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INTERNATIONAL SOCIETY OF PHARMACOVIGILANCE

ABSTRACTS

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INTERNATIONAL SOCIETY OF PHARMACOVIGILANCE

The International Society of Pharmacovigilance (ISoP) is devoted to developing its activities on a worldwide basis towards supporting safer use of medicines in clinical practice.

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P001. Reporting of ADRs by Hospital Pharmacists in the Holy City of Makkah During the Time of Hajj and Ummra

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Objective: To assess the contribution made by hospitals pharmacist in regard to adverse drug reaction reporting in seven hospitals in the Holy City of Makkah, Saudi Arabia.

Methods: A face-to-face structured questionnaire answered by 64 randomly selected hospital pharmacists of varying professional experience was conducted in seven different hospital in Makkah.

Results: Forty nine (76.5%) of the 64 pharmacists completed their questionnaires. More than half, 55%, agreed or strongly agreed in stating that ADR reporting should be compulsory and similarly 59% thought it was a professional obligation. However, concerning specific details as to what should be reported, 59% were unclear as exactly what to report. One problem in 53% of respondents was said to be the lack of reporting forms. A major limitation to successful reporting was the limited time available in existing clinical practice to make such reports and so the increased workload at the time of the Hajj time exacerbated the problem. Furthermore, the clarity of the reporting forms and the time taken to complete these forms were deemed to be major deterrents. Finally, Pharmacists were not dissuaded from reporting by the need to consult a medical colleague or by the absence of a fee. Education and training had a significant influence on pharmacists' participation in the Yellow Card Scheme.

Conclusions: Makkah's hospital pharmacists showed both positive knowledge and awareness toward pharmacovigilance and emphasised that future education and training was very important so as to both extend and enhance the ADR reporting by hospital pharmacists leading to greater patient safety.

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P002. Potential Drug-Drug Interactions in HIV-Infected Children on Highly Active Antiretroviral Therapy in Lagos, Nigeria

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Background: Multiple therapies are common for HIV children on highly active antiretroviral therapy (HAART). These children are at risk for clinically significant drug interactions (CSDIs). While CSDIs are under-recognized in developed countries, data are lacking for developing African countries. We aimed to investigate the prevalence of CSDIs between antiretrovirals (ARVs) and co- prescribed drugs for children attending a large HIV clinic in Lagos, Nigeria.

Methods: We retrospectively reviewed the case files of 80 HIV-infected children on HAART at the *AIDS Prevention Initiative in Nigeria* (APIN) clinic in Lagos, who were <15 years old, had used ARV drugs for at least a year, and had not progressed to full blown AIDS to assess the risk for clinically significant interaction between co-prescribed and ARV drugs. Of the 417 patients enrolled for treatment, 80 were eligible for inclusion. We defined CSDIs as 'major' (capable of causing severe or permanent damage, contraindicated, avoid or not recommended by the manufacturer, or requiring dose modification) or 'moderate' (manufacturers advise caution, or close monitoring, or capable of causing clinical deterioration).

Results: A total of 60 (75%) patients were at risk for a CSDI resulting in major interactions in 13 (16.3%) patients and could potentially lower the plasma concentration of antiretroviral drugs in 9 (15%) patients. Major interactions most frequently involved rifampicin in 9 (11.3%) patients and artemesinin combination therapies (ACTs) in 8 (10%) patients whereas moderate interactions frequently involved ACTs (48.8%), fluconazole (36.3%), and rifampicin (11.3%). Univariate analyses suggested that age ($p = 0.392$), gender ($p = 0.813$), and moderate ($p = 0.692$) or severe ($p = 0.788$) malnourished state of the children were not associated with risk for CSDIs.

Conclusions: Three-quarters of the children receiving ARV drugs were at risk for CSDIs. Strategies need to be put in place to prevent important drug interactions and to manage unavoidable interactions.

P003. A Study of Community Pharmacists Awareness of and Contributions to the ADR Reporting Systems in the Holy City of Makkah

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Aim: To determine and evaluate awareness, of the knowledge, and attitude of community pharmacists towards adverse drug reactions (ADRs) reported in the Holy City of Makkah in Saudi Arabia.

Method: Face-to-face interviews were carried out on 170 community pharmacists. Ethical approval has given by the Makkah Ministry of Health (MOH) randomly selected from a membership list from the MOH in the Holy City of Makkah.

Results: The pharmacists interviewed were employed in small, medium and large private pharmaceutical establishments, with over the counter retail facilities. From the data collected found the majority of community pharmacists 76% (n = 129) were continuing education

(1-5) hours per month. However, 86% (n = 146) were not aware of the ADR reporting program in the Holy City of Makkah. Similarly, 56% (n = 95) of the respondents were not aware of the existence of the Saudi National Pharmacovigilance centre (NPC) within the Saudi Food and Drug Authority (SFDA) and they were also unaware of the system of reporting ADRs through the appropriate channel and filling in the forms to report them. 88% (n = 150) of community pharmacists in the Holy City of Makkah did not use one of the fundamental tools of ADR reporting which was accessing and using the internet in their workplace. The majority of community pharmacists in the Holy City of Makkah commented on which department they considered was responsible for receiving and interpreting ADR reporting; 65% (n = 110) stated that it was the MOH. 65% (n = 110) of respondents considered the reporting of ADRs to be integral to this professional role as a pharmacist. Importantly, all community pharmacists decided to report ADRs in the future after the researcher explained to them the importance doing so. The main factors that discouraged ADR reporting were the lack of reporting forms being available, that it was time consuming, that they did not know how to report them and some commented on their indifference to the system.

Conclusions: The Community pharmacists could play an important role in ensuring the use of safe medications in patients. To achieve this aim they clearly require more education and training of knowledge about the importance of reporting ADRs through appropriate training courses.

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P004. Methods for Improvement of Drugs' Side Effects Reporting in Pharmaceutical Practice

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Introduction: Knowledge about drugs' side efects is one of the major requests for their safe and rational use. The participants in the clinical studies are often chosen in such a manner to fit a pharmacological profile of the investigated drug. Also, significantly larger population are using drug during post-registration period than that participating in the clinical study. General population may also have associated illnesses that could have an impact on the pharmacological effect.

Aim: The aim of this paper is to present how the system of pharmacovigilance in our community could be improved through better education of both pharmacists and patients about the importance of reporting side effects of the drugs.

Material and methods: The study was conducted for three months during which reports about side effects were collected through direct contact with pharmacists and patients. All patients were informed through pamphlets about the consequences of side effects reporting and its importance. The data about adverse reactions to the drugs were filled in the standard reporting forms and sent to The Serbian Agency for Medicinal Products and Medical Devices.

Results: The 40% of contacted pharmacies have reported side effects of the drugs. The total number of reports was 70, where 52 were reported by pharmacists and 18 were reported by the patients. The majority of the side effects were caused by the drugs for the cardiovascular diseases and anti-infective drugs. According to the data, dose dependent side effects (type A) have appeared in 70% of reported cases and allergic reaction (or type B) in 14%. In 16% of reported side effects there was no clear connection between use of the drug and side effect.

Conclusion: Through continual education of pharmacists and other medical professions, as well as education of patients, about the importance of adverse reactions reporting, significant improvements could be done in the system of pharmacovigilance.

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P005. Amiodarone-Induced Adverse Drug Reactions in Hospitalized Patients

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Introduction: Amiodarone is an antiarrhythmic drug of type III of Vaughan – Williams' classification with very high consumption in Argentina because of its utility in several types of arrhytmia. There are plenty of reports about the insecurity of this drug[1-3] because of its potentially severe Adverse Drug Reactions. The aim of this study was

to determine amiodarone-induced ADRs in a tertiary care hospital from Buenos Aires.

Material and Methods: This investigation was performed with the pharmacovigilance committee of Hospital General de Agudos ¨Dr Cosme Argerich¨, from Buenos Aires city. The period involved was from June 2008 to March 2012. Naranjo Score was applied to assess drug causality in every adverse medical event.

Results: In this period 2443 ADRs were reported. We detected 21 adverse drug reactions induced by amiodarone. The average age of patients who suffered these ADRs was 66.8 years (95% CI 59.1–74.5). 76,19% (95% CI 57.97–94.40) appeared in men and 23.80% (95% CI 5.59–42.02) in females. There were three cases of pulmonar fibrosis, two were severe and needed hospitalization; three cases of hypothyroidism that needed treatment with levothyroxine because they could not withdraw amiodarone; three cases of increased activity of acenocumarol because drug–drug interactions, one caused upper gastrointestinal bleeding with hospitalization. The ADR most frequently observed was hepatotoxicity (n = 8). Others were QTc prolongation and nephrotoxicity.

Conclusion: Considering the high consumption and the severity of arrhythmias treated with amiodarone we consider this was not a high number of ADRs. The types of ADRs were similar to the ones reported in international bibliography.

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P006. Drug-Drug Interactions – Induced Adverse Drug Reactions in Hospitalized Patients

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Introduction: Drug-Drug Interactions (DDI) can cause frequently adverse drug reactions (ADRs) or therapeutic deviations. Sometimes these complications of DDI can be preventable and happen because of ignorance of this interactions. Nowadays this is an increasing problem because of progressive polimedication in medical practice. The aim of this study was to determine drug-drug interactions – induced adverse drug reactions in hospitalized patients in a tertiary care hospital in Buenos Aires, Argentina.

