Riassunti delle relazioni finali dei progetti di ricerca svolti nell'ambito del tirocinio formativo di tutti gli studenti del master per l'anno accademico 2012-2013

Tools and search methods to conduct and create a safety profile of a licensed medicine: the example of Albumin-bound Paclitaxel

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ABSTRACT

Background: In the field of pharmacovigilance and safety of medicines for human use – a very important but particular area of pharmacology and clinical practice – it is essential to acquire expertise in the search methods and techniques useful to identify relevant data in the biomedical-scientific libraries and other electronic resources. In particular, to describe systematically a safety profile of a licensed medicine, we must gain a solid background knowledge of search strategies, syntax, and contents, which often are specific for each database or web resource, together with the capability to build explicit and efficient clinical questions.

Objectives: To purpose a standard model to describe a systematic safety profile of a licensed medicine. We focused our search on a new anticancer drug, Albumin-bound Paclitaxel; our aim was however to approach and describe general strategies to make these methods "replicable" and applicable generically as standard method to other medicines for human use.

Methods: We purpose a project in 2 phases. (1) We first approached large bibliographic, general databases of medical – scientific literature (e.g., Pubmed, Toxnet, Google Scholar, Clinical.Trials.gov). This step brought to the production of a first, completed paper, submitted for publication. (2) In the second step, we approached and searched specific Pharmacovigilance International registries and related Databases, either of public access or with restricted access (restricted to Controlling Authorities, such as Regional Pharmacovigilance Centres, National Entities, or members / participants to special Pharmacovigilance projects or programs).

Results: A comprehensive clinical opinion about the safety of the medicinal product investigated (Albumin-bound Paclitaxel) resulted from the first part of this project; the study showed that searches into "primary" bibliographic resources and generalist databases offer today a comprehensive list of papers and published data to provide the "state of the art" safety profile of a licensed drug. The second part of this study is ongoing, and points to draft and propose standard criteria to design what we call a "systematic safety profile" of a marketed medicinal product.

Conclusions: Generalist safety data about a medicinal product could find its ideal completion approaching and searching individual records, deriving from ICSRs, single case reports of ADRs, and evaluations produced by Controlling Authorities and large international Pharmacovigilance registries. Clinicians and heath professionals in general could have great benefits for both clinical practice and personal expertise, if a systematic safety profile of a licensed drug can be presented in a standardized, "at-a-glance" formatted model, with the final aim to improve quality and perform safe cares.

Keywords: Safety, Adverse drug reaction, Albumin-bound Paclitaxel, Cancer, Cytotoxic drugs

Pioglitazone and bladder cancer: analysis of a signal

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ABSTRACT

Background: Diabetes mellitus type II is characterized by insulin resistance and by progressive dysfunction of pancreatic β cell. Pioglitazone belongs to a class of hypoglycemic medications influencing insulin sensitivity of peripheral tissues. It was approved in 1999 as an oral antidiabetic agent; on September 2010, the FDA issued an alert about the possible relation between pioglitazone prescription and bladder cancer. On June 2011, France removed pioglitazone from the market, while German regulator body, being afraid of such risk, prohibited its use in new therapies. In July 2011, the EMA recommended new contraindications and warnings for pioglitazone in order to reduce the bladder cancer risk.

Objective: To analyze, focusing on the reports of patients who have developed bladder cancer following pioglitazone assumption, pioglitazone safety profile through the consultation of Italian spontaneous reporting system database.

Methods: Data of spontaneous suspected adverse drug reactions (ADRs) were obtained from Italian Rete Nazionale di Farmacovigilanza (RNF) reporting system database. Within this system, all reports related to pioglitazone have been consulted in order to analyze disorders profiles distribution according to the System Organ Class (SOC) classification. Subsequently, reports of patients developing bladder cancer upon pioglitazone assumption have been analyzed in detail. To obtain a more comprehensive view of this concern, data from three more databases have been consulted: the Dutch Lareb, the British MHRA and EudraVigilance.

Results: In RNF database, until December 2013, 226 spontaneous reports related to pioglitazone have been found, giving rise to 392 different reactions, 12 of which classified as bladder cancer. A detailed analysis of these cases has been performed. Up to November 2013, 712 spontaneous reports of suspected ADR have been recorded in MHRA database for pioglitazone, out of which 61 are classified as urinary tract neoplasms. In the same period, 127 spontaneous pioglitazone related suspected ADR reports have been reported in LAREB database, out of which 9 belongs to urinary tract neoplasms. Finally, up to December 2013, 12.973 reports involving pioglitazone have been recorded in EudraVigilance database. Surprisingly, most of these reports concern neoplasms, with more than 9000 reports. The great majority of them are classified as bladder cancer.

