Recommendation on pharmacovigilance surveillance and signal detection of veterinary medicinal products

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1. Introduction

Veterinary medicinal products (VMPs) are granted a marketing authorisation in the European Union (EU) based on demonstration of quality, safety and efficacy through experimental data involving the target species. There is however also the need to follow-up on the use of VMPs in practice to establish possible unknown and/or unexpected or increased frequency of known adverse events in animals or humans linked to its use. This activity is described under the general term "pharmacovigilance" and also includes the monitoring of possible lack of expected efficacy, environmental problems and investigations of the validity of the withdrawal periods in case of substances used in food producing animals.

Each individual serious adverse event report is being assessed by marketing authorisation holders (MAHs) and regulators and may lead to rapid alerts for possible urgent regulatory action in line with available EU guidance.

Pharmacovigilance surveillance involves a continuous evaluation of the benefit-risk balance of VMPs. A review of all pharmacovigilance information available to an MAH takes place periodically through the periodic safety update reports (PSURs) that are prepared by the MAH and evaluated by the relevant regulatory authority. The PSUR reviews all pharmacovigilance information of a defined period (6 months/1 year/3 years) and may result in regulatory actions if changes to the benefit-risk balance are observed. Following the availability of adverse event databases, such as EudraVigilance Veterinary (EVVet), post-authorisation surveillance also involves the screening and the assessment of data reported for a particular VMP and/or active substance (hereafter called signal management process). These databases cover the full life-time[1] of a product and facilitate continuous surveillance and grouping and comparison of VMPs. The necessary frequency of such surveillance may depend on the perceived risk associated with the use of a particular VMP or active substance. As a general principle, this surveillance activity often referred to as "signal detection" should follow a recognised methodology. The methodology may vary depending on the type of VMP it is intended to cover. This document describes the methodology recommended to be used by regulators for post-authorisation surveillance of VMPs in the EU and includes the following elements:

1. Signal management process

    a. Signal detection

    b. Signal prioritisation

    c. Signal validation

    d. Signal evaluation

    e. Recommendation for action;

2. Determination of the post-authorisation surveillance interval.

2. Scope

The aim of this document is to provide an initial framework that will allow further development of signal detection in veterinary pharmacovigilance, its practical modalities, interpretation and location in

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[1] Containing adverse event data at least from 2005 onwards for "older" veterinary medicinal products.

the signal management process. Surveillance has been implemented already for centrally authorised products in line with the document circulated in 2010: Recommendation for the basic surveillance of EudraVigilance Veterinary data.

Implementation of surveillance for nationally authorised products using EVVet data and the data warehouse query tools depends on the availability of product data in a central EU product database. The EU Veterinary Medicinal Product Database (EU VetMedProd DB)[2] only has a limited number of the total veterinary products authorised in the EU and therefore it is yet not possible to allow for efficient pharmacovigilance surveillance across similar products and across all Member States. The principles of this recommendation document can only be fully applied for nationally authorised products once sufficient product information is available in the EU VetMedProd DB. Until then, only Member States who have transmitted their product data or Member States which have their own analysing systems may benefit from the principles described in this document.

In this current framework the national competent authorities (NCAs) retain the final decision on the surveillance frequency and details for nationally authorised products.

3. Signal management process

As defined in the Report of Council for International Organizations of Medical Sciences (CIOMS) Working group VIII 'Practical Aspects of Signal Detection in Pharmacovigilance' CIOMS, (Geneva 2010), a signal is information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related adverse events, that is judged to be of sufficient likelihood to justify verificatory action.

During the last years, some MAHs and NCAs started using data mining tools as increased pharmacovigilance data become available. The rollout of veterinary pharmacovigilance databases, such as EVVet in the EU, is a further opportunity to bring veterinary pharmacovigilance to another level. Indeed, sharing adverse event data on a larger geographical scale will significantly increase the volume of available data and therefore increase the power of statistical and data mining techniques to support surveillance. Pharmacovigilance for medicines for humans has historically had a high profile and the availability of large databases has led to many publications related to signal detection and data mining techniques from which the veterinary field can benefit.