Material and Methods: The work was performed within the Pharmacovigilance comitee of Hospital General de Agudos ¨Dr Cosme Argerich¨, Buenos Aires, Argentina, between June 2008 and March 2012. Naranjo Score was applied to assess causality of drugs in an adverse medical event. Drug-drug interaction was considered when one drug altered pharmacologic effect or toxicicity of the other drug because of known pharmacologic mechanisms.

Results: In this period 2443 ADRs were reported and 77 were caused by DDI (3.15%; 95% CI 2.46–3.85). Of all DDI, 21 (27.27%; 95% CI 17.25–37.2) were serious, mainly because they caused hospitalization or prolonged it. 12 cases (15.58%; 95% CI 7.48–23.68) were decrease pharmacologic action of one drug (mainly antiepileptic drugs and other enzyme-inducing drugs); 13 cases (16.88%; 95% CI 8.51–25.25) were increase pharmacologic action of one drug (mainly increasing acenocumarol activity by amiodarone or furosemide) and 52 cases (67.53%; 95% CI 57.07–77.99) of increasing toxicity, mainly drug-induced nephrotoxicity or hydroelectrolytic problems.

Discussion: The relative incidence of DDI as a cause of ADRs was low. As reported in international bibliography,[1,2] antiepileptic drugs, anticoagulants and NSAIDs are the group of drugs most frequently involved. We consider that the clinical impact of DDI-induced adverse drug reactions can be avoided or diminished with tight pharmacological control.

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P007. The Alliance for Clinical Research Excellence And Safety (ACRES): An Innovative Approach To Reform Clinical Research And Safety

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There have been numerous efforts to improve the efficiency of global trials. However, they are often regional and confined within specific silos which means they progress slowly. There is a need for a global framework for clinical research and safety modelled on successful operational organisations and structures in other industries such as IATA, the global air transportation association. Such a framework is envisioned by the creation of a non-profit corporate entity, ACRES Inc. (The Alliance for Clinical Research Excellence and Safety), which will provide essential professional support to all clinical research stakeholders with a wide range of products and services, such as publications, training and consulting. ACRES Inc. will assemble a large network of industry suppliers and service providers, the ACRES Global Network, to provide expertise to the clinical research and safety endeavor.

ACRES, in support of safety, quality and ethics, seeks to promote and facilitate policy and process harmonisation and standardisation; operational integration, innovation and efficiency; and regulatory simplification according to the high standards of ethics, professional integrity, responsible conduct of clinical research and good business practices. These will all be embedded within an appropriate safety culture.

The ACRES Global Network will consist of thousands of independent, sustainable, clinical research sites, each with fully-trained and certified professional research teams. ACRES will explore the possibility of global accreditation. Through an alliance model embedded within a safety culture, these sites will utilize standardized operating policies and procedures, be focused on risk-based quality management and committed to guiding principles of safety culture. ACRES is exploring how the sites might be supported by a robust, interactive information technology platform to provide interconnectivity and data regarding safety, performance and quality. This neural net will enable real-time capture of important operational and safety data at the point of origin and facilitate sharing of critical, non-proprietary information for closed-loop coordination and mon-

itoring of the system performance on a continuous basis with feedback to support ongoing total quality management and pharmacovigilance.

Progress will be presented concerning ACRES task forces who will have developed an organization or 'development' infrastructure and defined what 'deliverables' or measures of success might mean.

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P009. Androgenic Events Reported During Treatment with Intrinsa® (Testosterone Patch) Therapy: Results from an Observational Cohort Study in England

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Background: Intrinsa® is a transdermal testosterone patch, indicated for use in hypoactive sexual desire disorder (HSDD) in bilaterally oophorectomised and hysterectomised women receiving concomitant oestrogen therapy. A Prescription-Event Monitoring (PEM) study was conducted to monitor safety (particularly androgenic events) and utilisation in general practice in England. The aim was to collect at least 2000 patients.

Objective: To characterise androgenic events reported and evaluate the reversibility of these.

Methods: An observational cohort post-marketing surveillance study was conducted. Exposure data were collected from dispensed prescriptions issued by general practitioners (GPs) April 2007–August 20.. Outcome data (indication, event, patient demographic and selected clinical characteristics) were collected by sending questionnaires to GPs ≥6 months after the drug was first prescribed for a patient. Summary descriptive statistics were calculated. Follow-up questionnaires were sent for reported androgenic events (e.g. hirsutism, alopecia, cliteromegaly, voice changes), requesting further details of the event, whether the event had resolved and if so the date/time to resolution. Time to resolution was defined as the time between the date of onset and the date the event was reported to have resolved.

Results: Final cohort = 3019 female patients. The median age of the cohort was 50 years (IQR: 44-55), with a median period of observation of 305 days (IQR: 258-409). There were 66 patients (2.2%) reported to have potential androgenic events; the most frequent was hirsutism (n = 31), followed by hair loss (n = 16). Follow up questionnaires were sent to gain further information for 66 androgenic events in 58 patients (1.9% cohort). For 15 events (22.7% androgenic events), the androgenic event was reported to have resolved, whilst for 17 events (25.8% androgenic events) this was unknown. For all other events it was unspecified if the event had resolved. Time taken for the event to resolve was reported for 5 patients, with a median of 122 days (IQR: 28-357 days).

Conclusions: These results provide an estimate of the frequency of androgenic events reported during treatment with testosterone patch therapy, along with details on the level of reversibility of these events. Overall, the frequency of androgenic events was low in the cohort and similar to the frequency reported in the SmPC, though a firm conclusion on the reversibility of these events was not possible. Nevertheless, these results contribute to the ongoing post-marketing safety assessment of Intrinsa®.

P012. Photoallergy Induced by Ketoprofen Gel and Cosensitisation with Octocrylene: Study of Cases Reported in Regional Pharmacovigilance Center of Nantes

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Background: Topical ketoprofen, a non-steroidal anti-inflammatory drug marketed in France since 1993, is a potent sensitizer, leading to serious cutaneous adverse events, and particularly photoallergy. The high number of recommendations made over the last 19 years is highly impressive, in spite of all recommendations being taken, photoallergies have continued to occur and an emmerging new allergy appears like cosensitisation with octocrylene. Octocrylene is a chemical sun filter belonging to the cinnamate family included in several cosmetic and care products in order to delay photodegradation.

Objective: The first cases of contact and photocontact allergy caused by octocrylene were reported in 2003, since then the number of cases has multiplied. We have studied this cosensitisation in the Regional Pharmacovigilance Center of Nantes.

Methods: The interrogation of Nantes cases in the French National Pharmacovigilance database was effected with the terms « Ketum® gel, Profenid® gel, Topfena® gel, ketoprofen gel ».

Results: Over the period of reference from 1 January 1994 to 31 October 2010, 148 cases of adverse effects were reported following use of ketoprofen gel. The patch and photo-patch tests were performed in 64 cases, 92% were confirmed by positive photo-patch tests with ketoprofen gel and 96% with Ketum® gel. Among 11 patients who had been photosensitized to ketoprofen, 7 patients also presented positive photo-patch test reactions to octocrylene, 1 positive patch test and 3 a negative one.

Discussion: The clinical studies show that octocrylene is both a photocontact and a contact allergen. Little is known about the reason for octocrylene's allergenic activity. The use of octocrylene in sunscreen products and cosmetics is rising and sensitization to octocrylene is therefore expected to increase in the near future. In our study, our photo-patch results are in agreement with earlier findings in the literature. Octocrylene has been included in the European Standard sun filter tests Series only in 2006. It would appear that in the case of cross-reactions between the molecules of fenofibrate, acide tiaprofenic, oxybenzone and ketoprofen, the diphenylketone group, benzophenone, is responsible for this reaction. Up to now, no studies have been reported that have identified the chemical structure responsible to explain this co-sensitisation. Knowledge of allergies is vital to avoid recurrence of cutaneous effects in case of subsequent application of a sunscreen containing oxybenzone or octocrylene.

P013. Comparison between Notifications of Adverse Drug Reactions Reported by Pharmacy Students and Physicians

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Background: Since 10 years, we have set up adverse drug reactions (ADRs) report collecting system thanks to pharmacy students by educational intervention. Each student was required to notify at least two reports during their internship.
Aim: The aim of this study was to analyze student reports comparing to physicians reports during the same study period.
Methods: The retrospective study was conducted in two French departments and involved forty-three students during their internship in pharmacies. Over the reference period from November 2010 to May 2011, each notification was classified by Anatomical Therapeutic Chemical (ATC) and System Organ Class (SOC). Data were analyzed using Fisher's exact test at the 0.05 significance level.
Results: Students (n = 43), reported 97 notifications with 192 ADRs for 129 drugs. Physicians (n = 32), reported 48 notifications with 60 ADRs for 48 drugs.
The descriptive and comparative analysis highlighted different characteristics for the two groups. The most reported ADRs by students were compared with those of physicians:

- ear and labyrinth disorders (13% vs 2%; p = 0.03) with a majority of vertigo;
- general disorders and administration site conditions (10% vs 0%; p = 0.02) observed with the use of patches and topical drugs;
- psychiatric disorders (13% vs 0%; p = 0.006) with a majority of insomnia.

