# Riassunti delle relazioni finali dei progetti di ricerca svolti dagli studenti nell'ambito del tirocinio formativo del master per l'anno accademico 2013-2014

## Pharmacovigilance awareness: from 2006 to now

**Francesco Abbate, Luana Riccardi**

Novo Nordisk SpA, Roma

**ABSTRACT**

*Background:* The attention to iatrogenic diseases is increased enormously in the last years. The dissemination of the culture of pharmacovigilance is a fundamental aspect and the awareness activity is one of the most effective instruments to engage all stakeholders.

*Objective:* In a Pharmaceutical company, employees are an important source of safety data. Anyway it is necessary an intense activity of training and awareness to raise their attention and to give operative tools in case they become reporter of safety information. The final goal is to spread the culture of Pharmacovigilance so employees do not feel interested only as employees, but also as citizens.

*Methods:* Every year a series of activities has been performed to engage employees and to give them some insights about Pharmacovigilance, updates, issues and procedures. The most important activity is the Day of Pharmacovigilance that requires a direct participation of all company population.

*Results:* Reports from employees have always been a substantial part of the total reporting flow in Novo Nordisk. This mainly originates from the intense educational activity performed. The gathering of safety data benefits also of more accurate information due to the direct contact with the primary reporter.

*Conclusions*: In a frame in which the Pharmacovigilance reporting is continuously growing, the awareness activity has always represented a useful tool to increase both number and quality of safety data in order to better meet the needs of the patient reaching ever higher safety standards.

**Keywords:** Awareness, Training, Employees

# A retrospective survey of Novartis submissions

**Francesca Ambrosin, Daria Russo**

Novartis Pharma SpA, Origgio (VA)

**ABSTRACT**

*Background:* The Directive 2001/83/EC addresses the legal requirements for which all Marketing Authorization Holders (MAHs) have to notify to the respective Health Authority (HA) every Individual Safety Case Report (ICSR) of which they become aware. Locally, the Legislative Decree 219/2006 states that all MAHs must notify every Adverse Drug Reactions (ADRs) of which they become aware to the pharmacovigilance responsible of the related health facility or, if this is not identifiable, to the European Medicines Agency (EMA) for serious cases and still to the Italian Medicines Agency (AIFA) for not serious cases.

*Objective:* A retrospective survey of cases submitted by Novartis was performed with the purpose to quantify how many cases entered the National Pharmacovigilance Network (RNF) after the submission and to characterize them in order to understand the factors affecting the inclusion of cases in RNF.

*Methods:* All submitted cases from November 2013 to February 2014 were classified by the source of reporting in unsolicited and solicited reports. Then a characterization was performed on type of sources, on suspect drugs (if under additional monitoring) and on type of ADRs (serious/not-serious and listed/unlisted).

*Results:* Overall, 258 submitted cases were analysed. As a whole, 41.1% entered the RNF. Frequencies of entering the RNF of the 3 major reporting sources, Non-Interventional Studies (n=79), Patient Oriented Programs (n=71) and Sales Representative (n=63), were 59.5%, 15.5% and 54.0%, respectively.

*Conclusion:* Frequency of inclusion in RNF doesn't seem to depend on characteristics of suspect drugs and type of ADRs, but on reporting source, which determines the completeness of cases and the feasibility of conducting follow-up.

**Keywords:** Submissions, RNF, ADR reports, Sources, Health Care Professionals

# New oral anticoagulant real-life experience highlights how education on appropriate use of drugs should be continuously supported

**Valentina Calderazzo, Ilenia Bocchi**

Boehringer Ingelheim SpA, Milano

**ABSTRACT**

*Background:* New oral anticoagulants (NOACs) are increasingly replacing vitamin K antagonists and older parenteral agents in clinical practice. NOACs offer several advantages compared with standard agents, including rapid onset of action, fixed dosing and no requirement for routine coagulation monitoring.

Pradaxa® is the NOA launched by Boehringer Ingelheim containing dabigatran etexilate (DE), a direct thrombin inhibitor that inhibits thrombin-dependent conversion of fibrinogen to fibrin, thus preventing the formation of thrombus. In detail, it inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.

As for all drugs, deviations from the recommended usage of Pradaxa can lead to an increase of incidence of serious and not serious adverse events.