When dealing with veterinary pharmacovigilance, one must keep in mind the specificities of the veterinary system, compared with human medicine, among which (but not limited to) are the following:

- a single adverse event report in animals may involve several animals. In some cases, a whole group or herd may be affected by herd treatment. Therefore, a "case report" does not necessarily refer to a single affected animal. Data can therefore be analysed by grouping the events of all animals involved in the same case report or by taking into account each animal showing a particular sign;

- some events are specific to the use of veterinary medicines and are subject to reporting in the same way as adverse events e.g.: investigations of the validity of the designated withdrawal period, environmental problems;

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[2] Established in 2015 (http://vet.eudrapharm.eu/vet/selectLanguage.do?NOCOOKIE=NOCOOKIE&NEW_SESSION=true)

- the global amount of available data is still limited as the pharmacovigilance system for veterinary medicines is not as extensive and has not been running for as long as for human pharmacovigilance.

3.1. Data sources for signal management

The sources and methods of identification of new signals are diverse and potentially involve all scientific information concerning the use of medicinal products authorised in the EU including information on quality, non-clinical, clinical and pharmacovigilance; this may include data from outside the EU. Sources for signals include spontaneous reporting systems, studies and informal sources of information as well as scientific literature.

Signals from spontaneous reports may be detected from adverse event reports, adverse event databases, articles from the scientific literature, PSURs or other documentation provided by MAHs in the context of regulatory procedures (e.g. variations, renewals, post-authorisation studies) or their on-going benefit-risk evaluation of medicinal products.

Informal sources of information include public websites, social networks, media reports or other systems through which practitioners and animal owners express adverse experiences with VMPs. These "new media" are increasingly used and are still developing further. Unfortunately, as the threshold for using them is fairly low, so is the quality of information available and it has not been possible yet to include these versatile sources as standard within the signal management process. Further reflection is ongoing and may lead to further specific guidance regarding the use of information available through the "new media".

3.2. Steps of the signal management process

3.2.1. Introduction

For the purpose of this guidance, data originating from the spontaneous reporting system are considered as the starting point of the signal management process. This process should also be used as a reference for data originating from other sources.

The signal management process can be defined as the set of activities performed to determine whether, based on an examination of individual adverse event reports, aggregated data from active surveillance systems or studies, literature information or other data sources, there are new risks associated with an active substance or a medicinal product or whether risks have changed. The signal management process covers all steps from signal detection to taking actions, regulatory or otherwise, to minimise or prevent risks:

1. Detection of potential signals;

2. Signal prioritisation: to promptly identify signals with important animal and/or public health impact or that may significantly affect the benefit-risk balance of the medicinal product in treated animals;

3. Signal validation: review of the case reports that generated the signal, to check if sufficient information exist to justify further evaluation;

4. Signal evaluation: review of the pharmacological, pre-clinical, clinical, epidemiological data from various sources, in order to conclude on a causal association, to quantify it and to identify the need for additional data collection or for risk minimisation measures;

5. Recommendation for action: to consider at any stage of the signal management process.

Although these steps generally follow a logical sequence, recommendation for action (followed by decision in accordance with the applicable legislation) and exchange of information should be considered "transversal" components that should be integrated at every step of the process.

3.2.2. Signal detection

Detection of signals may be performed based on adverse event reports originating from a spontaneous reporting system, adverse event reports from active surveillance or studies, or case reports published in the literature. Even a single report of a severe adverse event (for example, a death in a human being) may be sufficient for raising a signal and taking action. Considering that adverse event reports on food producing animals may affect an important number of animals in one report, also such a single report may constitute a signal.

The increase in volume of spontaneous reports, the introduction of electronic safety reporting and the mandatory electronic transmission of expedited reports from MAHs to regulatory agencies explain that signal detection is now increasingly based on periodic monitoring of databases of spontaneous reports of adverse events. Such databases allow data mining and the generation of statistical parameters presenting information on adverse events received over a defined time period for defined active substances or medicinal products. In addition to using their own database, competent authorities may perform signal detection in the EVVet database to increase the power of the analysis.

The principle of statistical analysis in databases of adverse events is to compare the frequency of a specific event-drug association with the frequency of this specific event associated with other drugs (used as baseline data). This comparison may generate signals of disproportionate reporting (SDR) for drug-event pairs. At the present time the European Medicines Agency (EMA, also known as the Agency) as well as the NCAs who have implemented or are currently developing statistical signal detection, mainly use the proportional reporting ratio (PRR) to generate SDR often associated with Chi-square. However, other statistical tools used to generate SDRs include the reporting odd's ratio (ROR), the information component (IC) and the empirical Bayes geometric means (EBGM). It is furthermore foreseen to implement the ROR instead of the PRR in order to allow for more advanced analysis that may require additional modelling for which the ROR is better suited.