Phyisicians reported more ADRs associated with drugs used in diabetes (15% vs 0%; p < 0.0001) half of which were cardiac disorders due to benfluorex, and more ADRs related to vaccines (10% vs 0%; p = 0.001) with nervous system and blood disorders.
Effects that occured with analgesics were mostly reported by students (12% vs 0%, p = 0.01), half of which were due to tramadol-containing medicines.
Students were more likely to report ADRs with generic drugs than physicians (42% vs 15%, p = 0.0006).
No significant difference was found in serious ADRs (students 8% vs physicians 19%; p = NS).
Conclusion: Quality of student's reports and their specific characteristics make them a valuable addition to reports received from physicians.
This collecting system contributes to enhance ADRs reporting even after the students became health professionals.
The community pharmacists must play a prominent role in ADRs reporting of over-the-counter products and generic drugs. In this purpose a pharmacy network has been constructed for the monitoring of drug safety.

P014. Intensive Pharmacovigilance in the Odontologic Diabetic Patient with Antimicrobial Prophylaxis Treatment

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The inadequate use of antimicrobial agents, the excessive and, in many times, the professional defensive way of prescription, lack of knowledge of the sensitivity profiles, taking into account the local oral flora of every community or institution, has led to the inefficiency of the antimicrobial medicines because of the emergence of resistant bacterial strains. People migration and agglomeration may also contribute to this. Prophylactic antiobiotic treatments are very frequent in the diabetic odontologic patient.
General aim: To demonstrate the generation of antimicrobial resistance and the increase of super infection risk in diabetic patients who will receive dental surgery or other invasive maneuvers.
Specific aims:

- To know the most important habits of professional antimicrobial prescription in diabetic patients, in the Faculty of Dentistry.
- To evaluate the antimicrobial medicines use social-economic impact in patients who will undergo dental treatment in the Dentistry Faculty's Oral and Maxilo Facial Surgery Department I and II.
- To minimize adverse drug reactions.
- To identify super infection presence.

Methodology: It is a prospective, randomized, risk I category clinical trial, according to MERCOSUR regulations, that will be conducted from February 2013 to February 2015, in the Dentistry Faculty's Oral and Maxilo Facial Surgery Department I and II.
Study population will be established (4 groups of patients according to pre-medical diagnosis, n = 50 each). Microbial flora of the oral cavity will be taken from mucous membrane, tongue and periodontal pocket, to perform identification, culture and interpretive antibiograms.
Expected results: Emergence of resistant bacterial strains will be evaluated, and the presence of superinfection in diabetic patients who receive antimicrobial therapy before undergoing dental surgery or other invasive maneuvers.

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P015. One Medicine, One Health: Human and Veterinary Medicine Pharmacovigilance Node in the University Network in Uruguay

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The concept of ''one medicine – one health'' has a strong implication for the integration of human and veterinary medicine, one important example is the epidemiological study of some emerging and re-emerging zoonosis, in which the same therapeutic tools are indicated for both human and veterinary patients. Several medicinal products authorized for human use, are administered in veterinary patients, without a specific control of possible adverse reactions. It is imperative to take into account, the risks of human exposure to medicinal prod-

ucts intended for veterinary use only, such as antiparasitic drugs for scabies and lice control.

Aim: To create a Pharmacovigilance Network formed by the Departments of Pharmacology and Therapeutics of the Faculties of Human Health and Veterinary Medicine of Uruguay, which will coordinate and centralize the consultations of all Health Areas nodes. It will follow the directives of the Ministerial Official Authorities of our country, thus involving all medical professionals and technicians; human patients and the veterinarian-client-patient relationship, and responding to the primary concept of "one medicine, one health"; it will contribute to the rational use of drugs and technologies that are nowadays, used in common clinical practice in both human and veterinary medicine.

Methodology: Experimental studies and controlled clinical trials in human and veterinary patients, from randomized treatments and, observational studies from *non*-randomized or controlled treatments. These studies will be selected based on exposure, pathology or undesirable effects, for case-control and cohort studies. A solid training for teachers, technicians and students of both human and veterinary medicine in pharmacovigilance and technovigilance will be promoted.

Expected results: Possibility to deal with specific situations, such as antimicrobial resistance, environmental chemical residues and an indiscriminate interspecies use of drugs. The development of an early warning system, with the active participation of all actors involved, will have a great social impact, because in Uruguay, as well as in other Latin American countries, Pharmacology and Pharmacovigilance concepts and learnings in human and veterinary medicine, are quite far away from each other. Diffusion will be made using all the systems according to the investigations importance and seriousness. Scientific publications will be published; academic conferences and seminars will be organized at our Universities and video-conferences will be broadcasted to Uruguay and to the rest of the region, which also could reach the population in general, in an accessible language.

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P017. What are the Perceptions of Professionals When Assigning Causality to Anti-Cancer Agents in Early-Phase Oncology Clinical Trials?

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Background: Causality assessment is a process that takes place in early-phase oncology clinical trials, whereby the clinician on staff determines whether an adverse event can be attributed to the drug/agent being tested or if it is due to an external cause. The purpose of this study was to develop a psychosocial understanding of how clinicians assign causality in order to improve the process of drug development within oncology clinical trial. There has been little research conducted on causality attribution practices of professionals working in oncology clinical trials.

Methods: To the best of our knowledge, this is the first qualitative study of its kind to explore causality assessment in early-phase oncology clinical trials. Thirty-two qualitative interviews were explicated with the aid of "Naturalistic Decision Making". Participants included experienced medical oncologists, hematologists and clinical trials coordinators, from academic cancer centres across Canada. A phenomenological research design employing an interpretive-descriptive research design was utilized. A thematic analysis was performed in which a textural and structural description of the interview data was used to create an invariant structure which served as the basis for a composite summary.

Results: The process of assigning causality is extremely subjective and full of uncertainty. Physicians had no formal training on how to assign causality. Communication issues exist between clinicians and their sponsors, as well as between clinicians and the patients on the trial. Clinicians also fear over-attributing causality to the agent under development, as this can be unfair to the drug development process, and are often pressured by patients to attribute causality in a certain way.

Conclusions: There are many problem areas when attributing causality, all of which have serious consequences, but clinicians used a variety of methods to cope with these problem areas.

P018. Using Analytical Concepts in Pharmacoepidemiology for Postmarketing Surveillance of Medical Devices

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Comparative efficacy research and medical device postmarketing surveillance have drawn increasing scrutiny from worldwide regulatory agencies. Product recalls for implantable and non-implantable devices in the US and EU has occurred. In the US, FDA's CDRH has specific postmarketing surveillance reporting requirements (CFR 803.1 through 803.5) as does the EC with MEDDEV 2.12-1 rev6 & rev7. While postmarketing surveillance of medical devices can be rigidly focused and based on device type and use, there are certain safety variables that are common to both drugs and devices. This led to the hypothesis that pharmacoepidemiology/pharmacovigilance analyses generally used for drugs could also be used for devices.

Using a random sample of ophthalmic medical device reports received during the first quarter of 2012, we reviewed coding of each report for risk-based purposes. In the US, medical device reports (MDRs) are coded using FDA Patient Problem codes. Internally, reports were also coded using MedDRA PT terms. All coding was done by Safety Scientists. We wanted to determine the adequacy of MedDRA for device risk assessment. Statistically we ran a disproportionality program on the device data[1] and a U-Chart. The remaining data was summarized using descriptive statistics. We found we could apply drug safety methodology concepts to device reports although limitations were noted. Coding deficiencies using both MedDRA and FDA Patient Problem codes were identified. Other limiting factors in the ana-

Table I. Comparison of drug and device safety data analysis

Type of data	Drugs	Devices
Demographics	Yes	Yes
Pareto, Grid, Tornado	Yes	Yes
Geographic Data	Yes	Yes
Serious-Expedited Reports/MDR Reports	Yes	Yes
U Chart	Yes	Yes
Disproportionality Analysis	Yes	Yes
External Safety Database Available?	Yes	Yes
ICSR Type Data	Yes	No

lysis included causality assessments (known as root cause analysis for devices), access to external databases (more difficult to retrieve medical device data than drug data), and lack of severity, concurrent therapy, co-morbidities and patient outcomes associated with device reports.

Device manufacturers can utilize drug safety pharmacoepidemiology/pharmacovigilance methods to assist in the postmarketing surveillance of medical device safety data as long as the limitations inherent in the analysis are understood.

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P019. Importance of Pfizer Medical Information Center (MIC) in Detection, Processing and Reporting of Adverse Events (AEs)

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The evaluation of safety of newly marketed drugs is a major public health problem. CIMs are important resource to facilitate the reporting of AE, with greater accessibility and which have health care professionals highly trained.

Aim: Demonstrate that CIM Pfizer performs an important role in promotion of drug safety, meeting company needs and local standards related to the reporting of spontaneous AEs as the main method of post marketing surveillance of products.