Conclusions: Data collected from RNF as well as from other local and European databases seem to suggest that the increased risk of bladder cancer associated with pioglitazone is concrete, but the absolute risk is relatively low. The topic is still controversial and further studies are necessary to clarify this issue.

Keywords: Pioglitazone, Bladder cancer, Rete Nazionale di Farmacovigilanza, Adverse drug Reaction

Impact evaluation of the new pharmacovigilance legislation on pharmaceutical companies

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ABSTRACT

Background: In 2012, the pharmacovigilance legislation was strengthened and rationalized with the aim to protect the public health and to cut the costs due to ADRs. It is estimated that in Europe 5% of all hospitalization are due to ADRs, which are the fifth leading cause of hospital death: approximately 197,000 deaths per year in the EU are caused by ADRs, and the total cost to the society of ADRs in the EU is about € 79 billion.

These changes have had a significant impact on the conduct of Pharmacovigilance activities by the pharmaceutical companies in terms of workload, human and economic resources.

Objectives: The aim of this analysis was the comparison between the previous and the new pharmacovigilance legislation, on the basis of previous and current workload carried out by GB Pharma, and the evaluation of the impact on pharmacovigilance staff and the global management of a pharmaceutical company.

Methods: GB Pharma, a pharmacovigilance consultant company, analysed the workload (in hour) spent to perform pharmacovigilance activities for 13 Marketing Authorization Holders (MAHs) for 2 years, the first one from 01-July-2011 to 01-July-2012 (named PRE) and the second one from 02-July-2012 to 02-July-2013 (named POST). A further analysis has been performed to evaluate the Pharmacovigilance activities carry out by headquarter Italian Companies (Global) and Italian affiliates (local), both PRE and POST.

Results: The analysis performed showed an increase of workload for most of POST pharmacovigilance activities. The total workload POST is doubled due to introduction of new activities as RMP and PSMF and implementation of quality system mainly for Headquarter Italian Companies.

Conclusion: The implementation of pharmacovigilance legislation has clearly led to an increase in workload for pharmaceutical companies with consequent increase of resource to be employed in carrying out pharmacovigilance activities.

Keywords: Pharmacovigilance legislation, Workload, Pharmaceutical Companies, Drug safety, Good Pharmacovigilance Practice

Lack of efficacy: management of the ICSRs

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ABSTRACT

Background: In the last years, several generic drugs have been introduced in Italy and in several other countries in order to reduce the medication prices and the economic burden on national health systems. Generic medicines behave very similarly to their originator counterparts; therefore, theoretically, they may show a similar efficacy. Some patients, though, using the generic drugs or switching from branded to generic drugs have showed decreased clinical efficacy or lack of therapeutic response.

Objective: The study describes in what way the management of the case reports is changed with the new Pharmacovigilance legislation, focusing mainly on case reports of drug lack of efficacy.

Methods: The lack of efficacy reports management involves the collaboration among Pharmacovigilance department, Quality Assurance department and production site, creating an efficient control network. The lack of efficacy reports was collected, processed and forwarded to headquarters and QA too. If initial case reports did not contain the batch numbers, follow ups were done to Local health Officer to request them. The Local Health Officers received answers were forwarded to Quality Assurance. The cases were closed after LHOs negative answers (because the batch numbers were not available), after three follow up attempts without answers or after end of the process with QA mail about batch analysis results.

Results: Over a period of three months, the pharmaceutical company received a total of 54 Individual Case Safety Reports (ICSRs) about olanzapine and a total of 40 Individual Case Safety Reports (ICSRs) about quetiapine. 54.0% of total olanzapine ICSRs and 57.50 % of total quetiapine cases were of lack of efficacy. All these cases were forwarded to QA. 17.0% of total olanzapine lack of efficacy cases and 26.0% of total quetiapine lack of efficacy cases reported in the source document the batch numbers, so there was no need of follow up with the LHO; however 83.0% of total olanzapine lack of efficacy ICSRs and 74.0% of total quetiapine lack of efficacy ICSRs needed follow up to the LHOs to request batch number of the product used by the patient. After follow up four situation occurred: 1) positive answer received from LHO (7.0% for olanzapine ICSRs and 17.0% for quetiapine ICSRs). Batch number was forwarded to QA. 2) LHO answered that batch number is not available (45.0% for olanzapine ICSRs and 35.0% for quetiapine ICSRs). QA was informed by email about it and the case was closed. 3) none answer was received from LHO. Second and third follow up attempts were done, after 1 month each other, (7.0% for olanzapine ICSRs and 17.0% for quetiapine ICSRs). After three unsuccessful follow up attempts, none answer was received from LHOs and the case was closed. 4) for 24.0% for olanzapine ICSRs and 5.00 % for quetiapine follow up attempts are still ongoing (third attempt sent to the LHO. Finally from a total cases of lack of efficacy (29 for olanzapine and 23 for quetiapine), only for the 24.0% for olanzapine and the 43.0% for quetiapine batch number was available and sent to production site for batch analysis. In all cases batch analysis gave negative result.