The interpretation and the applicability of such statistical tools should take into account the following points:

- Due to the intrinsic limitations of the statistical tool, analyses should only be calculated on an adequately sized dataset. As a consequence, the number of individual cases should be at least 3;

- A PRR value higher than 1 indicates a higher probability that the event under consideration occurs in animals treated with the considered product compared to this event occurring with other products. In addition, considering the uncertainty of the PRR value (illustrated by its confidence interval) only PRR values of at least 2 with the lower confidence interval higher than 1 will be considered as potential signals;

- In relation to the Chi-square test, if the calculated Chi-square value is higher than 3.84, then it can be concluded (with an error risk of less than 5%), that there is a statistical association between the reported event and the product;

- The assessor must take into account the overall breakdown of the database in terms of type of products and type of adverse events that are represented the most, since these make up the denominator value and will influence the PRR significantly. For example, because the incidence of

vomiting in dogs in the overall database is relatively high due to high reporting and use of non-steroidal anti-inflammatory drugs (NSAIDs) in dogs, the relative occurrence of vomiting for a particular product must reach a similar level to that seen following NSAID administration before it is detected using PRR. The assessor may perform specific queries in the data warehouse that allow stratification to compare signals calculated with or without certain product groups or products.

To ensure relevance and accuracy, the application of PRR-based signal detection to the surveillance of VMPs, must take into account several particularities linked specifically to veterinary pharmacovigilance, as well as factual elements related to the quality and availability of data:

- The number of individual events, may be analysed either by number of reports or by number of animals. However, at present the systems do not allow (yet) for systematic recording of e.g. the number of animals showing a particular sign in a single report. Experience with analysis at "animal level" will only be possible when such high quality data become available.

- For the PRR result to be fully relevant, it is essential that the reference population is defined carefully, taking into consideration the specificities of each type of product and event. As a consequence, in most cases, stratification of reports is necessary to adjust the interpretation: when comparing the statistical association between a particular NSAID and events of gastrointestinal ulceration, as this sign is a well-known possible effect of NSAIDs as a class, it will be relevant to limit the reference population to all animals treated with other NSAIDs (instead of any other VMPs). This will determine whether or not this VMP is significantly more associated with gastrointestinal ulceration than other products of the same class. Animal species is another criterion for data stratification that is essential when dealing with VMPs.

Signal detection is intrinsically a statistical and observational approach: potential signals emerge from the raw pharmacovigilance data and only allow conclusions to be drawn on the possible statistical association between the use of a VMP and the occurrence of a given event or type of event. This type of alert must not be seen as a "turnkey" solution, as statistical significance may in fact not be clinically significant or may be due to the underlying illness or other biases. Therefore, further steps of signal validation and analysis will be essential as prerequisites to any decision making.

Statistical reports may be designed to provide a tool facilitating the identification of signals that meet pre-defined criteria of frequency, severity, medical importance, novelty or statistical reporting association. The thresholds used in this filtering process (for example, at least 3 events reported) cannot be indiscriminately applied to all adverse events and all active substances, given the differences in the animal and public health impact of different adverse events and variation in the extent of use of VMPs. Similarly, absence of a signal does not necessarily exclude the possibility of a causal association between the concerned substance and the adverse event, and presence of a signal does not necessarily indicate that such causal association is present.

3.2.3. Signal prioritisation

A key element of the surveillance process is to promptly identify signals that have potential animal or public health impact which may affect the benefit-risk balance of the VMP in treated animals. In addition and for certain products with a high number of reports it is not uncommon to have a large number of potential signals that require prioritisation before further analysis.

The prioritisation process should consider the following:

- the strength, frequency and consistency of, for example a high number of events reported in a short period of time, high values for the measure of reporting disproportionality and rapid increase

of that measure over time, and identification of the signal in different settings (e.g. across multiple veterinary practices and in a diversity of clinical situations), different data sources and different countries;

- the potential impact to humans exposed or affected;

- the impact on animals affected, depending on the severity, reversibility, potential for prevention and clinical outcome of the safety issue, and the consequences of treatment discontinuation on the disease;

- clinical relevance: severity of the event and its outcome (e.g. events leading to fatal outcome or permanent disability), novelty of the reaction (e.g. new and serious adverse event);

- the animal health impact, depending on the extent of utilisation of the product in the general population and in a vulnerable population (for example, VMPs used in different reproduction status or age group) and the patterns of VMP utilisation (for example off-label use or misuse); the animal health impact should integrate as much as possible an estimation of the number of animals that may be affected by a serious adverse event, novelty of the adverse event, for example when an unknown adverse event occurs shortly after the marketing of a new VMP;

