Riassunti delle relazioni finali dei progetti di ricerca svolti dagli studenti nell'ambito del tirocinio formativo del master per l'anno accademico 2014-2015

Readability text of the labelling and package leaflet for medicinal products for human use

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ABSTRACT

Directive 2004/27/EC of the European Parliament (which amends Directive 2001/83/EC), transposed in Italy with the Legislative Decree 219/2006, states that all the information reported both in the package leaflet and in the labelling shall be easily legible, clearly comprehensible and indelible and that labelling shall reflect the results of consultations with target patient groups (Readability test) to ensure that the information contained are clear, readable and indelible to ensure patients a correct use of the medicinal products. The comprehension of the information reported in the package leaflet and labeling should help patients for a safer use of the medicinal products, in order to avoid predictable and avoidable risks related. This necessity arises because previously package leaflet reflected the information present in whole paragraphs of the SmPC, so a difficult language lead to confuse patients. EC directive and local legislative decree should ensure a safe use of the medicinal products through the help of the various Guideline that guide MAH to the drafting of a package leaflet "patient friendly". Before implementing the new leaflet, MAH should test the PIL content readability and get approval by the competent Health Authorities.

Keywords: Readability test, Package leaflet, Directive 2004/27/EC, Legislative Decree 219/2006.

"ISO-like Quality System in a Marketing Company": assessment of KPIs in pharmacovigilance activities

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ABSTRACT

Background: A range of new tasks and streamlined existing responsibilities for regulators and the pharmaceutical industries was introduced with the publication of the pharmacovigilance legislation by the European Medicine Agency (Directive 2010/84/EU, Regulation EU N. 1235/2010 and the Implementing Regulation 520/2012) with the primary aim to strengthen and rationalize pharmacovigilance activities and increase patient safety. In this regard, the directive EU 2010/84 specifies that each Marketing Authorization Holder (MAH) has to develop and maintain a Quality System (QS) for pharmacovigilance suitable to detect and control any issue impacting on the benefit-risk profile of the authorized medicines.

Aims: The primary aim of the study was to assess the KPIs that describe both quality and compliance of specific pharmacovigilance activities within the Italian AstraZeneca MC: the Quality Control (QC) process of ICSRs sent to the global safety database (Data Entry Site - DES); the timing for the submission of ICSRs to DES; the timing for the submission of ICSR Expedited to the Regulatory Authorities (RA). As secondary aim we compared the performance of ICSRs sent monthly to the DES by the Italian AZ MC with that of other European MCs.

Methods: The Italian MC has implemented a reporting quality system to manage the ICSRs sent to DES and to the RA. Therefore, we have evaluated the performance of this reporting system using specific KPIs:

1) a quality KPI, with a target threshold set to ≤2%, consisting of the percentage of ICSRs with error sent to DES and detected monthly during the QC process;
2) a compliance KPI, with a target threshold set to ≥97,5%, consisting of the percentage of the ICSRs sent monthly to DES on time;
3) a compliance KPI, with a target threshold set to ≥95%, consisting of the percentage of the ICSRs sent monthly to RA on time.

Then, we have compared the performance of the Italian MC with that of the whole group of MCs (GLOBAL). Moreover, we have selected the main European AZ MCs according to the number of ICSRs managed over the 2015 and we have divided them by the modality of reporting in two subgroups: the AZ MCs with an Italy-like reporting system (Italy, Spain and Belgium), and the AZ MCs with a different reporting system (UK, Sweden and Finland).

Results: As regards the quality KPI, we found that, during the observation period of one year, the target threshold was never achieved with a large monthly variability in the error percentage (range 2,6%-19,0%), without a correlation between the number of controlled ICSRs and the percentage of cases with error. Concerning the compliance KPIs we found that the percentage of the ICSRs sent on time to DES and to RA were always over the target thresholds for all the observed period, thus showing an excellent compliance of the Italian AZ MC. On the contrary, the data observed from the global AZ MCs showed a discontinuous trend with the target thresholds not always reached. Moreover, we found that the European AZ MCs with an Italy-like reporting system had a performance better than the AZ MCs with a different reporting system.

Conclusion: Our results show that the pharmacovigilance activities of the Italian AZ MC need to be improved with regard to the quality of ICSRs sent monthly to DES. However, the compliance of ICSRs sent to DES and sent to RA is markedly over the target thresholds, especially when compared to the performance of the other European AZ MCs. The continuous assessment of KPIs is a pivotal activity to improve and maintain the quality requirements of a pharmacovigilance system within a Marketing Company and represents the best way to guarantee a successful and efficient quality system.