Conclusion: The results obtained from batch analysis were negative: batch does not have quality problems. In the light of ICSRs great number without batch number and LHOs negative feedback, it is decided that the cases will forward to QA as soon as the batch number will available.

Keywords: Pharmacovigilance, Lack of efficacy, Quality assurance, Local Health Officer

From PSUR to PBRER: Evolution in the Benefit/Risk Evaluation of Medicinal Products

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Abstract

Background: Pharmacovigilance is the process and science of monitoring the safety of medicines and taking action to reduce the risks and increase the benefits of medicines. One of the aspect to pursue this scope is the continuous analysis of relevant safety, efficacy and effectiveness information throughout the lifecycle of a medicinal product promptly, as important findings occur, and periodically, to allow an overall assessment of the accumulating data. As a result, drug manufacturers are required to provide regulatory agencies with periodic updates of safety.

Objective: The aim of this job is to describe the evolution from Periodic Safety Update Report (PSUR) to Periodic Benefit-Risk Evaluation Report (PBRER) underlying the differences between the two documents and evaluating the advantaged of the PBRER.

Methos and results: Since July 2012, we have officially been operating under EU legislation Directive 2010/84/EU amending directive 2001/83/EC for National and Mutual Recognition processes and Regulation (EU) No 1235/2010 amending regulation (EC) No 726/2004 for Centralized processes. The Volume 9A guidelines have been replaced by 16 Good Pharmacovigilance Practices (GVP) modules enshrined in law and the GVP Module VII covers PSURs. The International Congress on Harmonization (ICH) released a guideline on PBRER, E2C (R2) whereby substantial changes to the PSUR model and scope have been made. The focus of the PSUR was on relevant new safety information in the context of patient exposure, to determine if changes were needed to the product information in order to optimize the use of the product.

Conclusions: The role of the PSUR in the spectrum of safety documents submitted to regulatory authorities has been reassessed to empathize the risk-benefit balance and the risk management planning of the product. The PBRER has a much more integrated view of a drug's usefulness in the patient population. MAH responsibility and engagement with drug safety monitoring will be enhanced for the sake of patient safety.

Keywords: Periodic Safety Update Report, Periodic Benefit-Risk Evaluation Report, International Conference on Harmonization, European Medicines Agency, Food and Drug Administration

Activities to guarantee the quality of safety data in a pharmacovigilance database and their relevance

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ABSTRACT

Objective: To assess the frequency of mistakes during the activity of data entry into a pharmacovigilance database, and to evaluate the importance of a good quality check and the relevance of a medical evaluation performed by a physician.

Methods: We have considered case reports both received through the National Pharmacovigilance network (RNF) and collected from medical and scientific literature associated to medicinal products of a Client of PhAST.

Results: A total number of 44 case reports were collected, 17 cases were received from AIFA through RNF and 27 were retrieved from literature search. During QC activity performed on spontaneous reports collected from RNF in 1 case (6%) there was a mistake regarding the causality between the suspected drug and the event; in 2 cases (12%) there was an error regarding the suspect drug; in 4 cases (23%) there was an error regarding listedness and in other 4 (23%) and error regarding dechallenge/rechallenge; finally, there were 5 cases with minor errors due to carelessness. Regarding cases retrieved from literature search: in 5 cases (18.5%) there was an error regarding the drug, in 4 cases (14.8%) there was an error regarding dechallenge/rechallenge, in 3 cases (11%) there was an error classified as "other errors" (minor errors due to carelessness), in 1 case (4%) a mistake regarding the outcome of the event was observed and in another case a mistake regarding the adverse event was revealed. For literature cases the medical review is more important than in the cases received from RNF. In fact, we should process initially the case only with an abstract and sometimes, it is difficult to find clear information on seriousness of the event, on the outcome of the event and clear information on the suspected drug.

The impact of good and correct data in the safety database is discussed.

Conclusion: A good quality check and most of all the medical evaluation performed by a physician guarantee that the data in the pharmacovigilance database are accurate, compliant to the source documents, and valid for all subsequent reporting to Authority, queries, reviews, aggregate reports and signal detection to allow pharmaceutical companies to maintain a good overview on the risk/benefit evaluation of their medicinal products.