- previous awareness: in principle, safety information which is already included in the summary of product characteristics (SPC) or which has already been assessed by the competent authority in the PSUR or which has been subject to a regulatory procedure does not represent a new signal; however, it may qualify as such if its apparent frequency of reporting, its temporal persistence, its severity, or change in the outcome or reported fatality, suggests new information as compared to the data included in the SPC or previously assessed by the competent authority;

- potential impact on the environment or on food safety in case of residues violation for products used in food producing animals, and lack of expected efficacy in particular in relation to antimicrobials and antiparasiticides.

3.2.4. Signal validation

A review of the corresponding adverse event reports should be performed to verify that the available documentation is strong enough to suggest a new potential causal association, or a new aspect of a known association, in order to justify further evaluation of the signal. The information to be reviewed should include the number of events (after exclusion of duplicate and invalid cases), the animal's demographics (e.g. species, age and sex), the suspected medicinal product / substance (e.g. dose administered) and the adverse event (e.g. signs and/or symptoms). The compatible temporal association, clinical outcome in relation to VMP continuation or discontinuation and presence of alternative causes for the adverse event should be considered as well as other concurrent medications administered, reporter's MAH/NCA evaluation of causality and plausibility of a biological and pharmacological relationship and possible VMP interactions and events occurring in specific populations (e.g. breeds).

3.2.5. Signal evaluation

The objective of signal evaluation is to draw conclusions on the presence or absence of a suspected causal association between an adverse event and a VMP, and to identify the need for additional data collection or for risk minimisation measures. This may also prompt the regulatory authorities to request the MAH for an additional analysis of its available data on a particular event under investigation.

This requires a thorough pharmacological and clinical assessment. When information is drawn from data sources, the strengths and limitations of each of them should be considered to assess the contribution it can provide to the evaluation of the safety issue.

Signals sometimes need to be assessed at the therapeutic or system organ class level. The search for information may need to be extended to other products of the same class and to other adverse events, using other terms linked to a complex disease, to a prior stage of the event or to clinical complications of the adverse event of interest (e.g. dehydration and acute renal failure).

3.2.6. Recommendation for action

Although the recommendation for action normally takes place in a logical sequence after signal evaluation based on the totality of the information, the need for action should be considered at any stage of the signal management process. The review of the available information at the signal prioritisation or signal validation stages may conclude that the evidence is sufficiently strong to require veterinarians and other health care professionals to be informed. In such situations, it is still necessary to proceed with a formal evaluation of the signal in order to confirm or refute the safety issue and prolong or lift the temporary action.

The range of regulatory or other actions that may be recommended as a result of the evaluation may vary according to the applicable legislation and the conclusion of the signal evaluation. If the evaluation concludes that there is no evidence of an increased risk for animals or humans, the competent authority/ the Agency may recommend that no further evaluation or action is required. It may, however, also decide that the issue needs to be reviewed periodically, for example through:

- Continue monitoring (no change of surveillance interval);

- Intensive monitoring (change of surveillance interval);

- Additional information from the MAH;

- Targeted PSUR from the MAH (targeted monitoring) or

- A post-authorisation safety study to investigate the potential safety issue.

Evaluation of the signal may lead to the conclusion that there is a potential or an identified risk and that actions need to be taken. These actions may include additional investigations or risk minimisation activities if there is the possibility of preventing or mitigating future similar adverse events. Whenever additional activities are requested by a competent authority/ the Agency to the MAH, the request should specify a timeframe by which they should be completed, including progress reports and interim results, proportionate to the severity, animal and public health impact of the issue. MAHs and competent authorities should consider the feasibility of conducting the study within the set timelines given the characteristics of the safety issue concerned, such as its incidence and the need for a prospective study design. Temporary measures to ensure the safe and effective use of the medicinal product or to remove the risk should be considered, including the possibility of temporarily suspending the product.

Where regulatory authorities find important signals and/or take regulatory action that may be relevant to other VMPs in the EU, the regulatory network should be informed using the existing tools such as the rapid alert and the non-urgent information system and when appropriate an article 78 (of Directive 2001/82/EC) procedure should be triggered.

4. Determination of the post-authorisation surveillance interval

The monitoring of pharmacovigilance data should occur with a frequency proportionate to the identified and the potential risk to allow efficient use of available resources for the overall surveillance of all VMPs in the EU.