Keywords: Pharmacovigilance system, GVP Module I, ISO 9001, KPI, Quality System.

Considerations about medication errors and their implications in the management of diabetes therapy

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ABSTRACT

Background: The European Medicines Agency (EMA) has developed specific guidance to support pharmaceutical industry and Regulatory Authorities involved in the reporting, evaluation and prevention of medication errors. It has been estimated that 18.7-56% of all adverse events that occur during hospitalization are due to medication errors.
Objective: The aim of this project is to analyze the data from the reports of the National Network of Pharmacovigilance involving medication errors, in order to assess their impact in terms of adverse drug reactions (ADRs) and their implications on management of diabetes therapy.
Methods: From the company's database of Novo Nordisk, all individual case reports (ICSRs) associated with medication errors and received from the National Network of Pharmacovigilance in 2015 were extrapolated and analyzed.
Results: 28 ADRs reported in the Italian Network of Pharmacovigilance were caused by a medication error (9% of the total). The majority of ADRs are severe hypoglycemia due to different type of error linked to dose, wrong drug and maladministration of diabetes therapy.
Conclusion: The quality of ICSRs is essential in order to properly evaluate the ADRs due to medication errors. After having identified the error and executed strategies to mitigate it, the company should track whether these corrective actions reduced errors and improved patient safety.

Keywords: Pharmacovigilance system, GVP Module I, ISO 9001, KPI, Quality System.

Adverse drug reactions reporting in Emergency Medicine Department: the Italian active pharmacovigilance project MEREAFaPS

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ABSTRACT

Objective: The main objective of the Italian active pharmacovigilance project MEREAFaPS (Monitoraggio Epidemiologico di Reazioni ed Eventi Avversi da Farmaci in Pronto Soccorso) was to describe frequency and characteristics of the adverse drug reactions (ADRs) leading to emergency department (ED).

Methods: This study was a prospective cohort one. It started in 2006 and included 94 Italian EDs. We presented a preliminary analysis evaluating records collected between April 2012 and September 30, 2014. Data are presented as numbers and percentages.

Results: The analysis included 29,648 ADR reports (0.3% of overall ED admission) and investigated 53,648 ADRs and 37,331 suspected drugs. Forty-one point one% of reactions (12,197 out of 29,648) was classified as serious. Twenty-two point eight% of reactions regarded skin and subcutaneous tissue disorders (12,252 reports), 17.1% gastrointestinal disorders (9201 reports), and 10.8% nervous system disorders (5803 reports). Seven point eight% of total ADRs presented warfarin as suspected drug, followed by amoxicillin in combination with clavulanic acid (6.7%), and acetylsalicylic acid (5.7%).

Conclusions: ADRs are a serious health issue in EDs. We present a clear picture, reporting on the frequency, seriousness, and preventability of drug-related visits to the ED.

Keywords: Adverse Drug Reaction, Economic Impact, Emergency Department, Pharmacovigilance, Preventability.

Biosimilar medicinal products: a review of requirements for approval and a proposal for integration of company procedures

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ABSTRACT

Biosimilar medicinal products are biopharmaceutical that have been assessed by Regulatory Agencies to have efficacy and safety similar to their reference products (comparators or innovators), and are approved by these Agencies according to specific evaluation pathways. For approval, a comprehensive dossier of analytical, preclinical, pharmacokinetic, pharmacodynamics and clinical data that demonstrates efficacy and safety comparable to those of its off-patent reference biopharmaceutical is required. This work provides an analysis of different requirements for biosimilar approval and a suggestion for specific procedures for Pharmaceutical Companies for biosimilar development.

Keywords: Biosimilar, Biological medicinal product, FDA approval, EMA guidelines.

Monitoring of adverse drug reactions in the emergency department of Rieti

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ABSTRACT

Introduction: In Europe, over the last years, much has been done to improve the post-marketing drug surveillance and pharmacovigilance systems. Adverse drug reactions (ADRs) have a considerable negative impact on healthcare costs, causing 3% to 5% of all hospital admission, 5% of all the already hospitalized patients develop an ADR and they are the fifth highest cause of death in hospital.

The Emergency Department presents the best opportunity for the monitoring of adverse reactions, also in consideration of the fact that the events that bring the patient into the ED are potentially more severe and therefore of great clinical importance.

Aims: To determine the incidence of ED visits due to ADRs of total admissions, differentiating by age and gender, and to analyze the reactions that occur more frequently, the drug classes (I Lev. ATC) and active ingredients mainly involved.