Real world safety evidences have been collected during the last 3 years. Particularly, after independent review, which evaluated patients treated with Pradaxa® or warfarin for non valvular atrial fibrillation (Medicare - FDA), and an independent project with the aim to assess the safety of approved drugs (Mini-Sentinel - EMA), FDA and EMA have not changed its recommendations regarding Pradaxa®, which provides an important benefits when used as directed.

*Objective:* Evaluation of appropriateness of prescribing dabigatran etexilate in patients in real-life clinical practice.

*Methods*: Spontaneous reporting of adverse drug reactions (ADRs) is the basis of safety evaluation in the post-approval phase. All data of spontaneous ADRs reporting are managed through the National Network of Pharmacovigilance (Rete Nazionale di Farmacovigilanza, RNF), a database that allows the collection, management and analysis of spontaneous reports of suspected ADRs, provided by health professionals, manufacturers or directly by patients.

Case reports discussed are four, have been retrieved from RNF and referred to the most significant inappropriate use of dabigatran etexilate during the period from 01 August 2013 to 31 July 2014.

In all cases the indication of use was atrial fibrillation; three patients were treated with Pradaxa® 110 mg and one with Pradaxa® 75 mg. In three of this four cases the outcome was exitus.

*Conclusions:* The proper identification of the right product for the suitable patient allows to reduce the risk of adverse events caused from an inappropriate use of drugs. The continued collaboration between healthcare professionals, pharmaceutical companies, regulatory authorities and patients is an essential element for performing it.

**Keywords:** Dabigatran etexilate, Atrial fibrillation, Inappropriate use, National Network of Pharmacovigilance

# The case of clopidogrel in Sicily: how to nullify the Italian pharmacovigilance system

**Michele Cugno, Enrico Magni**

ASGENIA srl, Roma

**ABSTRACT**

*Background:* In the period from March 2014 to February 2015, an increase in the reports of adverse drug reactions related to generic drugs was observed. The reports of adverse drug reactions have particularly involved drugs like clopidogrel, quetiapine, olanzapine, clozapine or other drugs such as antitumor activity drugs (capecitabine). All of these drugs have in common high prescribing margins and underwent to DPC.

*Objectives:* To demonstrate how the impact of the Assessorial Decree (AD) number 3/14 and its successive amendments has generated a bias in the Italian Pharmacovigilance Network and how often the reports of suspected adverse drug reaction are not related to the safety profile of drugs.

*Methods:* The reports form the Italian Pharmacovigilance Network related to some kind of generic drugs included in the territorial hospital formulary have been considered in this analysis. The period of time between 2014-MAR-01 and 2015-FEB-02 has been considered. The active substances, which did not exist in the reports of suspected adverse drug reactions (ADRs) from the Sicily region in the period considered, have been excluded by the analysis. It has also been excluded by the analysis the reports that contain only the active substance without specifying the Marketing Authorization Holder.

*Results:* In the period from 2014-MAR-01to 2014-JUN-11 in the Italian Pharmacovigilance Network 192 reports related to generic drugs were included compared to 12 reports included in the corresponding period of the previous year. The reports coming from the region Sicily, carried out from 2014-JUL-01 to 2014-AUG-31 have represented the 67.7% of the national reports. During the period that goes from 2014-SEP-01 to 2015-FEB-28 a powerful decrease of the reports of adverse drug reactions has been observed because in 6 months a total of 136 national alerts have been recorded in contrast with 63 reports detected in a period of only two months.

*Conclusion:* The analysis of the reports of adverse drug reactions inserted in the Italian Pharmacovigilance Network has showed that a probably bias have been generated. This distorting effect must be regarded both regionally and nationally if the safety of drugs with expired patent considered in this analysis should be taken into examination.