When adverse event data in EVVet are linked to the product data, the data warehouse query tools allow for monitoring at Member State level as well as EU level. A periodic review of statistical outputs (e.g. reaction monitoring reports) allows determination of whether there are new or changed risks in the safety profile of an active substance/medicinal product. The statistical outputs should contain adverse event reports in a structured hierarchy (e.g. VeDDRA hierarchy) by active substance(s)/medicinal product(s) and allow filters and thresholds to be applied on several fields as appropriate.

The recommended baseline frequency for reviewing the statistical outputs from EVVet is every 6 months until the end of the period covered by the last one year PSUR and thereafter yearly.

Generics follow the same surveillance interval as the originator, unless there are important differences (e.g. excipients, different target species or indications) that may influence the pharmacovigilance profile of a product (certain hybrid products).

Confirmation of a signal arising from the EVVet data monitoring activities does not necessarily imply that the product has to be more frequently monitored and a risk proportionate approach should be applied.

Table 1: Recommended surveillance intervals

6-monthly	For products until the end of the period covered by the last one year PSUR
Yearly	Thereafter

4.1. Intensive Monitoring

An increase to the baseline frequency of data monitoring in EVVet (intensive monitoring) may be decided by the regulatory authority if justified by the identified or potential risks of the product e.g. signal detection or at the time of a PSUR evaluation. Intensive monitoring should be every 6 months or shorter if required.

An existing product may also be put back on a 6-monthly monitoring schedule following authorisation of e.g. a significant new indication, addition of a new target species or sub-group/age-group etc., as recommended by the relevant regulatory body at EU level.

The following criteria should be considered to determine the surveillance cycle of the product.

4.1.1. Time on the market (≈ Time from authorisation)

Certain active substances have well-established pharmacological and toxicological profiles, while new and innovative active substances have a "pharmacovigilance profile" that has only been determined from the limited data obtained from controlled trials during the development of the product.

The "time on the market" has often been considered an important criterion to determine whether the use and properties of a VMP is sufficiently known to provide a stable "pharmacovigilance profile".

However, time on the market would require tracking the marketing of VMPs which adds to the administrative burden; therefore it is proposed to use "time from authorisation" which would be a sufficiently good surrogate to implement in practice. Sales data and actual exposure data should also be taken into account when available (e.g. PSUR).

4.1.2. Type of product

For certain types of products it is considered necessary to increase the frequency of monitoring because of the nature of the active substance, or any other property inherent to the product or its use, e.g. live vaccines may require more intensive monitoring to control the possible reversion to virulence, active substances belonging to a new chemical family may require more intensive monitoring at the beginning of their life-cycle because their safety profile is not completely known at that time.

4.1.3. Frequency and severity of adverse events

A high reported frequency of "known" events can be inherent to the type of product (e.g. some NSAIDs) the relative high exposure and use of certain products, or the circumstance in which a product is used e.g. some anaesthetics. For such products it is therefore the sudden increase of the number of adverse events reported e.g. incidence in PSURs, that may trigger more intensive surveillance monitoring. Also the occurrence of unexpected serious adverse events may warrant more intensive surveillance monitoring.

4.1.4. New target species / new indication / new route / new formulation or delivery device (also for well-established active substances)

The addition of new target species and clinical circumstances may also affect the risk of a particular product. VMPs with a novel indication/route/formulation/delivery device may require more intensive monitoring. This may also apply to hybrid products which may have different authorisation conditions that may require more intensive monitoring.

4.1.5. Risks to humans

VMPs classed as potentially addictive to humans and VMPs with particular safety concerns in humans may require more intensive monitoring. Events including the unintended death of a human or a permanent lesion in a human should always lead to more intensive monitoring. The experience of reporting of events of hospitalisation or other events which also fall under the legal definition of a serious human reaction have often been found to be quite unrelated to an actual serious clinical condition, and therefore should not automatically lead to intensive monitoring.

4.1.6. Lack of expected efficacy

The potential for evolving lack of expected efficacy can be another element that justifies more intensive monitoring. In particular, this aspect has to be considered for antimicrobials and antiparasitics, due to the possible emergence of resistance mechanisms.

4.1.7. Other elements

The following elements are considered important and may also contribute to the determination of the appropriate surveillance interval for specific VMP's, it is necessary to understand that such events may only occur occasionally.

4.1.7.1. Information regarding the validity of the withdrawal period

Findings of non-compliant residues in foodstuffs of animal origin of active substances for which MRLs have been established for substances intended for food producing animals could have a major impact on public health and may require more intensive monitoring.