Keywords: Pharmacovigilance database, Data entry, Quality check, Medical evaluation, Adverse drug reactions

Antihypertensive drug use during pregnancy

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ABSTRACT

Background: Methyldopa, labetalol and nifedipine are considered the drugs of choice for hypertension treatment. The use of ACE inhibitors and ARBs is contraindicated during pregnancy because associated with intrauterine growth retardation, neonatal hypotension, renal failure, oligohydramnios, and patent ductus arteriosus. Only a limited number of studies specifically focused on the use of antihypertensives and none of these studies was aimed to evaluate the adherence to the guidelines in routine clinical practice.

Objective: The study aimed to compare the pattern of antihypertensive drugs (AD) utilization in pregnant women with the recommendations of the main international guidelines. We also assessed the association between the use of non-recommended drugs and health and socio-demographic factors.

Design: Population-based descriptive study.

Setting: Women resident in the Lombardy region, Italy.

Population or sample: The analysis was conducted on a cohort of 86,171 women with singleton deliveries in the period 01/10/2009-30/09/2010. Women with first prescription of AD during pregnancy were considered as incident users.

Methods: The information on deliveries derived from the hospital discharge database and the birth register of the National Health Service. Maternal exposure to antihypertensive medications (during pregnancy and in the six previous months) was retrieved from the regional drug prescription database.

Main outcome measures: The prescription of methyldopa and calcium channel blockers was considered as "recommended"; all other antihypertensives were considered as "non-recommended". Odds Ratio (OR) of receiving "non-recommended" drugs and 95% confidence intervals (CI) were estimated.

Results: Among the 1,009 patients (1.2%) exposed to antihypertensive medications during pregnancy, 675 (66.9%) were incident users. Around 24% of incident users received "non-recommended" drugs; the proportion decreased during pregnancy, and reached 16% among women who started treatment in the third trimester. Women with at least four comorbidities before pregnancy were at increased risk of receiving "non-recommended" drugs (OR 4.46; 95% CI 1.15-18.81).

Conclusions: Our findings suggest that the proportion of patients receiving "recommended" antihypertensive increases during pregnancy. Nevertheless, about one third of all pregnancies received at least one "non-recommended" medication for the treatment of hypertension.

Keyword: Antihypertensive drugs, Pregnancy, International Guidelines

The Importance of the Endpoints as Safety Parameter into Evaluation Risk-Benefit Ratio of New Drugs: An Example of CRO OPIS Management of Endpoints

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ABSTRACT

Background: During the last year, accordingly with GCP guidelines, the utilization of endpoints led to obtain more information about new molecules in study into clinical trials. These, as well as to complete an efficacy profile of the new Investigator Medical Product (IMP), are able to individuate new findings in term of safety, and are collected and utilized to assess more accurate risk-benefit ratio of this IMP. The strategy to utilize more endpoints during the analysis of clinical data has proven successful, in fact in this way the statistic power of the study is improved, and pharmaceutical companies have developed a process to management of the endpoints.

Objectives: This work tries to explain the management process of secondary endpoints that CRO follow, to permit the analysis of the clinical information of new IMP.

Methods: To obtain the gold standard in randomize clinical trial, the pharmaceutical companies follow and apply the GCP guidelines in all part of the clinical study. Furthermore, given the importance of analysis of the endpoints, Sponsors develop a structural process to endpoints management.

Result and conclusions: We try to explain the importance of the management process of the endpoints, and at the same time we try to explain the its critical points.

Keywords: Endpoints, Safety, Risk-benefit ratio

Signal detection: method for a qualitative signal detection

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ABSTRACT

Objective: To describe the signal detection process performed to evaluate potential safety signals concerning a medicinal product and arising from the case reports of suspected adverse reaction stored in the pharmacovigilance database.

Methods: The evaluation process has been performed on case reports relating to nimesulide collected in a three years period (2011-2013). Due to the small number of adverse events contained in the database we used a qualitative method.

Results: A total of 286 adverse reactions (ADRs) has been collected in the study period (70 ADRs in 2011, 86 ADRs in 2012 and 130 ADRs in 2013). The most frequent adverse events identified were included in the SOCs "Gastrointestinal disorders", "Skin and subcutaneous disorders" and "Hepatobiliary disorders". Analyses showed an increased occurrence of following expected adverse events: abdominal pain upper, erythema, rash, generalised rash, urticaria, pruritus and generalised pruritus.

Conclusion: During the study period, neither unexpected nor particularly serious adverse reaction has been detected to justify special or restrictive actions. Nevertheless, an increased frequency of the listed events has been perceived and has to be maintained under close monitoring in the next evaluation.