Methods: The CIM Pfizer will conduct a retrospective analysis of spontaneous AEs reported to the Pfizer Drug Safety Unit (DSU) from January 2011 to September 2012, identifying the source of the report, age range of affected patients, timeline of reporting to DSU, the impact of AEs on the treatment and doctor visit, AEs most frequently reported and product related, including the number of AEs reported directly by the user and those detected by CIM Pfizer.

Results: During the time period considered for this paper, values for the methodology will be plotted.

Conclusions: The main purpose of spontaneous reporting of AEs is to provide an early warning or suspicion, which have not been recognized before marketing a drug because of the limitation of clinical trials. The training provided by Pfizer DSU allows reporting AEs in a timely fashion according to local and company requirements. With this, setting opportunities for educational interventions to promote safer use of medicines and proposing and implementing improvements to increase and enhance the quantity and quality of the information gathered, thus identifying valuable information to establish the safety profile of drugs. To demonstrate the effectiveness of this program will be sufficient to compare the number of cases detected by the CIM and reported directly by users. Impartially and objectively, are covered as far as possible the information requirements for an adequate assessment of causality.

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P020. Observational Study to Compare the Contents and Information Furnished in Commonly Used ADR Reporting Forms Filled by the Healthcare Professionals

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Background: Spontaneous adverse drug reaction (ADR) reporting form is a vital tool for collecting information about ADRs, which helps in establishing the causal assessment and generating a signal. This is feasible if quality information is translated into the reporting form by HCPs. Hence, present study was carried out to compare efficiency of HCPs in translating ADR information in CDSCO form, Yellow Card, Medwatch form and Blue form.

Methods: In a cross-sectional study, 50 doctors, 50 nurses and 50 pharmacists with the basic knowledge of pharmacovigilance were asked to fill different ADR reporting forms using simulated ADR case reports. Filled forms were analysed for their contents, information captured and time taken to fill these forms.

Results: All the forms had 24–26 items to furnish information. Patient information, description of the event, list of suspected drugs, date of reaction, relevant test, outcome of the reaction, date of starting and stopping the drugs, concomitant medication was common in all the forms. Information regarding dechallenge was lacking in

the Yellow card and Blue form. Blue form also lacked the information on rechallenge. Only CDSCO form had column to causality assessment.

Nurses took the longer time (range 11–20 min) to fill all the ADR reporting forms than doctors and pharmacists. Doctors and nurses took 9.8 min and 11.3 min respectively to fill the Yellow card. Pharmacists took 8.58 min to fill Blue form. Majority of the nurses and pharmacists had written the patients' full name instead of initials. Majority of HCPs missed to fill reporter's information in all the forms. In the CDSCO form, information on relevant laboratory data was mentioned correctly by 70% of the doctors, 10% of the nurses and 64% of the pharmacists. Nurses (90%) did not fill the information on concomitant medications in CDSCO form. In the medwatch form, nurses (90%) did not fill the information on concomitant medications. Information on starting/stopping was not mentioned by 80% of nurses in Yellow form. In the Blue form, nurses (100%) missed to fill the information on the treatment of reaction and comments, where 80% did not fill sequelae of reaction.

Conclusion: Yellow card and Blue form lacks the information required for assessing causality assessment. Study suggested that the quality of information translated by the HCPs was inadequate and they needs to be sensitized more on the elements of pharmacovigilance.

P021. Abacavir Hypersensitivity Reaction in an HLA B*5701-Negative Patient

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Introduction: Abacavir is a nucleoisde reverse transcriptase inhibitor used in the treatment of HIV. Abacavir hypersensitivity reaction (ABC HSR) occurs in approximately 5%–8% of patients. Studies have demonstrated the association between HLA B*5701 and the occurrence of ABC HSR. This has led to the routine testing of every HIV patient at diagnosis for this gene. The ABC HSR manifests commonly as fever, rash, fatigue, GI symptoms and respiratory symptoms. Studies have shown that the likelihood of ABC HSR occurring in someone that has tested negative for HLA B*5701 to be exceptionally low.

Case Report: 48-year-old Caucasian female patient. Diagnosed HIV positive in 2003, tested HLA B*5701 negative in 2006, started on Kivexa 1 tablet ON (abacavir and lamuvidine) and Efavirenz 600 mg ON in April 2007. Within 6 weeks of initiation of treatment patient presented with polymorphic, erythematous papular rash on both arms with associated cough and wheeze. Kivexa was discontinued and symptoms resolved within 7 days. Patient was subsequently prescribed Truvada one tablet ON in place of Kivexa.

Discussion: This case demonstrates a rare occurrence of ABC HSR in an HLA B*5701 negative patient. Various studies have demonstrated HLA testing to have a negative predictive value of between 97.8% and 100%. Our case report is also noteworthy due to the fact that the ABC HSR occurred in a Caucasian patient. The wealth of evidence on the relationship between ABC HSR and HLA B*5701 indicates that its use as a screening test is most sensitive in a White population.

Conclusion: Since the link between HLA B*5701 and ABC HSR was established it has become standard practice to test all newly diagnosed HIV patients for this HLA. Clinicians prescribing ABC should have a low threshold for suspecting HSR irrespective of HLA B*5701 status. This report shows that, although HLA testing has dramatically reduced occurrence of ABC HSR, there is no substitute for clinical vigilance.

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P022. HIV, Highly Active Antiretroviral Therapy (HAART), Pancreatitis: Is There a Relationship?

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Introduction: The frequency of pancreatitis with HIV infection per se is not well known. However viral infections have been implicated in acute pancreatitis. Common causes of pancreatitis are gallstones and excess alcohol consumption. We present 3 cases of pancreatitis in our HIV cohort.

Case reports: A 45-year-old man diagnosed with HIV in 1984, on highly active antiretroviral therapy (HAART) (Stavudine, Didanosine, Ritonavir) developed pancreatitis in 1998. He had no gallstones and was not known to take excess alcohol. His weight is normal for his height with a body mass index (BMI) of 25. His HAART was stopped and his pancreatitis resolved.

A 45-year-old man diagnosed with HIV in 2004, on HAART (Truvada, Nevirapine) developed pancreatitis in May 2010. Ultrasound scans (USS) revealed gallstones. He binge drinks alcohol monthly. His weight is normal with a BMI is 21. He was treated with standard therapy for pancreatitis and recovered. HAART was continued.

A 38-year-old lady diagnosed with HIV in 2004 also on HAART (Truvada, Atazanavir, Ritonavir) developed pancreatitis in 2012. USS revealed gallstones. She does not take alcohol. She is overweight with a BMI of 45. She had been having abdominal pains since July 2011. She was treated with standard therapy for pancreatitis and recovered. HAART was stopped.

Discussion: Pancreatitis related to HAART is uncommon. 157 cases of pancreatitis has been reported to the Medicines and Healthcare Products Regulatory Agency (MHRA) due to HAART in the United Kingdom (UK). This represents 2.3% of adverse drug reactions due to HAART. There are 36 cases of pancreatitis reported with Didanosine, 25 with Stavudine, 10 with Ritonavir, 8 with Efavirenz, 4 with Truvada, 4 with Tenofovir and 1 with Atazanavir. The first patient developed pancreatitis that was only diagnosed with laparotomy after various investigations. There were no gallstones. His pancreatitis resolved after his HAART was stopped. The second and third patients had gallstones. The second patient continued with his HAART but the third patient's HAART was stopped. It is unlikely that she developed pancreatitis due to HAART as she had been experiencing abdominal pains before starting HAART.

Conclusion: Pancreatitis due to HAART is uncommon especially for the newer agents, but it may occur. We need to bear in mind that

HAART is a possible cause for pancreatitis in HIV patients on treatment. However it is more commonly caused by gallstones as in the case of our 2 patients.

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P023. Review of Adverse Events Following Immunization (AEFI) Reports after 2011–12 Seasonal Influenza Vaccination in Taiwan

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Background: Taiwan National Adverse Drug Reaction Reporting System was put in place to collect and analyze spontaneous AEFI reports to ensure safety of seasonal influenza vaccination since 2010.
Objective: To identify potential safety concerns that warrant further evaluation after 2011–12 seasonal influenza vaccination.
Methods: All AEFI reports received from October 1, 2011 through February 8, 2012 following 2011–12 seasonal influenza vaccination were reviewed. Reported adverse events were categorized according to MedDRA System Organ Class. Reports of death and certain medically important conditions were followed up by medical charts review. We calculated age-specific AEFI reporting rates for serious and non-serious reports.
Results: We received 151 reports after 2 572 037 doses of 2011–12 seasonal influenza vaccines administered (reporting rate 5.87 per 100 000 doses administered); 53 (35.1%) reports were classified as serious, including 1 report of death. 87 (35.1%) reported events were related to general disorders and administration site conditions, followed by 38 (15.3%) events of nervous system disorders and 37 (14.9%) events of skin and subcutaneous tissue disorders. The reporting rate of serious reports was the highest among the age group of Mycoplasma infection whereas the SJS case had no other identifiable etiologies attributable.
Conclusion: On our review of adverse events following 2011–12 seasonal influenza vaccination, no potential safety concerns were recognized. Nevertheless, reports of SJS following seasonal influenza immunization shall be carefully monitored because of its high morbidity and mortality. Package insert was suggested to be added with related information to warn health care professionals and the public on this potential risk.