**Keywords**: Italian Pharmacovigilance Network, Reports of suspected adverse drug reactions, Clopidogrel, Assessorial Decree (AD) number 3/14 of 2014-JAN-08

# Monitoring of adverse reactions to biologics at the Hospital S.G. Moscati of Avellino

**Luana De Gruttola[1], Luciana Giannelli[1], Annalisa Capuano[2]**

[1] A.O.S.G Moscati, Avellino
[2] Second University of Naples, Campania Regional Centre for Pharmacovigilance and Pharmacoepidemiology, Department of Experimental Medicine, Naples, Italy

**ABSTRACT**

*Background:* Clinical trials of new drugs, based on randomized controlled trials (RCTs), represents only part of the best method available for determining the profile of effectiveness and safety of new drugs; in fact, clinical trials have still significant deficiencies for the exact definition of the risk/benefit profile of a new drug. The target therapy (therapy with biologics) represents a new frontier not only for cancer treatment but also in the approach to inflammatory bowel disease (IBD) and autoimmune disease. Although clinical trials have shown a good safety profile of biological drugs, there are no reliable data on the safety profile of long-term, because the period of time elapsed the start of the use in humans and the length of the major clinical trials are still too short to complete this assessment. Therefore, the project of Pharmacovigilance on the use Biological Drugs was started at the A.O.S.G. Moscati-Avellino under the coordination of Campania Regional Centre for Pharmacovigilance and Pharmacoepidemiology.

*Methods:* The project consists of four phases: I) In the first phase was evaluated the Biological Drugs presence in the PTO Company and the Operative Units that used them; II) In the second phase, through scheduled meetings, clinicians have been clarified about the procedures, the operational path and objectives of the project and III) In the third phase were intercepted and selected naïve patients from departments identified by the project. Data collection were completed by the analytical description of any adverse reactions (ADRs). All suspected serious adverse reactions and non-serious, known and unknown due to the drug have been reported to responsible for Pharmacovigilance of the Hospital, who has inserted the reports into the National Network of Pharmacovigilance (RNF).

*Results:* In 2014, 63% of 102 naïve patients recruited at U.O.C. of Hematology where were largely (77%) patients diagnosed with non-Hodgkin lymphoma treated with infliximab (Mabthera). A more detailed analysis of the age range of the patients treated with a biologic drug showed a high prevalence of patients over 65 years old at both the UOC of Dermatology and Hematology where that correspond respectively to 57% and 58% of patients recruited in each of these departments. During the survey period considered (2014-2015) the total number of events reported was of 262 and the results of this analysis showed a prevalence of note reactions that reached 74% and not serious 76%. 42% of reported ADRs was unchanged, in 31% was found an improvement in the reported event and for 22% the outcome was placed in a condition of complete resolution. An analysis by System Organ Class (SOC), diseases of the skin and subcutaneous tissue disorders and gastrointestinal disorders were by far the most frequent but were generally not serious.

*Conclusion:* Our data show an acceptable tolerability profile, especially in view of the fact that the largest number of reported events was already known in the Summary of the Product and thus more easily manageable by the doctor. The implementation of the project "Pharmacovigilance on biologics" has undoubtedly been a major breakthrough in the management of the safety profile of these drugs.

**Keywords:** Pharmacovigilance, Biological drug, Adverse Drug Reactions, Monoclonal antibodies, TNF-α antagonists

# The new clinical trial regulation: implications for pharmacovigilance

**Maria Serena De Lucia, Stefano Bonato**

Bayer HealthCare – Pharmaceuticals, Bayer SpA, Milano

**ABSTRACT**

*Background:* Directive 2001/20/EC was superseded by a new one that is more focused on patient safety and ethical protection. So, on 16 April 2014 a new clinical trial regulation has been introduced.

*Methods:* In this observation it was evaluated the differences between the new regulation and the directive 2001/20/CE especially as regards the topics related to Pharmacovigilance. It was analyzed the responsibilities of the Investigators, the Pharmaceutical Companies (industry sponsor), the Health Authority as well as and the Ethics Committees.

*Results:* Over my stage period in a local branch of a multinational pharmaceutical company (Bayer *SPA*) the number of clinical trials were over 80 with about 20 investigational drugs. During the same period, the adverse events reported to Local Pharmacovigilance department were over 2,500. According to new regulation, to the Sponsor will be reported also all the adverse events (but not SUSAR) that may impact on the benefit/risk profile of the development drug, within 7 or 15 days according to the seriousness criteria.

*Conclusion:* In view of that it has been calculated that additional 5,000 cases of adverse events (not SUSAR) will be reported after coming into force of new Directive so owing to that the Local Pharmacovigilance department will have to dedicate 2 additional officers for such a task to the present one. It has been estimated, so, that there will be a threefold increase of workload, with all related implications in terms of time, human and economical resources.