Keywords: Signal detection, Good pharmacovigilance practices, System organ class, Adverse drug reactions

How improving ADR spontaneous reporting system by Pharmacists and citizens

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ABSTRACT

Background: Spontaneous reporting is the core data-generating system of pharmacovigilance, relying on healthcare professionals and consumers to identify and report any adverse events to their national pharmacovigilance center, health authority. The spontaneous reporting system is still the principal mechanism by which signals of such rare, but serious, adverse events are currently detected. Spontaneous reports are, by definition, submitted voluntarily although under certain circumstances these reports may be encouraged, or "stimulated" by the local health authorities, through information and awareness raising projects. The signaling process involves the whole population, from the prescriber and the dispenser of the drug to the end user. Using his technical expertise and his relational skills, the Pharmacist should make aware the population of the importance of spontaneous reporting.

Aims: To develop a project targeted at increasing spontaneous reporting by the pharmacists and the citizens. Activities included the information and the education of both pharmacists and the citizens about the appropriate use of drugs and the importance of adverse event reporting.

Methods: The project was carried out in the 23 community pharmacies in the in the area pertaining to the city of Cosenza. It included the organization of information meetings on the proper use of medicines, and the distribution of ad hoc informative documents to instruct both health care professionals and citizens in the spontaneous reporting. In order to facilitate the reporting and, therefore, the flow of information to the pharmacovigilance centers, information days were organized in the pharmacies that offered, in addition, direct assistance.

Results: The reporting rate of pharmacists in the first quarter of 2014, in addition to that of 2013, has risen by 4.3 percentage points. The same thing happened to the citizens, whose reporting rate has risen by about one percentage point: that shows that the increase of reporting coming from the citizens is less important than those recorded for pharmacists. Both percentages reached a good level, showing increasing interest and awareness in pharmacovigilance, as result of the project. We could estimate a higher number of reports at the end of the year. Besides, both the targets of the intervention showed a good level of satisfaction.

Conclusions: The project resulted in an increased reporting in the territory of competence and in an improved exchange of information between Pharmacists and citizens on ARDS and Pharmacovigilance. The processing of data obtained will allow providing the basis for the development of a new project focused on the problems emerged in the planning of local pharmacovigilance system.

Keywords: Pharmacovigilance, ASP Cosenza, Pharmacists signalling, Citizens signaling

Quality control of adverse event processing by local affiliates: a case study

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ABSTRACT

Background: The responsibility of any marketing authorisation holder (MAH) is to ensure the safety, efficacy, and quality of all marketed products. A Pharmacovigilance system should be designed to ensure that the collected reports are authentic, legible, accurate, consistent, verifiable and as complete as possible for their clinical assessment. The whole process from collection to retrieval and analysis must follow rigorous procedures to try to guarantee the highest possible quality of data, and of its management, at every step in the process.

Objective: Define the quality control level in the data entry process of spontaneous adverse event after the introduction of a new global process by 1 July 2013, and aimed at improving the quality of the management and the transmission of spontaneous reports to the central data entry site of AstraZeneca.

Methods: In this study all reports of spontaneous cases received in the months of June, July and August 2013 have been taken into account in order to estimate the error rate, an indicator of the quality process (defined as the ratio of the number of cases with errors to the number of cases quality controlled).

Results: During the three months of study, AstraZeneca Italy collected and managed 898 spontaneous report of adverse reaction (287 in the month of June, 324 in July and 287 in August) after the implementation of a new process. The total cases with error increased from 8 of June to 19 of August, through the value of 10 of July and the error rate therefore has been increased during the period of study (2.8% in the first month, 3.2% and 6.7% in July and August relatively).

Conclusion: Changing in the pharmacovigilance process is a consequence of the need to continuously develop and improve the quality in the managing of individual case safety reports and to adhere to the European legislation and standard required. The results obtained have suggested that new actions should be taken in order to further improve the process and its quality.

Keywords: Quality control, Pharmacovigilance process, Data entry, Spontaneous report

Herbal drugs and natural products: a glance on postmarketing surveillance and adverse reactions identification. Pharmacovigilance or Phytovigilance?

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ABSTRACT

Background: Many people take herbal drugs and natural products in the effort to be well and stay healthy. With so many supplements available and so many claims made about their health benefits, how can a consumer decide what is safe and effective? Indeed, it must be said that federal regulations for herbal supplements are very different from those for prescription and over-the-counter drugs. For example, a dietary supplement manufacturer does not have to prove a product's safety and effectiveness, before being marketed. Contributing to the knowledge of the potential risks associated with the use of "natural" products, may define the real dimensions of the problem and identify possible strategies for prevention and intervention: these are the objectives of the surveillance system put in place, starting from 2002, by the "National Institute of Health (Istituto Superiore di Sanità, ISS)", in collaboration with the Italian Medicines Agency (AIFA) and the Ministry of Health.

Objective: To provide an overview of the current state of pharmacovigilance activities for herbal medicines at the national level and to explore the challenges that pharmacovigilance of herbal medicinal products presents, considering relevant emerging issues and what steps could and should be taken to improve safety monitoring for herbal products in the future.