P024. Perception of Causality Terms, a Personal View

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Background: For the assessment of spontaneous reports, causality assessment is a common approach. Many schemes are available for causality assessment which use subjective causality terms like "doubtful", "possible", "probable" and "certain". Although used on a large scale, it is not clear if these terms are perceived in the same way by everyone.
Objective/Aim: To map out the perception of the above mentioned terms by three target groups: pharmacovigilance experts, health care professionals and consumers. Also possible differences in perception were studied when ADRs were associated with drugs or vaccines.
Methods: Data were collected by the use of a web based questionnaire presented to health care professionals and patients who reported an adverse drug reaction at the Netherlands Pharmacovigilance Centre Lareb, and pharmacovigilance experts worldwide. All three target groups were asked to indicate an upper and lower limit (0–100%) for the probability of an adverse drug reaction in relation to causality terms, both for vaccines and drugs. These terms were presented in a random error. It was tested whether the data were normally distributed. In the event of a non-normal distribution, data were compared with the Mann-Whitney U test. All the tests were performed using SPSS 16.0.
Results: All four causality terms were rated in a logical order by all of the three target groups. Significant differences existed between the rating by the various target groups. Most differences existed between healthcare professionals and consumers. Pharmacovigilance professionals and consumers were most similar in their rating.
No statistical significant differences existed between the rating of the causality terms related to adverse reactions caused by drugs and vaccines, with the exception of the rating of the lower limits of "probable" and "certain" by pharmacovigilance professionals. The number of years of experience with pharmacovigilance has no influence on perception.
Discussion: When communicating about safety issues using causality terms, one should be aware of differences in perception, which may result in over- or underrating of the causal relationship. Despite scrutinous assessments aimed at establishing the causal relationship between suspected drugs or vaccines and ADRs we risk failing to get the message across in a consistent way.
Conclusion: The causality terms "doubtful", "possible", "probable" and "certain" are rated in a logical order by pharmacovigilance professionals, healthcare professionals, and consumers. However, large differences in perception exist, not only between target groups but also within groups.

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P025. Communicating Comprehensive Safety Data Gained from Clinical Trials to the Scientific Community: Opportunities and Difficulties from an Example with Moxifloxacin

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Table I. Population analysed (number of patients [moxifloxacin/comparator(s)] from actively controlled trials [phase II – phase IV studies - 1995-2010])

Study design	Double blind: 11299/11p70	Open label: 3682/3953	
Route of admin.	PO: 10613/10685	IV/PO: 3431/3415	IV: 937/923
Risk groups	PO	IV	PO
Age = or >65	2451/2403	1373/1334	170/191
Diabetes m.	777/717	923/917	80/72
Renal impair.	1283/1229	888/863	203/218
Hepatic imp.	146/163	183/196	46/46
Cardiac disor.	1476/1404	1167/1136	106/104
BMI = or <18	318/365	116/115	45/53

Introduction: Comprehensive safety data assembled from clinical trials are communicated to Regulatory Authorities but rarely appear in detail in publicly available literature (often focusing preferentially on efficacy). This may cause disconnection between labeling and daily clinical perception and creates uneasiness amongst clinicians (who may feel they are shown only the tips of potentially important safety issues).
Aim: Our aim was to test a new approach consisting of presenting the randomized controlled clinical trials safety database of a widely used drug in a form accessible to clinicians while maintaining scientific integrity.
Methods: Moxifloxacin, a fluoroquinolone antibiotic, was selected based on (i) its large clinical use (140 millions prescriptions to date [PO, IV/PO, IV]) and (ii) questions raised about its safety (general suspicion about the whole fluoroquinolone class; possible adverse clinical outcomes of QTc prolongation; specific actions taken by EMA following occurrence of rare but serious cases of hepatotoxicity and skin reactions). The table shows the analyzed populations (all actively controlled trials). Crude incidences (with filters to highlight the most meaningful differences) and relative risk estimates (Mantel–Haenszel analysis stratified by study) for AE, ADR, SAE, SADR, treatment discontinuation due to an AE or ADR, and fatal outcomes related to an AE or ADR were calculated (overall and by study design, indication, comparator(s), and risk groups).
Results: The study took about 2 years to complete due to the need for extensive analysis of original data, compilations, construction and assessment of the filters, and integrity checks. It required involving 2 employees of the manufacturer (with their supporting staff), 1 independent author, and a writing bureau. It essentially showed that the safety of moxifloxacin was comparable to that of comparator(s) (that were all standard therapy[ies]) at the time each trial was designed. Results of the study have now been accepted for publication as an original research paper (less than 6000 words) in an on-line journal with supporting exhibits and supplementary material.
Conclusions: Clinicians currently assess risk based on information in the label of a drug and spontaneous reports. The approach described here (i) is costly in terms of manpower effort, (ii) provides information on patients enrolled in clinical trials only, and (iii) cannot detect very rare side effects. However, it allows clinicians making direct comparisons of the risks of one drug vs its accepted comparators for its main indications based on data compiled over a long time period.

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P026. Drug-Induced Hypersensitivity Reactions in Hospitalized Patients

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Background: Drug-induced hypersensitivity syndromes including cutaneous adverse drug reactions (ADR) are some of the most prevalent induced ADR. These reactions are unfreqently serious, but because of its high prevalence they are one of the most common causes of drug - related admission. Some of them, like DRESS, can be very serious and life threatening. The aim of this study was to determine the prevalence, types and seriousness of these entities in a tertiary care hospital.
Methods: The study was performed by the pharmacovigilance system of a public tertiary care hospital (Hospital Argerich) in Buenos Aires, Argentina. The period included was between June 2008 and April 2012. All hospitalization rooms were evaluated, and Naranjo score was applied to asses the causality of a drug in a medical adverse event. Certain and probable reactions were included.
Results: We detected 2463 ADRs in this period, 163 (0.62%; 95% CI 2.8–10.43) were hypersensitivity reactions. 130 (78.31%; 95% CI 17.09–48.85%) were non serious cutaneous ADRs, 16 (9.82%; 95% CI 5.25–14.38) were considered serious cutaneous drug reactions and 17 (10.24%; 95% CI 7.54–12.93%) were other serious hypersensitivity reactions. The drugs that most commonly cause serious cutaneous ADRs were antiepileptic drugs 5 (31.25% 95% CI 8.54–53.96) cases, antibiotics 6 (37.5% 95% CI 13.78–61.22) cases, and there was 1 case of nonsteroidal anti-inflammatory drugs, 1 case of filgrastim, 1 case of allopurinol, 1 case of tenofovir and 1 case of dexamethasone. Other hypersensitivity reactions were 8 cases of angiooedema, 2 anaphylactic shock and a case of transfution related lung injury (TRALI).
Discussion: We found a relative low incidence of cutaneous drug reactions according to other international bibliography and there has been a similarity considering the drugs involved. A high percentage of these ADRs were serious including a fatal case.

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P027. Causality Methods in Cosmetovigilance: Comparison of Colipa and PLM versus Global Introspection

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Background: The European Cosmetics Regulation requires a post-marketing system for detection of undesirable effects on human health of cosmetic products. Colipa, the European cosmetic, toiletry and perfumery association, provided guidelines for causality assessment of these effects. In addition, another causality method originally designed for causality rating in Post Launch Monitoring (PLM) of novel foods has been employed to assess causality of cosmetic products.

Objective/Aim: In this study these two causality schemes for consumer cosmetic products were validated against clinical assessment, using the method of global introspection (GI), based on the method of the World Health Organisation (WHO)
Methods: Information upon the nature of undesirable effect(s) by use of cosmetic products was obtained directly from the consumer by use of a questionnaire. A total number of 100 reported cases were randomly selected, which were spread among different product categories. For all cases, causality assessments were independently performed by three experienced assessors in pharmacovigilance. Spearman correlation coefficients for the comparison of the outcome of the GI method versus the Colipa and PLM schemes were calculated using SPSS 16.0.
Results: The overall Spearman correlation coefficient was 0.74 for comparison of Colipa versus GI, whereas this was 0.50 for PLM versus GI. The sensitivity was 0.95 for both the Colipa and PLM method, specificity was 0.84 for Colipa and 0.40 for PLM.
Discussion: Although the PLM method originally was designed for the causality rating novel food products, over the years experience had been also been gained with topically applied products. The main difference between Colipa and PLM, which would account for the difference in concordance, is the course of the reaction which is not taken into account in PLM. Both Colipa and PLM do not allow for a short latency – seconds to minutes- between reaction and suspected product to be taken into account. Moreover, both methods, being presented as an algorithm, are based on strict answers as yes/ no/ unknown, whereas the GI method is less rigid and more closely resembles clinical observations. This explains some of the remaining differences in causality outcomes between Colipa or PLM and GI.
Conclusion: From these results it can be concluded the performance of the Colipa causality method yielded better correlation to GI than PLM causality method. The factor identified from comparison of these two schemes as having greatest impact was the course of the reaction.