Methods: After an initial research of ADRs from 2011 to 2015 in the reports of the emergency department of Rieti (ED) through ICD-9 codes, it was verified that only the code 99527 - "Other Drug Allergy" was utilized. Furthermore the reports of the year 2015 closed as other drug allergy were analyzed in details. After verification and integration of missing information, the suspected adverse reactions have been included in the national pharmacovigilance network (RNF).

Results: The most represented age group is between 51-65 years, the majority of which is female, severe reactions were 71.4% for both male and female. The more involved ATC class is J (antibiotics) and the reactions that occurred more frequently are the diseases of the skin and subcutaneous tissue.

Conclusions: In the Emergency Department, a pharmacist facilitator would be helpful within an active pharmacovigilance program, who would be useful for the training of the staff and for analyzing results.

Keywords: Pharmacovigilance, Adverse Drug Reactions (ADRs), Emergency Department, Italian National Pharmacovigilance Network.

PMS-RMP: from the screening for HLA B*5701, as a tool of differential analysis in the management of HIV-infected patients, to the positivity of abacavir benefit-risk balance

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ABSTRACT

Background: The multisystem clinical pattern of the HIV-infected patient is associated with the multifactorial approach of medical therapy, the aim of which would be the "right patient", to ensure the beneficial results expected rather than an increased clinical risk, often preventable and therefore avoidable. Post-Marketing Surveillance is a main actor in the achievement of this goal, through intensive monitoring, trying to bridge the gap between clinical efficacy and therapeutic effectiveness, collecting and then analyzing all ADRs potentially caused by HIV therapy with ABC. The results obtained from these activities allowed: first, to identify the correlation between the use of ABC and the incidence of HSR (hypersensitivity reaction) in treated patients; subsequently it gave evidence to the hypothesis that HSR is a pharmacogenetic effect, due to the presence of the HLA B * 5701 gene in some individuals, thus highlighting a valuable tool in the therapeutic management of HIV infected patients.

Aims: Define the benefit-risk profile of abacavir, throughout abacavir history, to retrace the procedural steps taken and achievements obtained by pharmacovigilance which, thanks to the collection, analysis, signal detection and risk management, expanded its horizons, promoting the effective and safer use of ABC.

Methods: The analysis has been carried out evaluating the data of Individual Case Reports (ICSRs) extracted from the Italian National Pharmacovigilance Network (RNF) related to Ziagen© tablets and oral solution, Trizivir© and Kivexa© tablets, in which ABC is one of the active ingredients, in years 2000 - 2015. These data were crossed with the database of GSK Pharmacovigilance Dept. regarding exposure data of the above drugs; we assessed how, in the light of risk management activities implemented, the relation to the ABC exposure and the evolution of knowledge about HSR changed.

Results: The rate of patients reporting suspected HSR to ABC is around 2%; the number of life-threatening or fatal reactions remains small despite a large increase in the number of patients treated with ABC, also thanks to a better quality of information.

Conclusions: No new safety concerns were raised, the risk minimization measures continue to be effective via routine pharmacovigilance activities, the safety profile remains positive after 16 years of marketing experience in the treatment of HIV infection.

Keywords: Drug Hypersensitivity (HSR), Human Immunodeficiency Virus (HIV), RMP, Abacavir (ABC), Safety.

Analysis of Adverse Drug Reactions to medicines under additional monitoring

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ABSTRACT

Background: The three main common points prior to submission a new drug application are quality, efficacy and safety. Whereas the first two criteria must be satisfied before any consideration can be given approval, the issue of safety is less certain. Safety is not absolute and it can be judged only in relation to a positive benefit-risk balance. It is then necessary that the safety of all medicines is constantly monitored throughout the whole period in which the product is on the market. Pharmacovigilance, or drug safety monitoring, is an essential element for the effective use of drugs and for high quality medical care. There is a special kind of monitoring called "additional monitoring" for drugs with limited information available, for example because they are new to the market or there is limited data on their long-term use, for medicinal product for which a new safety concern has been identified, and for all biological medicinal products. The European Medicines Agency (EMA) is responsible for drawing up the List of medicines under additional monitoring and the aim is to raise awareness and encourage health professionals and ordinary citizens to report any adverse drug reactions (ADRs) to all the medicines on the List.

Aims: To carry on a qualitative and quantitative analysis of reports of medicines under additional monitoring in the Lombardy region, with a focus on the reports from the University Hospital "Luigi Sacco".

Methods: We selected and analysed the spontaneous reports in National Network of PharmacoVigilance Database, limited to Lombardy Region, from 1st January 2001 to 31st December 2015. We retrieved the List of medicines under additional monitoring by the web portal of the EMA, using the most up to date version from December 2015. Data were analysed in respect to the total number of reports, gender and age of the average patient involved in ADRs; in relation to their seriousness, outcome, and belonging to a System Organ Class (SOC). We focused the medicines under additional monitoring more involved in ADRs in Lombardy and at University Hospital "Luigi Sacco".