Methods: The following databases have been searched: Medline, EMBASE, the National Research Register, ClinicalTrials.gov (United States), and bibliographies of retrieved articles. The majority of the results were reported from the data available at ISS, since company policy did not allow to present the data at our disposal.

Results: 819 reports of suspected adverse reactions, relating on natural products have been collected from 2002 to 2013 and analyzed at ISS. Fifty seven percent of the products responsible for the adverse reactions were food supplements, 18% were herbal products, the 11% were homeopathic complexes, 0.85% of the products belonged to the ayurvedical medicine and 0.73% to domestic preparations. An important result comes from the 38% of the reports, in which the adverse reactions were due to the concomitant intake of herbal drugs together with synthetic molecules.

Conclusions: To protect the public healthcare from the risk of adverse reactions to products derived from herbs, a warning should be added on the packaging of these products. Quality assurance and control measures, such as national quality specification and standards for herbal materials, good manufacturing practices (GMP) for herbal medicines, labelling, and licensing schemes for manufacturing, imports and marketing, should be in place in every country where herbal medicines are regulated. These measures are vital for ensuring the safety and efficacy of herbal medicines.

Keywords: Pharmacovigilance, Phytovigilance, Dietary supplements, Post-marketing surveillance, Adverse reactions identification

The role of the pharmacist in adverse drug reaction reporting on behalf of the citizen: the Italian interregional project

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ABSTRACT

Background: Adverse drug reaction (ADR) reporting by citizens is now a well established practice in many countries around the world. The Directive 2010/84/EU implemented by AIFA (July 2012) and the positive experience of the pilot project in Veneto (2010) prompted the launch of an inter-regional project, promoted by the Veneto Region with the participation of several regions including Lazio Region. This project was approved by AIFA and aimed at community pharmacists to support ADR reporting by citizens.

Methods: The study duration was 3 months (phase interviews with citizens). Each pharmacist, using a special monitoring form, interviewed approximately 20 people per week chosen at random among users aged ≥18 years who had taken at least one drug in the last month. Recorded information included: sex, age and whether or not an adverse reaction was observed. If so, official reporting cards for patients who had an ADR were filled. If patients refused to do so, the reasons were recorded. The citizen sent the ADR reporting form in one of several options including postal mail, fax, e- mail or directly returning the form to the pharmacist, preferred choice.

Results: The number of participating pharmacies was 388. Pharmacists who initially participated numbered 831 in total, 615 of which completed the project (74%). Overall 115,055 patients were interviewed, of whom 58% were female and 69.3% were under 65 years old. Out of 115,055 interviewed patients, about 10% reported an ADR (12,185). Of 48,166 men surveyed, 4,369 (about 9%) reported ADRs, while of 66,889 women surveyed, 7,816 (about 11%) reported an ADR. Finally, the completed and returned report forms numbered 3,944. About 60% of the ADR reports were suitable for data input in the national network of pharmacovigilance (RNFV) database. This suggests that the majority of patients would comply with such a pharmacovigilance scheme with pharmacist support.

Conclusions: The large number of ADRs reported in the study indicates that the project has filled a need in monitoring drug safety. The project has helped to promote the role of pharmacists in ADR reporting by citizens and helped to achieve a concrete foundation for a possible future launching of similar pharmacovigilance projects. In fact, the community pharmacist is the first health professional to whom drug safety issues are addressed and their role as promoter of pharmacovigilance activity could be the driving force for ADR reporting.

Keywords: Pharmacovigilance, Adverse Drug Reaction, Citizen reporting, Spontaneous reporting system, Underreporting

Pharmacovigilance: System Master File. Utility, maintenance and implementation

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ABSTRACT

Objective: Evaluating the central role of the PSMF in a corporate contest, illustrating its maintenance and implementation. Demonstrating the importance of this document for a safe and effective use of medicinal products.

Methods: To carry on this project, the GVP's Module II was consulted and the following Annexes were updated: Annex B – MAH Organization; Annex G – Quality System; Annex H – Products; Annex E - Pharmacovigilance Process and written procedures. Every revision was recorded in a specific logbook.

Results: This project was more concentrated on changes that came regularly and in an expected way. The most updated Annex was the type H on Products. Furthermore, the maintenance of the PSMF was an articulated activity that involved the collaboration of many company's departments.

Conclusions: The PSMF is an essential document for the pharmacovigilance system. Its maintenance and implementation has become more complex compared with the previous document, called DPPS. It allows to better comprehend the different activities related to the drugs' safety and their connection to reach a common purpose: to create a pharmacovigilance system able to effectively evaluate the risk-benefit profile of medicines.