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P028. VaccineVigilance: Safety Profile of Influenza Vaccine - Guillain Barré Syndrome

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Background: Influenza viruses are among the most important pathogens affecting humans, since they can cause severe asymptomatic infection, including death. For these reasons, major medical societies recommend vaccination for all people from six months old. An important aspect to be considered in the implementation of vaccination programs is the proper orientation to allow the public understanding of the characteristics of the vaccine, its benefits, limitations and possible adverse events following immunization (AEFI).
Objective: To review, in the indexed literature, articles which present a possible association of influenza vaccines, including vaccines against influenza A (H1N1)/2009 and seasonally used in national vaccination campaigns, in particular about the development of Guillain Barre Sydrome (GBS).
Materials and Methods: The methodology used in this paper is to review and analysis of articles in Portuguese and English and relate to suspected adverse events after influenza vaccine (seasonal and/or pandemic). The databases used are the Web of Science, PubMed and Scielo. Were also searched conference abstracts on the subject.
Results: There were 15 studies that met the inclusion criteria: 12 studies for review and three epidemiological studies. There are few epidemiological studies regarding GBS.
Conclusion: The studies collected showed that the frequency of occurrence of GBS after vaccination does not exceed the occurrence of other etiologies, both are considered seasonal or pandemic influenza vaccine A/H1N1 2009.
Considering the 2009 H1N1 influenza vaccine, the frequency of serious adverse events temporally related to the vaccine was similar to the estimates presented in the literature. The occurrence of GBS was not higher than expected incidence in the general population. Still, it was found that the safety profile of the vaccine is compatible with other influenza vaccines in use worldwide.
While these data indicate that the positive safety profile of influenza vaccines, it is necessary to improve the system for capturing and reporting of adverse events in the world, there may be underreporting of events reported since it is not mandatory for health professionals in some countries. Moreover, there is a need to improve the quality and timeliness of investigations AEFI because many events are reported incompletely and in most cases the follow-up for investigation of cases is difficult. The use of influenza vaccine continues to be an important factor to control influenza virus infection in the world.

Table I.

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P029. A 5-Step Approach for Disproportionality Analysis

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Introduction: Disproportionality-analysis (DA) is becoming increasingly important in the analysis of spontaneous reporting databases. An example is the Eudravigilance Database where DA will have an important role in highlighting potential signals. Due to selective reporting, there are however large differences in the composition of the various datasets which make interpretation of the results of this approach complex. A detailed knowledge of the dataset set on which DA is conducted is needed for a correct interpretation.

As a routine, DA is usually carried out on the entire dataset. Factors influencing the internal validity like bias, confounding and misclassification may strongly influence the outcome and thus the signalling abilities of the databases. In addition, clinical and pharmacological knowledge is not taken into account in this routine screening. For this reason, a more detailed and structured analysis is needed to understand the nature of the signal. We propose a five-step approach enabling a better integration between the clinical, pharmacological and statistical data. These five steps can be defined as:

Step I Selection of dataset: DA should be limited to those reports representing patients at risk. In example, when analyzing reported ADRs for a pediatric drug, a comparison with similar reports is advisable.

Step II Selection of cases: One or more preferred terms can be combined when analyzing a specific clinical entity. As a consequence, the other ADRs in the selected dataset are considered as controls.

Step III Define drug exposure: Likewise separate drugs or groups of drugs can be selected.

Step IV Define co-variables for stratification: Consider stratification of various co-variables like age, gender, therapeutic class, country or source. Based on these stratification criteria, contingency tables can be displayed by which confounding and effect modification can be studied in more detail. Similarly drug-drug interactions or syndromes can be studied.

Step V Select method to be used: Although the various measures of disproportionality have their own advantages, differences are limited when more than 4 reports are received.[1] Only suspected or all medication can be taken into account in the analysis.

Signals represent clinical events and the design of DA should be tailored for retrieving the optimal information. By using this stepwise approach and making well-considered choices in the design, DA is a powerful tool for strengthening the signals under study. In this presentation we will illustrate our approach by means of some practical examples.

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P030. Methylphenidate Off-label Use

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Introduction: Methylphenidate is a piperidine derivative structurally and pharmacologically similar to amphetamin. Methylphenidate is indicated for Attention Deficit Hyperactivity Disorder (ADHD) in children aged 6 years of age when remedial measures alone prove insufficient. In adults, its indication, except in narcolepsy, is not defined. Methylphenidate received its regulatory approval 60 years ago with a first registration in Switzerland in October 1954.

Objective: To evaluate the off-label use and its characteristics from a database of spontaneous reports.

Methods: This study analysed data from the French Pharmacovigilance Database of adverse drug reactions spontaneously reported by health professionals from 1985 until December 2011. Off-label use was evaluated with respect to age.

Results: In the French Pharmacovigilance database, 181 adverse drug reactions have been reported with methylphenidate. Neuropsychiatric effects were the most frequent adverse event reported (41%) followed by cardiovascular and cutaneous side effects (14%). 143 children are concerned, 113 boys and 30 girls (mean age 10.6 ± 3.3 years), of which 46 off-label use (30%). There are 38 adults (20 men and 18 women), of which 32 off-label use (88%). In adults, methylphenidate was used for the indication of depression; this was associated with serious adverse events of drug dependence, overdose and suicide attempt. Off-label use was detected in 43% of cases.

Discussion/Conclusion: More than 40% of the patients with drug reaction received medical treatment off-label use. A "contract of care" was instituted in 2008 followed by a temporal decrease of off-label use, which has increased in 2011. These signals can not be ignored. Pharmacovigilance database of spontaneous report are not appropriate to evaluate the extent of the problem. In the US, treatment for ADHD gave the largest number of adverse drug reports for both groups age 2-10 and 11-16 years. Despite 60 years of marketing, methylphenidate safety has not been evaluated for long-term use. The SPC states that safety has not been evaluated for long-term use. Additional long-term exposures and independent clinical studies are necessary to establish the long-term profile safety of methylphenidate. ADHD diagnostic and methylphenidate indication should be more respected and guidelines prescription status controlled. Proactive information of the different stakeholders is needed.

P031. Comparing and Contrasting the Utility of Risk Management Plans and Periodic Safety Update Reports in Pharmacovigilance: A Regulatory Viewpoint

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Objective: This paper compares and contrasts the utility of RMPs and PSURs in pharmacovigilance.
Summary: A Risk Management Plan (RMP) is a description of the risk management and mitigation measures set up by the sponsor to deal with the anticipated risks associated with their product and should be submitted during the pre- and post-authorization phases of the product's life cycle. The Periodic Safety Update Report (PSUR), a risk management tool for regulated marketed health products, is designed as a stand–alone document. Signals of new or increased risks associated with the marketed health products may be identified from these assessments and appropriate risk mitigation or management measures put in place to mitigate these risks.
The RMP may be defined as a set of pharmacovigilance activities designed to identify, characterize, prevent, or minimize risks related to the medicinal product; assess the effectiveness of those interventions and to communicate those risks to patients and health care providers. Further pharmacovigilance activities after marketing use the PSURs as an important post-market tool for the evaluation of the benefits and risks of a medicinal product and to support ongoing risk management initiatives, as well as a tracking mechanism to assess the effectiveness of such measures.
Description: Regulatory requirements regarding submission frequency and content of PSURs and RMPs vary with regulators in the different regions worldwide (EU, Japan, US, Australia and Singapore). While both PSURs and RMPs provide important information about the safety of regulated health products, in PSURs the data on adverse effects of drugs is used to identify new safety signals, particularly for rare or unusual events. The RMP includes identified, anticipated risks and additional information on the planned mitigation actions for each anticipated safety concern.
Outputs: Both RMPs and PSURs are important information tools in pharmacovigilance. They permit continuous surveillance of any public health risk associated with a health product and together are vehicles used to identify and manage the risks in question. Both need to be submitted regularly to regulators in order to enable continuous evaluation of the benefit-risk profile of therapeutic products.
Outcomes: The PSUR helps in the identification of the risks associated with drug use, while the RMP provides a means to minimize and/or mitigate the risks, anticipated or newly identified. Both play significant but complementary roles in the continued monitoring and management of the safety of health products throughout their life cycle. They're not mutually exclusive.