**Keywords:** Directive 2001/20/EC, Regulation (UE) no 536/2014, AE, SAE, SUSAR.

# Evaluation of the signal of stroke in patient treated with growth hormone during childhood

**Benedetta Ferranti**

Safety Evaluation and Reporting (SER), Worldwide Safety and Regulatory (WSR), Worldwide Research and Development (WRD), Pfizer Italia srl. Pfizer Group Inc., Milano

**ABSTRACT**

In August 2014, a publication from the French Safety and Appropriateness of Growth hormone treatments in Europe (SAGhE) study, which evaluated the risk of both ischaemic and haemorrhagic stroke in patients taking somatropin, identified an increased risk of haemorrhagic stroke among patients treated with growth hormone (GH) during childhood (Poidvin et al., 2014). Upon release of the publication, the Company (Pfizer Inc.), Marketing Authorization Holder (MAH) of Genotropin® (somatropin), categorized the findings from the publication as a new safety signal and initiated its signal evaluation process. Further, in the Preliminary Assessment Report (PAR) dated 12 September 2014 for the somatropin Periodic Safety Update Report (PSUR) covering the reporting period of 01 April 2011 through 31 March 2014, the Assessor requested the Company to comment the impact of the Poidvin et al. publication on the risk benefit of somatropin, the need for additional risk minimization measures and the need for inclusion of information on a possible increased risk of haemorrhagic stroke, subarachnoid haemorrhage and intracerebral haemorrhage in the Summary of Product Characteristics (SmPC)/Patient information leaflet (PIL).

Review of safety database data were initiated as well as a Benefit –Risk Evaluation was performed. The review of cases reporting cerebrovascular disorders did not reveal an increased risk of stroke with somatropin. Cases retrieved from the safety database were either confounded by other factors, or missing essential information for a meaningful assessment.

The Company concluded that the benefit-risk balance remains positive and unchanged for somatropin. The known safety profile is consistent with the reference safety documents. The Assessor's requests were addressed by the Company and due to several limitations of the published study by Poidvin et al., the Rapporteur agreed that the causal relationship between GH treatment and stroke remains uncertain. The Rapporteur concluded that the revision of SAGhE study does not change the current somatropin benefit-risk balance, and do not support an update to the SmPC/PIL or further risk minimization measures based on the new data.

**Keywords**: Subarachnoid hemorrhage, Intracerebral hemorrhage, Ischemic stroke, Benefit/risk evaluation, Safety database

# ADRs of the triple therapy for chronic hepatitis C and hepatic cirrhosis in adults

**Sabrina Gambino[1], Gabriella Di Fresco[1], Fabio Tinè[2]**

[1] Farmacia, P.O. Cervello, Azienda Ospedaliera Ospedali Riuniti Villa Sofia-Cervello.
[2] Gastroenterologia, P.O. Cervello dell'Azienda Ospedaliera Ospedali Riuniti Villa Sofia-Cervello

**ABSTRACT**
*Background:* Hepatitis C is an inflammatory disease of the liver caused by a hepacavirus (HCV). This disease is asymptomatic in most of the cases, and it may remain so for decades, but this disease becomes chronic in 85% of cases, and as such may progress to liver cirrhosis and hepatocellular carcinoma (HCC). The standard antiviral therapeutic treatment involves a dual therapy, that is, the association between pegylated interferon alfa-2b (PegIntron) and ribavirin (Rebetol), of variable duration depending on the viral genotype; but this therapy gives unsatisfactory results in cases of hepatitis C genotype 1. In this regard, in adult patients with HCV genotype 1, the new therapies lead to the association of protease inhibitors of hepatitis C to the dual therapy; this new regimen is defined triple therapy. The triple therapy, however, causes significant adverse reactions, primarily anemia, thrombocytopenia, leukopenia, but also skin rash and metallic taste.
*Objectives:* To evaluate the adverse drug reactions (ADRs) caused by this triple therapy in a group of 11 patients with chronic hepatitis C and compensated liver cirrhosis.
Methods: Individuals enrolled in this study were patients with chronic hepatitis C and compensated liver cirrhosis under treatment at the Unit of Gastroenterology of the P.O. Cervello of the A.O.O.R. Villa Sofia-Cervello and, in the specific case, a group of11patients followed in acourse of treatment, which lasts one year, with the triple therapy.
*Results:* During this period, 16 ADRs, which occurred during the administration of triple therapy in 11 patients, were found; these ADRs were caused in some cases only by one of the three drugs (telaprevir or boceprevir + peginterferon alfa plus ribavirin), but in some cases by all three, giving rise to different adverse events.
*Conclusions:* The data obtained from the analysis of adverse events confirm that the triple therapy shows a profile of intolerability significant in terms of safety for patients treated as suggested by phase 2 clinical trial and confirmed by post-marketing surveillance. Then the benefit/risk profile of these drugs is confirmed to be unsatisfactory even in this small sample of patients in a clinical practice setting.