Results: The female patients were mostly involved in ADRs reports and the greatest numbers of ADRs cases were observed in the age groups 18-64 years old and over 65 years old. The 41% of total ADRs reports retrieved were classified as serious, and the 55% not serious. The most serious ADRs leading to hospitalisation and extended stays in hospitals were the 60%. Nevertheless, in general the ADRs were completely resolved. Skin and subcutaneous tissue disorders (23%), gastrointestinal disorders (17%) and blood and lymphatic system disorders (17%) were the SOCs most frequently occurring. Revlimid®, Depakin® and Tysabri® were the most drugs involved in ADRs reports. The most recurrent Anatomical Therapeutic Chemical Classification System (ATC) was class L, namely antineoplastic and immunomodulating agents. For medicines under additional monitoring at University Hospital Luigi Sacco 22 drugs were reported, which resulted in 85 ADRs. The quality of ADRs and the predominant gender affected matched with the data recorded for Lombardy.

Conclusions: In our analysis, we confirmed that medicines under additional monitoring often result in serious ADRs, in accordance with the data of the international scientific literature. However, we have verified the insurgence of ADRs that are unknown at the moment. This has helped us to further understand how these medicines must be carefully monitored.

Keywords: Pharmacovigilance, Addition Monitoring, List, ADRs, National Network of PharmacoVigilance Database.

Concomitant usage of ibuprofen and paracetamol in the treatment of fever in pediatric age: a winning couple or an unnecessary risk?

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ABSTRACT

Background: The Italian report on the National Drug Administration "Osservatorio Nazionale sull'Impiego dei Medicinali (OSMED)" related to 2015 shows that ibuprofen and paracetamol were respectively the second and the third molecule of self-medication that were bought in that year, a trend which was confirmed also in the report of 2014. These data have confirmed once again that they are two of the most administered drugs in Italy. Paracetamol and ibuprofen have been on the market since decades and they are the only antipyretic and the only Non-Steroidal Anti-Inflammatory Drug (NSAID) to have a pediatric indication for fever and pain treatment. Recently, a new therapeutic treatment appeared in adults, which is the alternated or combined usage of paracetamol and ibuprofen to treat fever and acute pain. Being a successful combination in adults, and present in every house, these two molecules are often administered off-label also to treat feverish children. Due to the complexity of these therapeutical regimens, parents and HealthCare Professionals (HCPs) often commit medication errors as over dosage. In November 2010, the Italian Competent Authority "Agenzia Italiana del Farmaco" (AIFA) was forced to write a Recommendation about the usage of NSAIDs and paracetamol in children due to an increase of Adverse Drug Reaction (ADR) reports starting back in 2006, especially for ibuprofen. This trend was confirmed in the OSMED report of 2014 in which ibuprofen and paracetamol are among the first 14 molecules (in 2014) and 20 molecules (in 2015) with the highest number of reports.

Objective: To characterize and evaluate the efficacy and the safety of alternated or combined use of paracetamol and ibuprofen compared to monotherapy and to demonstrate, in favour of the monotherapy, that the alternated or combined use of paracetamol and ibuprofen is not strictly necessary.

Methods: Screening of PubMed and Google Scholar databases was performed by using keywords. Safety data were obtained from the Italian Pharmacovigilance Network (Rete Nazionale di Farmacovigilanza, RNF) in the period between 1st of January 2013 and 1st July 2015 using the account of Boehringer Ingelheim Italia S.p.A. (BITSPA). Then the American Early Drug Alert database and Summary of Product Characteristics (SmPC) of most known antipyretics for children were used as other sources of data.

Results: What emerges from the available literature, consisting in clinical trials and systematic reviews, is the higher efficacy of combined or alternated use of paracetamol and ibuprofen respect to the efficacy of monotherapy; on the other side, however, it is not able to give a clear idea on safety and on the reduction of children discomfort. Due to this nebulous evaluation, the majority of international guidelines are sceptic about the usage of this new treatment and they advise to use paracetamol or ibuprofen singularly. The four case reports retrieved through the RNF screening seem to confirm this uncertainty by showing an apparent increase in child discomfort and a worsening of children's clinical conditions.

Conclusions: Despite the alternate and combined use of paracetamol and ibuprofen is widespread, there is the lack of valid scientific evidences that certify their higher efficacy compared to the single use of paracetamol or ibuprofen to treat feverish children. In addition, initial doubts about the safety of this new treatment are rising. In this confusing situation, where also International Medical guidelines are not able to come to an agreement with each other to decide which the right clinical protocol is, it is advisable to use the monotherapy.