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P032. Increased Risk of Hepatosplenic T-Cell Lymphoma Related to Combination Therapy with Anti-Tumor Necrosis Factor and Purine Analogue Drugs

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Objective: This paper highlights the need for surveillance and vigilance for cancer events in patients treated with the two product classes.
Summary: The risk of developing lymphoma is a significant safety issue in the management of Inflammatory Bowel Disease (IBD).[1] Although IBD patients have an increased risk of developing several cancers, study data show a particular increase in the risk of a rare, usually fatal lymphoma called hepatosplenic T-cell lymphoma (HSTCL), affecting primarily adolescent and young adult IBD patients treated with Tumor Necrosis Factor (TNF) blockers in combination with purine analogues (azathioprine and/or 6-mercaptopurine). Results from a meta-analysis suggests that IBD patients treated with purine analogues have a 4-fold increase in the risk of developing lymphoma for the same patient population.[2] Although examination of lymphoma risk in patients receiving TNF blockers is often confounded by previous or concomitant use of immunosuppressive agents, the risk of HSTCL appears to be increased in patients where TNF blockers are used together with or following purine analogue drugs.[3]
Outputs: Many studies have demonstrated an increased incidence of lymphoproliferative disorders in IBD patients receiving TNF blockers as well as with purine analogues.[4,5] Worldwide case reports have shown an increased risk of HSTCL, primarily affecting adolescent and young adults with IBD who were treated with TNF blockers and azathioprine and/or 6-mercaptopurine either in combination or in close succession.[6] This raises the need for awareness and caution as well as a requirement to weigh the benefits against the risks for the use of these products in this fashion.
Outcomes: In North America, product safety information for TNF blockers used in the management of IBD indicates the risks and benefits of using TNF blockers, together with or following azathioprine, and/or 6-mercaptopurine therapy. A black boxed warning highlights the risk of HSTCL for patients receiving concomitant treatment of a TNF blocker and purine analogue(s). Safety information for the pertinent purine analogues have been similarly updated in several regulatory jurisdictions to reflect this increased risk. Such use should be carefully weighed when prescribing these drugs to children and young adults, especially for the treatment of IBD where there may be alternative treatment means. Whether these risk management strategies are sufficient to minimise risk of HSTCL or if need for more stringent measures is warranted, remains to be seen.

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P033. Monitoring of Drug Usage as a Tool to Predict Institutionalization in the Elderly Population

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Introduction: Institutionalization is often used as a marker of frailty in observational studies conducted in the elderly population. The ability to predict the likelihood of institutionalization based on patterns of drug usage may be a useful tool in clinical practice.
Aim: To develop and assess the reliability of a model to predict institutionalization through patterns of drug usage in the elderly population.
Methods: Potential predictors of institutionalization were identified through literature review and clinical expertise. A case-control analysis nested within a cohort of community-dwelling elderly patients (N = 62 172) was conducted, using data from the Quebec prescription claims databases (2000–2009). Patients institutionalized during the follow-up period were retained as cases. For each case, on the date of institutionalization, up to 4 controls were selected through risk set sampling. Controls were matched on the year of entry in the main cohort of elderly, age (65–74, 75–79, 80–84, 85 and over), and gender. Exposure to the selected drugs (potential predictors) was assessed through the presence of at least one dispensing in the prescription database during the year prior to index date. Conditional logistic regression models and c-statistics, which represents the proportion of cases of institutionalization that can be predicted by these factors, were used to develop the predictive model.
Results: Drugs associated with an increased risk of institutionalization were: antipsychotics (OR: 3.45; 95% CI: 2.91-4.08), antidepressants (OR: 1.45; 95% CI: 1.25-1.68) and hypoglycaemic agents (OR: 1.63; 95% CI: 1.38-1.92). Protective effects were found for the use of statins (OR: 0.64; 95% CI: 0.53-0.78) and antihypertensives drugs (OR: 0.72; 95% CI: 0.63-0.83). No statistically significant association was found with drugs prescribed for osteoporosis, glaucoma, urinary incontinence, or respiratory drugs, diuretics, proton-pump inhibitors, cardiovascular drugs, antiparkinsonians. Using the c-statistics for assessing the level of predictability, all together, these factors predict 81% of the probability of institutionalization in the elderly population.
Conclusion: This study shows that drug use may be a useful tool to predict institutionalization in the elderly population. Since institutionalization is a reflection of frailty and is part of the pathway leading to death, monitoring of drug usage may be a useful tool for clinical practice.

P034. Pharmacovigilance in Dentistry. Temporomandibular Disorders and Bruxism are Related with CNS Drugs Use

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McNeill defines with the generic term "Temporo Mandibular Disorders" an heterogeneous group of psycho-physiological disorders with common features of orofacial pain, masticatory dysfunction, or both. Okeson defined them as multifactorial pathologies where the triggers were conditioned by predisposing and perpetuating factors. In Uruguay, Riva showed in a national survey a high prevalence of 55% with at least one symptom of TMD (57% Montevideo 53% and in the country side and other cities) and 44% with at least one sign of TMD (47% Montevideo and 41% in the country side and other cities). In the same study they found the para functional wear out facets presence as an indicator of being suffering or have suffered Bruxism with a high prevalence, Montevideo 71.95% and 62.17% country side and other cities. It is important to emphasize the role of bruxism as the cause of TMD. Secondary Bruxism is related to irregular sleeping cycles or oral movement disorders such as dystonia or dyskinesias induced by drugs. There is evidence that CNS drugs exacerbate and/or worsen the bruxism and TMD either. The female population between 20 and 50 years old was the most affected and 7 out of 10 benzodiacepine consumers are women; the effects of antipsychotics occur more frequently in female population.
General aim: To find a link between drug use, bruxism and TMD.
Specific aim: To analyze the data of the 1st National survey conducted in Uruguay about the prevalence of bruxism and TMD, relating to the consumption of drugs, discriminating by gender and age.
Methodology: Analysis of data obtained in the survey made with two populations in Uruguay, Montevideo and, crossing the different clinical variables and *anamnesis* with reports of psychopharmacological agents usage. At the variables intersection, 2 sub-populations will be taken: on one hand men and women who use this kind of drugs and on the other hand, men and women who do not use. This way you can compare how this variable affects the prevalence of both conditions.
Expected results:
To determine the prevalence of both conditions in men and women who use and do not use drugs.
To apply intensive pharmacovigilance at the Department of Diagnosis and Treatment of TMD patients.

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P035. The Utilisation of Ivabradine in Primary Care in England; Focus on Compliance with Licence

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Background: The anti-anginal ivabradine (Procoralan™) reduces heart rate (HR) by inhibiting the sino-atrial node's funny current (I_f). It was licensed in Europe in October 2005 for chronic stable angina (CSA) with normal sinus rhythm (NSR) and a contraindication or intolerance for beta blockers (BBConI).[1] In October 2009 a licence extension allowed concurrent beta blocker use.[2] A Modified Prescription-Event Monitoring (M-PEM) study was conducted for post-marketing surveillance.
Objectives: To describe utilisation characteristics and to examine off-label use in patients prescribed ivabradine in England under real-life primary care conditions, prior to the licence extension.
Method: This study used an observational single exposure cohort design. Exposure data were collected from dispensed prescriptions issued by General Practitioners (GPs) from Nov 2005 to May 2009. Outcome data (indication, prescriber, patient demographic, clinical characteristics) were collected by sending questionnaires to GPs 6 months after each patient's first GP prescription. Summary descriptive statistics were calculated. Percentages presented exclude missing data.

Results: The evaluable final cohort consisted of 4624 patients. Median age = 68 yrs (IQR 60–77), 57.6% (2663/4624) male. Ivabradine initiated by hospital specialist in 82.8% (3683/4447). Starting dose 5 mg bd (as per SPC) in 74.7% (3300/4418). Indication affirmed to be CSA in 80% (3204/4007). BBConI in 56.6% (2352/4159). HR measured prior to starting in 77.1% (1693/2195) of these, 84.3% (1428/1693) had NSR. Other indications reported include tachycardia (4.9%, 227/4624) and myocardial infarction (2.9%, 136/4624). Ivabradine stopped in 33.3% (1542/4624); 1551 reasons for stopping given for 1155 patients; most common; 'not effective' (9.7%, 112/1155) and cardiac surgery (9.2%, 106/1155).
Conclusion: Ivabradine was mostly initiated by hospital specialists for CSA at the recommended starting dose. NSR was present in the majority where HR was measured. The reported prevalence of BBConI suggests lower prescriber compliance with this requirement. High hospital initiation rates may explain frequently missing pre-treatment HR data in GP records. In one third of the cohort ivabradine treatment was stopped. This was most frequently reported to be because ivabradine was not effective. Ivabradine was also stopped in patients where cardiac surgery had improved the indication condition to the extent that ivabradine was no longer required.

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P036. Patients' Knowledge of ADR in the Eve of the New European Pharmacovigilance Legislation

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Background: According to recent changes in Directive 2001/83/EC, Member States shall record all suspected adverse drug reactions (ADR) occurring within their territory which are brought to their attention by health professionals.[1] In connection with the alleged adverse effects reported by patients, Member States may decide whether they shall report directly or through health professionals. This change in European legislation is to be soon introduced in Bulgarian pharmaceutical legislation. Due to lack of experience there is a need to explore the possibilities and examine the patients' potential for adverse drug events reporting.
Aim: The aim of this study was to investigate patients' knowledge about ADRs and preferable contact point for their reporting.
Methods: The study was conducted in Bulgaria. A direct voluntary anonymous standardized questionnaire was conducted with patients in community pharmacies in three cities – the capital Sofia, a major regional city – Blagoevgrad and a small town – Kyustendil. The sample was pseudo-randomized by choosing every third visitor with personal prescription in the pharmacy for a period of 10 days during the winter season in 2011 (end of November).
Descriptive statistics and chi-square tests were used for the purposes of the analysis.
Results: 153 people agreed to be interviewed with prevalence to females (60.9%). More than 40% had university education. Chronically ill were 46.4% of the participants. The majority of them claimed to know what an ADR is (86.1%). However, only 12.6% considered that they might have had experienced an ADR. More than half of the patients would like to discuss their pharmacotherapy and eventual ADRs with their physician, followed by pharmacist with 43, 7%. The preferred contact point for ADR reporting were physicians (48.3%) and pharmacists (40.4%). There was no observed statistical significance between the knowledge of ADRs, education and health status of the interviewed.
Discussion: Based on the results, the interviewed patients paradoxically considered themselves well aware of the problem of ADRs. The small percent who claimed to might have had ever experienced an ADR suggests the need of educational and awareness campaigns regarding the spontaneous reporting. The factors that would affect the quality of the reports need to be further investigated.
Conclusion: The introduction of direct patient reporting in Bulgaria is a challenge because of possible low quality of patients' reports and significant noise in the system.