4.1.7.2. Potential environmental problems

Potential environmental problems are reported relatively infrequently through pharmacovigilance tools. Hence, few or only one single serious event may trigger more intensive monitoring.

Appendix: Short clarifications on Chi square test and proportional reporting ratio

This appendix aims at providing some simple and accessible explanations on notions that are dealt with in the "Recommendation on pharmacovigilance surveillance and signal detection on veterinary medicinal products". The information presented here is not meant to be a comprehensive lesson on statistics.

Definition

The chi-square (χ^2) test is a statistical test, i.e. it is used to identify statistical associations between a risk factor (here: being administered a specific drug) and a condition (here: reporting a specific adverse event). Chi square test allows the comparison of two percentages, in order to determine if they significantly differ or not (a significant difference means this difference is not due to sampling fluctuations i.e. to chance).

The Proportional Reporting Ratio (PRR) is similar to a relative risk, i.e. it is used to measure the strength of the statistical association between a risk factor (here: being administered a specific drug) and a condition (here: reporting a specific adverse event). The PRR allows the comparison of frequencies of reporting, in order to determine if there is a disproportionate reporting of a specific adverse event with a specific drug compared to other adverse events and other drugs. The confidence interval of the PRR can also be used to identify statistical associations between a specific adverse event and a specific drug (in the same way as the Chi square test does).

The **Reporting Odds Ratio (ROR)** is similar to an odds ratio, which also is a measure of the strength of the statistical association between a risk factor and a condition, and its confidence interval can be used to identify statistical associations.

Calculation

The same contingency table is used to calculate a Chi-square value and a PRR, a ROR and their confidence intervals. Depending on the structure of the database from which figures are extracted, a, b, c and d may be numbers of reports, or numbers of animals affected in the reports received.

	Event	All other events	
Product X	**a**	**b**	**a + b**
All other products	**c**	**d**	**c + d**
	a + c	**b + d**	**a + b + c + d**

$$p_1 = \frac{a}{a+b}$$

$$p_0 = \frac{c}{c+d}$$

$$\chi^2 = \frac{(ad - bc)^2 \cdot (a+b+c+d-1)}{(a+b) \cdot (c+d) \cdot (a+c) \cdot (b+d)}$$

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$$PRR = \frac{p_1}{p_0} = \frac{\dfrac{a}{a+b}}{\dfrac{c}{c+d}}$$

Lower and upper bounds of the confidence interval of the PRR:

$$PRR(-) = e^{Ln(PRR)-1,96\sqrt{\frac{b}{a(a+b)}+\frac{d}{c(c+d)}}} \qquad PRR(+) = e^{Ln(PRR)+1,96\sqrt{\frac{b}{a(a+b)}+\frac{d}{c(c+d)}}}$$

$$ROR = \frac{a.d}{c.b}$$

Lower and upper bounds of the confidence interval of the ROR:

$$ROR(-) = e^{Ln(ROR)-1,96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}} \qquad ROR(+) = e^{Ln(ROR)+1,96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$$

Interpretation

The **Chi square** value is compared to a tabulated value. For one degree of freedom (i.e. a 2X2 table) and a 5% risk to wrongly conclude on a significant difference, this value is 3.84.

If $\chi^2 > 3.84$: there is a significant difference between the compared percentages p_1 and p_0 = there is a statistical association between drug X and the event

If $\chi^2 < 3.84$: we don't reveal a significant difference between the compared percentages p_1 and p_0 = we don't reveal a statistical association between drug X and the event

The **PRR** can be interpreted in the same way as a relative risk. For a 5% risk to wrongly conclude to a significant difference:

If the 95% confidence interval of the PRR does not contain the value 1 and if PRR > 1, there is a disproportion of reporting in the sense that the specific event is more frequently reported in association with drug X than with other drugs.

For example, if PRR = 5 and its confidence interval = [4; 7] we can conclude that the risk of having a specific adverse event reported with drug X is 5-fold the risk of having the same adverse event reported with other drugs.

If the 95% confidence interval of the PRR does not contain the value 1 and if PRR < 1, there is a disproportion of reporting in the sense that the specific event is less frequently reported in association with drug X than with other drugs.

If the 5% confidence interval of the PRR contains the value 1, we don't reveal a disproportionate reporting.

If the event is "rare" in the population (in practice, if $p_0 < 1\%$), the **ROR** can be interpreted like a PRR.

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