Keywords: Pharmacovigilance System Master File, Maintenance, Implementation, Departmental interaction

Cosmetovigilance: commitment and compliance in a pharmaceutical company with the entry into force of the regulation (EC). N°1223/2009

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ABSTRACT

Background: On 11th of July 2013 entered into force the Regulation n° 1223/2009 of the European Parliament and the Council of 30 November 2009. This Regulation provides a method for the implementation of a cosmetovigilance system with the aim to harmonize European normative of all Member States about cosmetic products. In order to increase the safety of these products, the regulation is addressed to Health Authorities, industries, health care professionals and for the first time to consumers too.

Objectives: This paper has the aim to describe the steps required and performed by a pharmaceutical company, which also markets cosmetic products, to comply with the new Regulation, for the management of safety issues.

Methods: The process started with the collection of the documents related both to old and new legislation and effective SOPs, proceeded with the analysis of the documents retrieved, going through the sharing of this information with the company functions involved in the management of cosmetic products (Regulatory Affairs, Pharmacovigilance, Quality Assurance Units and Sales Force). Afterwards an official document was created for managing the safety of cosmetic products: an updated Standard Operative Procedure. Before the implementation of Reg. 1223/2009, HA had the central role in the notification of undesirable effects, while the HCP and the consumer have only a marginal role. The regulation introduces the concepts of reporting serious undesirable effects to local Health Authorities. It gives a central role to the consumer who has, for the first time, an easily access to the information regarding undesirable effects, composition, labelling and packaging, and the possibility to report the undesirable effects experienced directly to Health Authorities. This paper describes the advantages obtained by Consumers, Health Care Professionals, Member States and Companies, with the entry into force of this regulation.

Conclusions: The paper shows how a pharmaceutical company becomes compliant with the Regulation n.1223/2009 in the managing of cosmetic products.

Keywords: Cosmetic product, Cosmetovigilance, Serious undesirable effect (SUE), Regulation 1223/2009, Pharmaceutical company

Estimating the impact of switching psychiatric patients to a new therapy: a MCMC (Markov Chain Monte Carlo) based approach

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ABSTRACT

Background: The low reimbursed price of some typical antipsychotics can lead pharmaceutical industries to withdraw these drugs from the market as a consequence of the difficulty in balancing their production costs with revenues. The aim of this work was to evaluate the clinical implications in terms of efficacy and tolerability for the patients that, in such an occurrence, would have to be switched from first generation to second generation antipsychotics.

Methods: A Markov model was developed to identify all the possible scenarios related to the transition process from Chlorpromazine and Haloperidol (as possible examples) to Quetiapine. To replicate the "prognosis" of a large number of hypothetical individual patients, a Monte Carlo simulation was performed. The outcomes of the switching and their impact were assessed using the mean frequency values of the "lost in follow-up", "died", "stable condition" states, plus the overall number of visits and of ADRs.

Results: The "work" simulations were performed with 500 cohorts of 2000 subjects because in the "test run" it was observed that the minimum cohort size to obtain significant outcomes (visit, ADRs, lost in follow-up- stable conditions) was 500 and that the simulations went to convergence at 26 cycles.

Inference analysis allowed us to assess that 91% of the patients in treatment with Chlorpromazine and Haloperidol were in stable conditions after one year from changing to Quetiapine and that the incidence of ADRs" in were 24 for 100 patients. During one year of treatment with Quetiapine each patient returned to the prescribing physician between 2-3 times before finding or not finding a benefit in the new treatment.

Conclusions: The present study confirms that for patients treated with Chlorpromazine and Haloperidol "staying" with their present therapy proves to be a better solution than changing to another one.

Keywords: Schizophrenia, Treatment Outcomes, Switch, Antipsychotics, Monte Carlo, Markov Chains, Simulations

Signal Detection based on the evaluation of adverse drug reactions received by a Marketing Authorisation Holder

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ABSTRACT

Background: The target of post-marketing pharmacovigilance is to timely detect signals of a change in the safety profile of a medicinal product; pharmacovigilance activities, aimed at highlighting and studying safety signals, are known as Signal Detection and are mandatory according to the European legislation.

Objectives: The aim of this project was to describe the process of the signal detection, performed by a Marketing Authorisation Holder, set according to the law requirement in the European Community.

Methods: The Company performs signal detection on a quarterly basis, according to a process described in the Company's Standard Operating Procedures and in line with the signal management process set forth in the Guideline on good pharmacovigilance practices (GVP) Module IX - Signal management.

Results: In my project, I supported the Pharmacovigilance Department of an Italian Marketing Authorisation Holder in the signal detection process. No statistical analysis was carried out by the Company due to a low number of cases received per product. Only a qualitative review of cases (case by case) was performed. The signal detection was made on all Company products with a special focus on two active ingredients: ketoprofen lysine salt and thiocolchicoside.