Keyword: Paracetamol, Ibuprofen, Fever phobia, Medication errors, Children.

Evaluation and handling of procedures regulating the quality and safety information flow between a Contact Research Organization and parties involved in medicinal products commercialization

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ABSTRACT

Background: Pharmaceutical companies respond to the challenges of decreasing productivity and increasing costs by relocating part of their activities to Third Parties (TPs). TPs are defined as all those players entering at different levels and with different roles into the Pharmacovigilance (PhV) supply chain. For instance, licensee, sales dealer, distributor, producer and eventually an external company such as a contract research organization (CRO) are all actors with whom the MAH can have a partnership. Even if the nature of the contracts between the actors might be different, the PhV Quality System (QS) must always be guaranteed at every level of the supply chain in order to be compliant with the current legislation and to ensure a constant evaluation of the risk/benefit ratio for a given medical product.

Objectives: Aim of the present project is to analyze and evaluate the different procedures and requirements apt to guarantee constant information flow regarding the safety data to fully satisfy customer needs and expectations. Instruments to assure a quality system within a CRO will be reviewed.

Methods: A contract research organization supports several pharmaceutical companies that market many different medical products by offering a complete range of PhV activities. A CRO has been examined in order to study which are the approaches that are currently undertaken to guarantee the highest standard quality in the management of the safety information flow. Quality internal procedures, Third Parties agreements and PhV internal quality tools have been analyzed.

Results: The analysis performed, shows that quality systems in a CRO operate at different levels. One first level takes into consideration all the internal actions that a CRO implements as operative instruments to efficiently regulate and monitor processes that take place inside the Company (internal quality system). A second level, instead, considers all the actions undertaken by the CRO to satisfy external partner needs and expectations (external quality system).

Conclusions: In order to provide high quality products and services to fully satisfy customer needs and expectations, and to guarantee the legal obligations of the MAH towards the authorities, CROs are required to establish, manage and monitor their internal quality system in PhV and both, CRO and customer need to monitor the exchange of information concerning the activities that have been outsourced.

Keyword: Pharmacovigilance, Quality System, Standard Operating Procedures, Pharmaceutical Company.

Comparative safety profile of biosimilar and originator erythropoietins: data from the Italian spontaneous ADR reports database

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ABSTRACT

Background: Biosimilars are medical products derived from biological sources, similar to the reference products (originators) for which patent is expired. The similarity between originators and biosimilars is investigated through a stepwise head-to-head comparison but some differences, intrinsic to the production process, can compromise efficacy and security of biosimilars. Mainly for this reason, in Italy, biosimilars of erythropoietin (EPO) are accepted with skepticism by clinicians. We conducted an analysis to compare the safety profile between originators and biosimilars of EPO, on the basis of adverse drug reaction reports in the Italian database (RNF).

Methods: Reports of suspected Adverse Drug Reactions (ADRs) due to EPO, between 1 January 1991 and 30 September 2015, were extracted from RNF. ADRs were coded using MedDRA terminology. To evaluate the correlation between drug use and occurrence of ADRs a disproportionality analysis through Reporting Odds Ratio (ROR) was performed. An analysis for drug-reaction pairs and a comparison between all originators vs biosimilars was applied.

Results: Four hundred and thirty-six ADR reports associated with EPO, 57% related to originator, were retrieved. The main source of reporting for both drug categories were hospital doctors. Patients characteristics were comparable among originators and biosimilars groups, but some differences has been detected between the Italian regions. Most reports concerned products containing EPO-alpha (Eprex®, Binocrit® and Retacrit®). For biosimilars, significant disproportionality was observed for headache (ROR 4,01; CI 95% 1,24-12,91), sickness (ROR 4,80; CI 95% 1,29-17,91), drug ineffective (ROR 4,26; CI 95% 1,94-9,35) and lack of therapeutic response (ROR 8,19; CI 95% 2,35-28,57).

Conclusions: No new safety signals have been found. The ADRs related to therapeutic inefficacy of biosimilars probably are not due to quality concerns, but they could be interpreted also as the attempt to switch from biosimilars to originators. Also evidence from literature confirm the similar efficacy and safety profiles between biosimilars and originators containing EPO. Clinicians should be encourage to prescribe biosimilar erythropoietin.

Keywords: Bbiosimilar, Eerythropoietin, Epoetin, Pharmacovigilance, Adverse Drug Reaction.