**Keyword:** Liver, Chronic hepatitis, Liver cirrhosis, Dual therapy, Triple therapy

# Clinical risk management of intravitreal therapies for the treatment of maculopathy: an example of root causes analysis

**Raffaella Guida, Maurizio Pensa**

A.O.S.G Moscati, Avellino

**ABSTRACT**

*Background:* A program of Clinical risk management analyzes adverse events by using reactive and proactive methods. The Root Causes Analysis (RCA) is configured as a reactive method that studies accidents ex post, and is aimed both to determine their causes and to evaluate the quality and the safety of the patient in order to ensure a safer healthcare process.

*Methods:* The RCA is a step in the process of the Clinical Risk Management, so it has been chosen as a method for the analysis on intravitreal treatment clinical risk for patients suffering from maculopathy. It was identified a test team, and then was selected the adverse event to be submitted in RCA. Once the causes that led to the event have been identified, corrective actions have been proposed.

*Results:* In the first step, the process has been mapped, and then stakeholders and activities have been identified. RCA allowed to evaluate a deviation from ordinary procedures on the day that an event occurred, and to identify the three root causes that led to the error: no written procedures and guidelines, excessive workload for clinicians and nurses, and shortcoming of computerization of the path. The proposed solutions have had all the objective of increasing patient safety through awareness of health professionals on the subject of risk management.

*Conclusion:* The RCA technique enforcement, further to improve patient safety, allowed to report potential latent failures, to map risks, and plan improvement programs through the application of the recommendations suggested by the analysis team.

**Keywords:** Root Causes Analysis, Macular degeneration, Intravitreal therapies, Risk management

# Screening of non indexed medical and scientific literature: regulatory obligation or something else?

**Simona Masucci, Daniela Bernardini, Matteo De Petris**

Astrazeneca SpA, Basiglio (MI)

**ABSTRACT**

*Background:* Adverse drug reactions (ADRs) represent an important risk for the patient and has a significant economic impact on health systems. Because of this strong impact in public health, regulatory authority worldwide are implementing new pharmacovigilance legislation to promote and protect public health by reducing the burden of ADRs through the early detection of safety signal. The main aim of pharmacovigilance is to provide a safety signal. Marketing authorisation holders (MAHs) should ensure the evaluation of the benefit-risk profile of their medicinal product during its whole lifecycle. Although most of the safety signals originate from reports reported by healthcare professional, relevant safety information can also be obtained from other sources, such as scientific and medical literature. For this reason, marketing authorization holders (MAHs) are obliged to monitor scientific and medical literature as outlined in the Good Pharmacovigilance Practice (GVP) guideline, Module VI (1). In accordance with Directive 2001/83/EC and Regulation (EC) No 726/2004, MAHs shall monitor all other medical literature and report any suspected adverse reactions to the regulatory Authority.

*Aim:* The aim of this project is to identify any possible safety signals related to AstraZeneca drugs through screening of non-indexed literature and to define a pharmaceutical company approach on how periodic non indexed literature researches is performed, to discuss the pro and cons when performing these searches and to highlight any possible value for the detection of case reports and any impact within the company (i.e. interaction with other department).

*Methods:* The periodic screening of paper and electronic scientific local journals was carried out according to GVP. The results obtained after a 22-week analysis have been evaluated. Sixteen scientific journals were monitored. The screening of the journals was performed once a week from July 2014 to December 2014. The presence of ADRs (adverse drug reactions) related to Astrazeneca drugs has been investigated. Furthermore, articles that could have been of interest for every department of the company have been evaluated.

*Results:* A total number of sixteen journals have been monitored from July 2014 to December14. During the screening, no valid cases for reporting to Regulatory authority have been detected. At the same time, some interesting article, for a business perspective (focused on the major therapeutic area of interest for the company) have been identified and shared with colleagues of other department.

