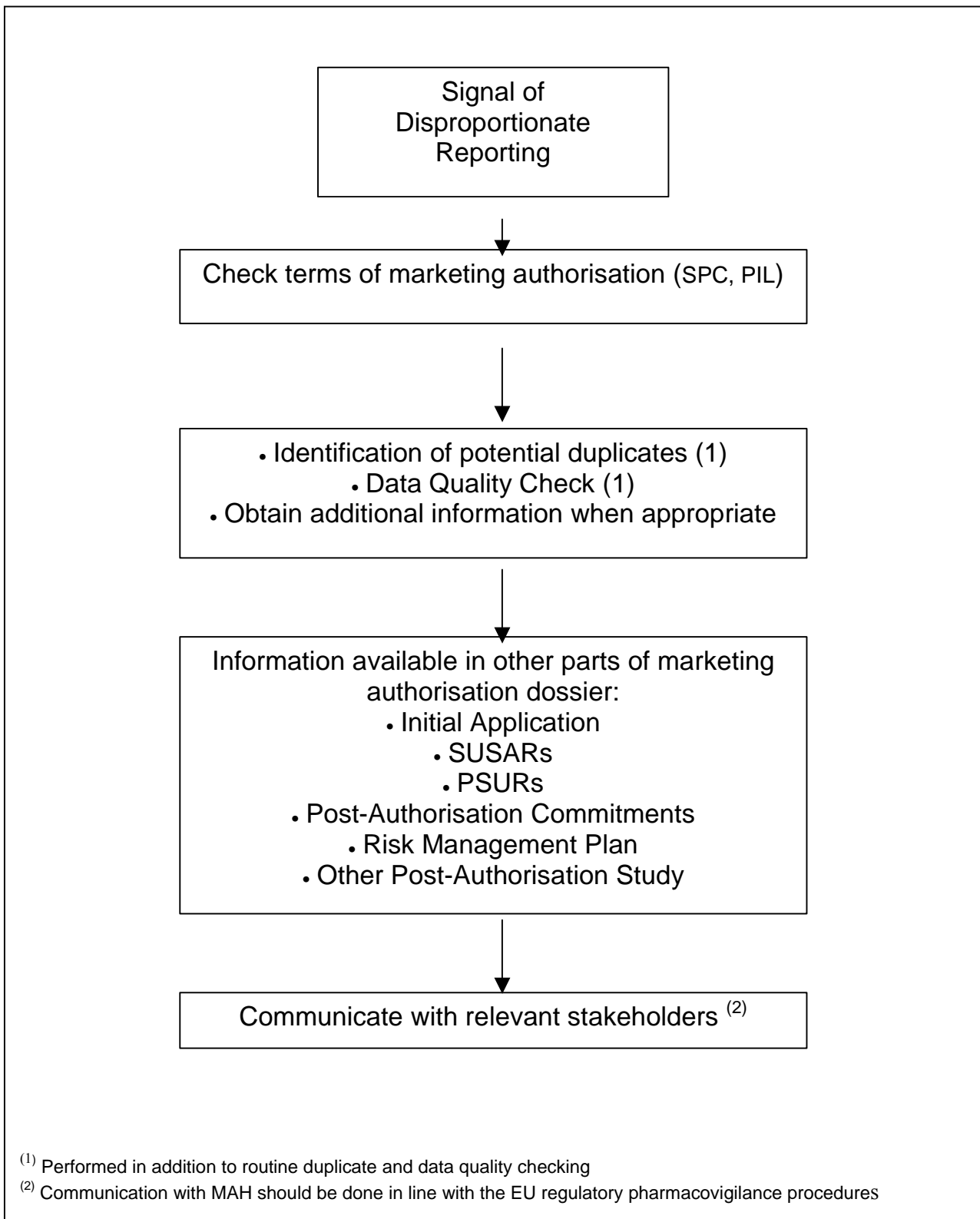
The critical aspect of the integration of statistical methods with the classical methods of ‘signal detection’ in pharmacovigilance is the systematic evaluation of the SDRs. *There is scientific consensus that signals of disproportionate reporting identified with statistical methods should always be medically assessed.*

The steps outlined in diagram 1 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 cases 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 case 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:* 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 diagram 1 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 [13].

**Diagram 1 Steps of SDR review process**



(1) Performed in addition to routine duplicate and data quality checking

(2) Communication with MAH should be done in line with the EU regulatory pharmacovigilance procedures

## 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 [19, 20, 21]. These aspects are discussed in specific EU guidelines which have been published or which are under preparation [19].

This guideline on quantitative methods in EudraVigilance will be updated according to the evolution of the knowledge and the experience gathered in these areas.

## 8. TARGETED MONITORING AND RISK MANAGEMENT PLANS

The detection, monitoring and evaluation of potential risks are addressed in the risk management plan submitted by Applicants or Marketing Authorisation Holders [11]. The adoption of the risk management plan should include specific aspects on the monitoring of identified and potential risks.

To facilitate the monitoring of these risks, Targeted Medical Events (TMEs) based on the safety specification [11] and presented in the Risk Management Plan will be implemented in EudraVigilance as described in table 8. All new ICSRs received in EudraVigilance will be screened against these TMEs.

Identified risks that require further evaluation	MedDRA terms
	List of terms. These terms can be HLGT, HLT , PT , LLT or SMQ
Potential risks that require further evaluation	MedDRA terms
	List of terms. These terms can be HLGT, HLT, PT, LLT or SMQ .

*Table 8: Presentation of TMEs based on identified and potential risks that require further evaluation during the life cycle of a medicinal product*

Additional TMEs may be set up to focus on the following aspects:

- The potential for overdose, the transmission of infectious agents and the potential for misuse for illegal purposes.
- The potential for off-label use (in adults or in paediatric population) with analyses conducted on the indications and patients characteristics reported.
- Special populations not studied in the pre-authorisation phase (such as children, elderly, pregnant or lactating women).
- Interactions between medicinal products or other forms of interactions (e.g. with food) will also be specifically monitored in EudraVigilance.
- 

These TMEs may be part of the risk management plan agreed between the Applicant/Marketing Authorisation Holder and the National Competent Authorities or part of additional pharmacovigilance activities and action plans.

## 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 [17]
- The adherence to general pharmacovigilance practices as outlined in ICH E2D [18] 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.

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