The computerised prescription and pharmacist's notes: a method to decrease medication errors

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ABSTRACT

Background: The Ministerial Recommendation No. 7 suggests the tools to reduce medication errors, which occur during the main phases of the medication management process in the hospital, points out how the Health Authorities should choose appropriate solutions (eg. Computer technology and methodologies of work) to provide a therapeutic treatment that is correct and complete in all its aspects. Doing just that, the Perugia Hospital adopted "Galileo e-Prescribing", an electronic health record and clinical repository, which has the aim to reduce medication errors during the prescription and administration phases and allows the physician to send orders and oversee laboratory, radiology and anatomical pathology reports. However, it allows the pharmacist to oversee and evaluate the appropriateness of therapy through pharmacological assessments entered in "the pharmacist's note" field.

We have monitored the daily drug prescriptions and laboratory analysis of each patient in each of the wards present on the electronic health records. Literature data demonstrated that many adverse reactions involving the chemical-clinical parameters are caused by drugs, an example being the thrombocytopenia induced by angiotensin receptor blockers. Other examples are the alterations in lipid and blood sugar levels associated with the use of antidepressants and the onset of type A and B liver damage (eg. acute hepatitis by ACE-inhibitors).

Objective: The aim of the pharmacist's note was to encourage the correct use of drug prescription and administration by proposing the possible side effects of prescribed drugs repeatedly on the "Screen Alert" to help the physician make the right therapeutic choice.

Methods and Results: The literature data has been researched using Pubmed, pharmacology texts and Summary of product characteristics (SmPC). The collected data allow us to enter information into "the pharmacist's note" about the possible clinical data alterations caused by each administered drug.

Eighty-six notes have been entered into the clinical repository "Galileo" based on the collection of scientific data in order to set a constructive dialogue with physicians about choosing the right drug in the presence of patient laboratory data alterations. The most chemical-clinical parameters analysed were: platelets, blood glucose, triglycerides, alkaline phosphatase, amylase, lipase, creatinine, and erythrocyte sedimentation rate.

Conclusions: The main benefit of the computerised prescription system is the reduction of clinical risk derived from occurred errors during the prescription phase. The pharmacist's note is an important tool that can functionally communicate with physicians to prevent adverse events and to decrease prolonged hospitalisations due to medication errors.

Keywords: Medication errors, Galileo e-Prescribing, the Pharmacist's note.

Description of methods used to maintain under control the Medical Literature Monitoring (MLM) performed by EMA

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ABSTRACT

Background: Article 27 of Regulation (EC) No 726/2004 sets out the provisions for the monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agency. The medical literature monitoring (MLM) service covers a range of active substances including herbal active substances as well as designated medical literature based on the use of literature reference databases.

Aim: The aim of this project is to describe the process and the methods to manage the MLM search and to report some results associated to a medicinal product, containing as active ingredient diclofenac, as observed during a period of about three months.

Methods: According to the PhAST procedures, we check at least once week the list of ICSRs found by EMA in order to select and download the reports of interest for the client company. Case reports related to client companies are downloaded from the EV ICHICSR Export Manager and entered into the safety database for signal detection purposes and for the preparation of periodic reports.

Results: During this period, we received 5 case reports associated to diclofenac in MLM. The confirmed case reports were imported in our database all together with other cases found from the weekly search performed through "Reactions Weekly" by avoiding duplicated cases. The reconciliation of the literature case reports on diclofenac have demonstrated that the cases found in MLM do not always coincide with those reported on Reactions Weekly. Only one reference article (Scherneck S. et al., 2015) was found in both searches.

Conclusions: The use of MLM service allows to increase the number of cases found with other methods of weekly literature search and can facilitate companies due to the fact that these cases can be imported into our pharmacovigilance databases. However, at the present, this is an adjunctive work because it does not substitute our literature search and all companies had to update the standard operating procedures (SOP) to manage the weekly literature search.

Keywords: MLM, EV ICHICSRs, Export Manager, Diclofenac, XML, Module VIGVP.

EMA Medical Literature Monitoring service: the impact on Pharmacovigilance activities of Marketing Authorization Holders

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ABSTRACT

Background: The scientific and medical literature is a significant source of information for monitoring the safety profile and the risk-benefit balance of medicinal products. To improve safety monitoring of active substances and simplify pharmacovigilance activities for companies, European Medicine Agency (EMA), through Medical Literature Monitoring (MLM) service, has become responsible for monitoring selected medical literature for reports of suspected adverse drug reactions related to certain active substances of medicines authorized in the European Union.

Aims: To evaluated the effects of MLM-service, highlighting its benefits and limits and its impact on the daily pharmacovigilance activities.