Conclusions: This process, based on subjective evaluation of each individual case, may appear time consuming and potentially impaired by human errors. Despite this, the qualitative analysis of cases that the Company performs, through an experienced person, and validated by the Safety Review Board, entails a detailed and complete review of each concerned case report, and represents an important and satisfactory tool to detect any possible new safety signal.

Keywords: Signal Detection, Marketing Authorisation Holder, Adverse Drug Reaction

Pharmacovigilance national requirements in Hungary, Germany, Italy and Portugal during the interim period

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ABSTRACT

Background: New European pharmacovigilance legislation (Regulation EU No 1235/2010 and Directive 2010/84/EU) has the purpose to strength the Europe-wide system for monitoring the safety and benefit-risk balance of drugs, creating a supra-national database for collecting ADRs (Eudravigilance), establishing a European Advisory Committee (PRAC), promoting a centralized assessment of Periodic Safety Update Reports (PSURs). Moreover, until the EMA could ensure full functionality of all activities planned in the above mentioned Regulation and Directive (such as the centralised assessment of PSURs and full functionality of the Eudravigilance database), and until Member States have implemented new Directive, pharmacovigilance activities could vary in the different European Member States. The MAHs, which have medicinal products authorized and marketed in different EU countries, have to know national requirements applicable during the interim period.

Objective: To examine the current pharmacovigilance arrangements in Hungary, Germany, Italy and Portugal, in order to allow a Marketing Authorisation Holder, which have medicinal products authorized in these Member States, to fulfill national Pharmacovigilance requirements.

Mehods: A complete analyses of National Competent Authorities Official website, decrees implementing at national level Directive 2010/84/EU and European interim period arrangements, has been performed to compare ICSRs and PSURs management, request of a local pharmacovigilance contact, risk minimization tools and direct healthcare professional safety communication, between the above mentioned different Member States.

Results: Hungary, Germany and Portugal have already implemented Directive 2010/84/EU, while in Italy, length of parliamentary procedures did not allow to finalise the decree, even if, adequately measures have been laid down to ensure compliance with the new pharmacovigilance requirements. In all these Member States, now also patients/consumers can report ADRs, even if in different ways; Italy and Portugal have in common a national portal of pharmacovigilance, all NCAs have adopted a policy of transparency publishing DHPCs on their web sites; however, management of serious and non-serious ICSRs is different in the different countries, as detailed described in this article.

Conclusion: This work adequately describes the similarities and differences, in the national pharmacovigilance requirements, between Hungary, Germany, Italy and Portugal. Heterogeneity of national systems has been partially reduced implementing Directive 2010/84/EU, however, NCAs have adopted different solutions to manage Pharmacovigilance activities, almost regarding ICSRs reporting and MAHs responsibilities. The shift from the interim arrangements to the final ones, could present some difficulties.

Keywords: Reporting requirements of ICSRs, EURD List, Decreto-Lei n.º128/2013, Arzneimittelgesetz (AMG), Hungarian Decree of the Ministry of Human Resources on Pharmacovigilance

Drug safety in generic medical products: an original approach aimed to an efficient Pharmacovigilance System

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ABSTRACT

Background: Asgenia was the expression of the will of Assogenerici, the Italian Generic & Biosimilar Medicines Industry Association, to provide an efficient support to all the activities related to Pharmacovigilance of the members Companies Marketing Authorization Holders (MAH) of generic medicines. The activity was created with the purpose to provide answers and solutions through a new and innovative approach, offering a technical and valid support for conducting Pharmacovigilance activities.

Objective: To develop a procedure allowing a unique download of each individual case safety report (ICSR) for Active substance (AS) from Italian Pharmacovigilance Network and a unique search of adverse drug reaction (ADRs) in International Medical Literature Researches and their correct management and distribution to MAH.

Methods. To enable procedures which led to unify the reports obtained by the Italian Pharmacovigilance Network in order to work on a single report, then to forward it to the groups of Companies which are MAH of a product, containing the same active substance, thus working only one time for each active substance which is common to more the one MAH.

Results: The result of this work is the production of a CIOMS (Council for International Organizations of Medical Sciences) and XML (extensible Markup Language) file for MAH. Asgenia provides a centralized service in term of research, download, management and storage of data, as well as some other supplementary services. The Assogenerici member companies which joined this service are fully provided with all the Pharmacovigilance data they might collect, organize in their own database, and manage the information according to EU Legislation.

Conclusions: This new way to manage Pharmacovigilance activities allow to reduce the work load that pharmaceutical companies are dealing with, through the production of the same common standard output for all member companies. This original way to operate permits a significant spare in term of costs, resources and time for member companies.

Keywords: ADR, ICSR, RNF, Safety Drugs Application, XML/CIOMS form