*Conclusions:* During the period under review, through the screening of non-indexed literature has not been possible to identify case reports valid and possible to be notified to the regulatory authorities.

**Keywords:** ADRs, Literature screening, Update for MAH, Safety signal

# Evaluation of the quality and effectiveness of Follow up in the Italian Pharmacovigilance Network

**Vanessa Sabatino, Enrico Magni**

ASGENIA srl, Roma

**ABSTRACT**

*Background:* Pharmacovigilance is defined by the World Health Organization (WHO) as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. In the Follow-up section, there are additional information about the initial case report. This information can be entered as a result of specific requests from Pharmaceutical Company or AIFA (Italian Medicines Agency) or Responsible for Pharmacovigilance.

*Methods:* The updated ICSRs (Individual Case Study Report) were processed through a database (SafetyDrugs), a web-based application created to manage the ADR (adverse drug reaction) accurately and simply. The software, using the "compare" function had compared the updated ICSRs with their initial version or it compared the latest updated version, if they had Follow up previously. So the "compare" function had controlled the added/removed data in the updated case reports.

*Results:* The attention of Responsible for Pharmacovigilance frequently is on specific sections of the case report such as "suspect drug" and "adverse reaction" and less interest on sections, important equally, such as "concomitant medications" or "patient medical history etc ..." that they would contribute to provide a clear clinical picture of the patient but a better medical evaluation of ADR, too.

*Conclusions:* Hopefully, the Follow-up quality can still improve, trying to obtain a more uniform and complete distribution of information in the ICSR.

**Keywords:** ADR, ICSR, RNF, Safety drugs application, Follow-up

# Research of ADRs in the scientific and medical literature: proposals for the screening of not indexed local literature

**Angela Scalzo, Enrico Magni**

ASGENIA srl, Roma

**ABSTRACT**

*Background:* Scientific and medical literature is an important source of information for monitoring safety profile and risk-benefit ratio of the drugs mainly related to the identification of new signals needed to improve their safety profile. The most important databases cover the majority of indexed scientific and medical journal however relevant information may be collected in medical fields which are specialized for certain types of products or within sources where the safety of the drug is not the subject of a clinical research. Currently the lack of guidelines and detailed rules by the regulatory authorities for proper investigation of ADRs in the not indexed local literature puts the marketing authorization holders, and therefore the other companies that provide services to these latest, in the condition to not know which sources to be monitored are more proper.

*Methods:* Asgenia make searches for ADRs in the international and national literature through Pharmacovigilance Insight, a very large database that submit it to continuous screening about 8000 journals. Weekly Asgenia receives an "alert" by the database managers according to the marketed active substances and search criteria established by Asgenia for each company. Each ADRs retrieved is processed, transmitted to the companies and stored through the Safety Drugs database.

*Results:* The search for ADRs in the local literature does not allow a broad detection of significant signals, while searching for reports from not indexed publications or from particular sources so far not monitored, such as web for example, could provide a precious source of information.

*Conclusions:* The guidelines and rules that currently govern the pharmacovigilance activities do not consider, much less promote, the expansion of these activities through the use of new technologies, such as web searching or in the network conversations, to discover ADRs not reported through traditional channels (Pharmacovigilance National Network), interactions unusual and abnormal connections between use of drugs and special comorbidity. A collaboration between AIFA, Regional Commissions, pharmaceutical companies and administrators of sites containing the most important forum could be an important starting point in order to identify appropriate solutions to develop unconventional pharmacovigilance activities that are necessary to get more complete information.

**Keywords:** Scientific and medical literature, Pharmacovigilance insight, ADR and web

# Effects of the European restrictive actions concerning nimesulide prescription on hepatic and gastrointestinal adverse reactions

**Silvia Scupola, Paola Magnani**

PhAST Consulting srl, Monza (MB)

**ABSTRACT**

*Background:* On 10 April 2002, Finland notified the CPMP (now CHMP) and EMEA (now EMA) Secretariat of a referral under Article 31 of Directive 2001/83/EC as amended, requesting the CPMP to give its opinion on the risk-benefit balance of all nimesulide containing medicinal products, especially in view of the hepatic toxicity. Based on the serious hepatic reactions occurred in the territory and taking into account the relatively non-serious conditions for which nimesulide is indicated for as well as the existence of numerous alternative treatments, the Marketing Authorisations of nimesulide containing medicinal products for oral administration have been suspended in Finland and in Spain on March and May 2002, respectively. Moreover, EMA initiated a new referral in February 2010 for a full risk-benefit assessment of nimesulide. The objective of this work is to evaluate whether the regulatory measures concerning nimesulide have resulted in a change of the gastrointestinal and hepatobiliary adverse reactions reported, considering a time frame of four years, from 2011 to 2014.