Methods: Description the process of literature screening conducted by the EMA provider and the consequential management activities implemented by Marketing Authorization Holder (MAH) after the introduction of MLM service.

Results: The introduction of the new system has changed the Company's approach toward the literature monitoring, resulting in a more difficult management of this activity with scarce advantages with respect the expectations.

Keywords: Literature, MLM service, ICSRs research.

Management of the processing case quality system in Asgenia Srl

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ABSTRACT

Background: With the development of pharmacovigilance (PV) system, a quality system that would guarantee the validity of data was necessary. Regulatory agencies have made it clear that quality is integral to drug safety, and pharmacovigilance quality systems constitute the foundation of pharmacovigilance operations. The importance of properly established and managed quality control and quality assurance systems with their integral well-written Procedure Operative Standard (SOPs) and other quality documents for the achievement of Company business objectives cannot be ignored. One of the instruments reported on SOPs are the Key Performance Indicators (KPI). KPI are indicators that provide information for measuring how well a pharmacovigilance programme is achieving its objectives.

Aims: Aim of this project is to check the quality system in processing case in Asgenia Srl.

Methods: To perform this analysis the reference source was the internal SOP_QA_3.0 "Gestione della qualità". Different cases processed by Asgenia between November 2015 and February 2016 were the source of information. Some of the Key Performance Indicators (KPI) reported on the SOP_QA_3.0 were considered and monitored; they were applied on the processed cases.

Results: The analysis of the data showed that Asgenia's procedures in processing case and its quality control system are effective. Despite this, trying to improve and optimize results is necessary since the concept of quality although quantity is not absolute.

Conclusions: Trace the activities carried out and demonstrate their compliance with legislation are the bases to ensure the effectiveness and efficiency of the quality systems.

Keywords: Pharmacovigilance System, Pharmacovigilance Quality System, Procedure Operative Standard (SOPs), Key Performance Indicators (KPI).

Evaluating the effectiveness of company pharmacovigilance systems through inspections

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ABSTRACT

Pharmacovigilance is one of the most controlled and regulated activities in the pharmaceuticals companies, and great effort, particularly in the European Union, has been made by Regulatory Authorities to assure a complete, effective and continuous monitoring and revision of safety profile of medicines for the purpose of having a safety system that is able to ensure the health of citizens, patients and all stakeholders. These requirements have led to an implementation of inspections practices with high level of attention and professionalism by Regulatory Authorities. The aim of this project was the analysis of the purpose and organization chart of a pharmacovigilance inspection with focus on the drafting of the CAPA (Corrective Action/Preventive Action) plan by companies, on how these activities can improve the management of pharmacovigilance systems and consequently guarantee patient care and safety, and moreover to protect the public health. The inspections, and in particular the inspectors, could not be considered as enemies of companies, rather they are a starting point to examine the shortcomings in Pharmacovigilance activities and to improve and implement the pharmacovigilance systems, always keeping the focus on public health.

Keywords: GVP, Pharmacovigilance Inspections, Pharmacovigilance quality, Quality Systems.

Pharmacovigilance as Hospital activity to prevent ADRs or interactions through the monitoring of prescription for PPIs pantoprazole, lansoprazole in dismissed patients

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ABSTRACT

Background: One of the main roles in active Pharmacovigilance is the prevention of ADRs drug-interactions produced. This paper deals pertinence in prescriptions of PPIs that in Italy represent the type of drugs with higher risk of inappropriateness. The Continuity Therapeutic Pharmacy of Ivrea's Hospital is operative since January 2014. It provides specific assistance for the first cycle therapy to discharge patients from Intern Medicine, Nephrology, and Oncology Departments, and all drugs of direct distribution system. The Hospital pharmacy, in addition to counselling and therapeutic activities reconciliation, monitors some therapeutic classes of drug high-risk unsuitability prescription in discharge: the PPIs.

Aims: To verify if and how guidelines application of ASL TO4 influences PPIs risk interactions. In order to obtain the rational use of PPIs, there is a control activity; especially the Hospital Pharmacist monitors discharge letters appropriateness; presence/absence of AIFA notes and co-prescribed drugs. The TO4 ASL (Torino- Azienda Sanitaria Locale) has also worked in the drafting of PPIs prescription guidelines written by an internal multidisciplinary team in 2015.

Methods and Results: This project compares appropriateness of PPIs prescriptions in the first cycle therapy of dismissed patients from Medicine, Nephrology and Oncology departments between January to April 2014 (first quarter), and January to April 2015 (second quarter) through a retrospective analysis. Results shown a reduction of inappropriate prescriptions in 2015 compared to 2014 of PPIs.

Conclusions: The appropriateness principles observation (evaluating discharge letters, comparing AIFA notes and guidelines) by Doctors and Pharmacists, affects in positively on the prevention of any risk of interactions.

Keywords: PPIs Interactions, Prescriptive Appropriateness, Risk Reduction.

The Pharmacovigilance system of Sanofy Pasteur MSD SpA: compilation of a Pharmacovigilanza Quality Manual

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ABSTRACT

Background: The need for a Quality System in Pharmacovigilance is imposed by the EU Directive 2010/84, which places among the fundamental tasks of a Marketing Authorization Holder (MAH) to possess and maintain a Pharmacovigilance System for fulfilling its legal obligations, adequately sufficient to monitor safety and detect any change in the benefit / risk profile of its authorized medicinal products.

Aims: To write a pharmacovigilance quality manual for SPMSD S.p.A. (referred to as SPMSD Italy hereafter) to be linked with the existing ISO 9001 based quality manual of the organization with the aim of establishing a pharmacovigilance quality policy and describing the pharmacovigilance system for SPMSD Italy, including its organizational structure, responsibilities, procedures, processes and resources as well as appropriate resource management, compliance management and record management. The purpose of this document is geared towards "inspection readiness", to have an effective and efficient control of all local pharmacovigilance processes and to allow, in case of audits or inspections, a rapid collection of all the pertinent information.

Methods: Based on an analysis of the existing legislation, particularly Module I of the GVP and the UNI EN ISO 9001: 2008, we have taken into account the pharmacovigilance system of SPMSD Corporate as described in the Pharmacovigilance System Master File (PSMF) and the quality system of SPMSD Italy as described in the Quality Manual for Health and Safety (Manuale del Sistema di Gestione per la Qualità, Salute e Sicurezza).

The organizational structure, its responsibilities, the pharmacovigilance activities of SPMSD Italy and the interactions with the Pharmacovigilance & Risk Management Corporate Department, were carefully analyzed and the manual was structured according to the processes identified.

Results: Based on the characteristics of the company's organizational structure we:

1) identified all the processes applicable to the local pharmacovigilance;

2) defined the criteria and methods needed to ensure the effective operation and control of the identified processes;

3) identified the parameters to monitor, measure and analyze the processes in order to implement the actions necessary to achieve the expected results and work on continuous improvement of each process.

All of the identified processes have been described using the template available in the Manuale del Sistema di Gestione per la Qualità, Salute e Sicurezza. The PV Quality Manual was finalized as a quality document and included in the Company Quality Documentary System (Issuing Country, ID, version).

Conclusions: The Quality Manual is part of the documentation concerning the quality system of an organization and is the document that establishes the scope of the quality management system, highlights the policies and procedures that govern it and describes the interactions between the various identified processes. We decided to construct a Quality Manual for the exclusive use of Pharmacovigilance but still connected to the organization's existing quality manual. Our ultimate goal was to create a document that allows the organization to have an effective and efficient control of all local pharmacovigilance processes facilitating a rapid collection of all crucial information in case of audits and/or inspections.

Keywords: Quality System, Pharmacovigilance System, Quality Manual, Key Performance Indicators, Audit.

Benefit-risk analysis of a medicinal product: Periodic Safety Update Report assessment under the new pharmacovigilance legislation

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ABSTRACT

The benefit-risk (b/r) evaluation of a medicinal product is carried out throughout its lifecycle to promote and protect public health and to enhance patient safety through an effective risk minimization activity. After a marketing authorisation is granted, it is necessary to continue the monitoring of the benefits and risks associated with the use of a medicinal product in the actual use, to confirm that the risk-benefit balance remains favourable and to characterize the pharmacological profile of the medicine, since preauthorisative studies shows several limitations.

The Periodic Safety Update Reports (PSURs) are pharmacovigilance documents intended to provide an evaluation of the b/r balance of a medicinal product; they are submitted by the marketing authorisation holders at defined time points during the post-authorisation phase. The main objective of a PSUR is to present a comprehensive, concise and critical analysis of the b/r balance of the medicinal product taking into account new or emerging information in the context of cumulative information on risks and benefits. PSURs are submitted for evaluation to National Competent Authorities, and represent a potent tool to investigate the b/r profile of a drug during its postmarketing life.

The European pharmaceutical legislation in force has set up a worksharing procedure to assess the PSURs of all the medicines containing the same active ingredients marketed in EU Countries in a shared way among Member States. This study was aimed to present the procedure in place and to manage this procedure at national level at the Pharmacovigilance Office of the Italian Medicines Agency (AIFA).

Keywords: Risk-benefit ratio, PSUR, PSUSA, EURD list, Delapril.