*Methods:* We have evaluated case reports both received through the National Pharmacovigilance network (RNF) related to a medicinal product of a pharmaceutical company and collected from medical and scientific literature associated to the active ingredient nimesulide. The information pertained to these case reports were obtained from the pharmacovigilance database in the form of line listings and summary tabulations, one for each of the four years considered. Then an analysis of the occurrence and frequency of total, hepatobiliary and gastrointestinal ADRs has been performed.

The frequency of occurrence of the ADRs has been calculated by considering the number of each group of ADR in relation to the patients' exposure to the drug as sales data.

*Results:* Overall 160 serious and non-serious adverse events regarding to the SOCs Gastrointestinal disorders and Hepatobiliary disorders have been registered in the safety database from 1st January 2011 to 31st December 2014, against a total of 456 ADRs collected during the four years. In 2013 there has been a spike in total ADRs, corresponding to 90% of more reports than 2012 and to 46% more than 2014. Distinguishing serious gastrointestinal- and then, separately, hepatobiliary- reactions from non-serious ones, and expected reactions from unexpected ones, the occurrence of liver reactions proved to be far less than GI ones within which, moreover, it has not been registered any unexpected ADR.

*Conclusion:* The hepatic nimesulide-related ADRs are a rare event. The average frequency over four years was found to be equal to 0.0764% and no deaths, cases of fulminant hepatitis or of liver transplantation occurred. The risk of gastrointestinal ADRs is more frequent, but the frequency of these ADRs with nimesulide is in line with other NSAIDs. The results, even though with the limit of our case reports, confirm that there was not an increase of hepatic ADRs. Then, the measures taken by Health Authorities to limit liver damage due to high doses and/or prolonged treatment with nimesulide can be considered effective.

**Keywords**: Nimesulide, Hepatotoxicity, Gastrointestinal toxicity, Prescription restrictive measures

# Considerations about the inclusion in the National Network of Pharmacovigilance of cases reported by Pharmaceutical Companies

**Alessio Vezzoli, Manuela Colombi**

Janssen-Cilag SpA, Milano

**ABSTRACT**

*Introduction and Aim:* Most recent laws about pharmacovigilance have regulated the collection and submission of ADR reports by pharmaceutical companies, with the intent to increase the number of collected cases and therefore the power of generated signals. As a result of this legislation, companies have increased the collection of cases from sources other than the National Network for Pharmacovigilance and their transmission to AIFA. However not all documents that are sent to the pharmacovigilance responsible person of ASL are then actually added to the National Database: this analysis is to highlight and discuss the different steps of this process and how it could be possibly improved.

*Methods:* The analysis was performed on the database of Janssen-Cilag SPA, with queries by year, from 2006 to 2014, and by case origin: Poison Control Center (CAV), non-interventional studies and health care professionals (HCP), directly or via sales representatives. Results were entered into an Excel spreadsheet, using which it was possible to generate graphics, which allowed the rapid visual identification of the ratio between cases sent and included in the National database.

*Results:* The percentage of inclusion looks rather scarce, but not equally distributed: reports from Health Care Professional are quite often included in the National Database, but the same does not happen to those from CAV or non-interventional studies. The aggregated data show a positive trend over time, but about 50% of cases are lost.

*Discussion:* We deem this analysis to be interesting, also in consideration of the future development of Eudravigilance. It is necessary to raise awareness of local managers to the importance of entering into the National database all of the cases transmitted from pharmaceutical companies. If resources for this type of job are minimal or missing, it is necessary to start evaluating the possibility for pharma companies to send these reports directly to Eudravigilance, once it will be declared fully operative. This decision needs a new piece of National legislation.

**Keywords:** National Network for Pharmacovigilance, Eudravigilance, AIFA, Databases, Records