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P037. Influencing the Reporting of ADRs in Primary Care

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Objective: General practitioners (GPs; family physicians) at one time provided almost 70% of United Kingdom spontaneous ADR reports. Since the advent of new reporters (nurses, pharmacists, patients) this has dropped to 25%, with only a modest increase in the total number of reports. Underreporting of ADRs is a drawback of spontaneous reporting schemes,[1] and may be made worse by a lack of knowledge or awareness.[2,3]
Aim: We wished to examine the effect of reminding GPs about ADRs and the Regional Centre. We randomly allocated GPs by postcode sector into two groups. Approximately half the practices in any particular PCT were targeted. There was no intervention in one-third of the PCTs.
Method: Both groups included both good and poor reporting areas and both rural and inner city areas. One (intervention) group received a letter in September 2011 from the Centre offering advice and tips about reporting, and enclosed a number of yellow cards (including those for patient reporting). The other (control) group received no specific communication. We compared the change in reporting in the three months before and after sending the letter and cards between intervention and control groups using the number of reports from each post code sector received from the MHRA each quarter.
Results: The results are shown in table I. The number of yellow cards received from the West Midlands increased generally between the two quarters but the increase was greater in the areas randomized to receive the communication. Total reports increased by 15 (61%) in the intervention group, but by only 2 (+3%) in the control group. GP reports increased by 63% in the intervention area and by only 3% in the control area.
Discussion: Our study was small and of short duration but suggests that a timely reminder through the post together with a supply of cards which

Table I.

	Quarter before mailing	Quarter after mailing	Change
GPs			
Letter and yellow cards sent	16	26	+10 (+63%)
No letter or cards sent	39	40	+1 (+3%)
Patients			
Letter and yellow cards sent	7	12	+5 (71%)
No letter or cards sent	22	23	+1 (5%)

can jog memories or be given to patients to use if they have any concerns may be a simple method of maintaining the rate of ADR reporting in a spontaneous reporting scheme. We will be keen to see whether the effect is maintained. Such reminders may not work electronically, as reporters and patients may be inured to messages seen as unwanted spam.

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P038. Risk Management in a Latin America Named Patient Program (NPP) for Lenalidomide

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Lenalidomide, which is structurally related to thalidomide, a powerful teratogen, is indicated for the treatment of multiple myeloma and myelodysplastic syndrome. Before approval of the product, and where applicable regulations permit, the product was first introduced in Latin America under a Named Patient Program (NPP). The lenalidomide NPP was started in February 2008 under a commitment to make the drug available through a risk management program (RMP).

As of March 2012, about 400 patients across Latin America had been recruited into the NPP. Of these, about 2.5% were categorized as females of childbearing potential (FCBP). As part of the RMP, pregnancy tests are routinely performed to mitigate fetal exposure to lenalidomide. Over 3000 healthcare professionals, including physicians and pharmacists, have been trained on the requirements of the lenalidomide risk management program and are registered with the program. The lenalidomide NPP is still operational in a few Latin American countries where the product is yet to gain marketing authorization. As of April 2012 there were no lenalidomide fetal exposure reports in females of childbearing potential (patients and female partners of male patients). This is principally attributable to the implementation of the NPP risk management program early on and solicitation of input from relevant stakeholders to design and implement a program that is both practicable and acceptable without compromising patient safety and placing undue burden. The NPP has offered the opportunity to test the practicality and offer room for improvement in executing the prescription and dispensing of a product that requires a strict controlled distribution system.

P039. The Thalidomide Pregnancy Prevention Program (PPP) in Greece: A Retrospective Study Monitoring Adherence

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Background: Thalidomide is approved for the treatment of multiple myeloma (MM) in Greece. Due to its teratogenicity, thalidomide is only available under the conditions of a pregnancy prevention program (PPP), and the Special Order Form (SOF) is an integral tool of the program.

Methods: The SOF provides critical data that allows for the assessment of adherence and effectiveness of the thalidomide PPP in Greece. We therefore performed a retrospective evaluation of Special Order Forms (SOF) received in the period January 2009–August 2010.

Results: Out of 822 SOFs reviewed in this survey, 99% documented the signature of a physician that had been trained on the PPP. Indeed, in 1% of cases where the SOFs were not signed by a physician not trained on the PPP the orders were put on hold until appropriate training was provided. In 98.3% of SOFs the patient identifiers were complete. In the remaining 1.7% the patient identifiers were only partially completed. Among the SOFs indicating MM as the indication (93.8%) for thalidomide prescription, females of childbearing potential (FCBP) represented 1.17%, with females not of childbearing potential (FNCBP) and males accounting for 43.8% and 48.78% respectively. In the off-label indications (6.2%) the percentage of prescriptions for FCBP, FNCBP and males was 0.6%, 2.8% and 2.8% respectively. The compliance on the pregnancy tests was also verified. Pregnancy testing was performed in total in 84% (72/86) of cases of FCBP. Out of these 7% (5/72) where not performed within the recommended timelines and had to be repeated. SOFs for which pregnancy testing was not compliant with the PPP requirements were put on hold until appropriate pregnancy testing was performed.

Conclusion: There is good compliance to the measures instituted as part of the thalidomide PPP in Greece. The use of the SOF is an effective way of monitoring adherence to the PPP and providing early opportunity to intervene in case of non-adherence on part of the physician (training those not trained on the PPP) and patient (e.g. ensuring a pregnancy test is undertaken before product prescription).

P040. Increasing Adherence to a Norwegian Risk Management Plan Designed to Prevent Fetal Exposure to Teratogenic Medicinal Products

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During 2010 a retrospective survey assessing compliance with the thalidomide and lenalidomide Pregnancy Prevention Programs (PPP) among prescribing physicians was carried out in Norway. Data were collected by surveying a total of 22 physicians distributed over 19 hospitals, with the physicians representing about 69% of all prescribers that had treated patients with at least one of the two products in the preceding 12 months.

The results of the survey revealed that the implementation of some PPP elements were not followed by a majority of the prescribing physicians, prior to initiating thalidomide or lenalidomide therapy. In general the patients were not actively informed by the treating physician about the teratogenic risk and the PPP forms, provided for use in the healthcare professional kits, were neither completed and signed by doctors nor included in the patients' medical records. However, women of childbearing potential (n = 3), with the exception of 1 patient who was very sick, were actively counselled about the teratogenic risk.

To improve adherence of physicians to the PPP requirements the following strategy was developed and is being implemented: improving the communication and understanding of the PPP, including use of short quizzes deployed on iPads; broadening ease of access to PPP educational materials; heightening the involvement of stakeholders in the PPP (e.g. Nordic Myeloma Study Group and the Norwegian Hematology Association).

The results of the survey provided a good overview of adherence to the thalidomide and lenalidomide PPPs, and formed the basis for developing a comprehensive action plan to improve uptake. A follow-up survey is planned, and it will demonstrate if the intervention strategies to change prescriber behavior and increase adherence have been effective.

P041. Verification and Qualification of Methods Measuring the Effectiveness of Risk Minimization Activities: A Case Study in the UK

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Background: As part of the marketing authorization in the UK for thalidomide, Celgene instituted a pharmacy mandatory self-audit intended to provide a retrospective review of the Prescription Authorization Forms (PAFs), and hence monitor compliance to the Pregnancy Prevention Program (PPP) by registered pharmacies. This self-audit is performed annually on the 20 most recent PAFs processed. In order to verify and qualify the results of the mandatory self-audit, the MHRA requested Celgene to undertake a more extensive audit, providing a retrospective review of all PAFs processed by a certain selection of pharmacies.

Methods: Participation in the extensive self-audit was offered to the top 60 dispensing pharmacies registered into the PPP during the audit period (10 December 2009 to 10 December 2010). Pharmacies were required to evaluate all PAFs received in the period of interest. Based on the PAF data, pharmacies provided information on: number of PAFs audited/processed in the last 12 months; dispensing episode versus number of PAFs processed; indication; patient age category; dispenses greater than 4/12 week supply (according to patient risk category); PAFs for each patient risk category; confirmation of counseling; confirmation of contraception/pregnancy testing as relevant and prescriber/pharmacist's declaration.

Results: Out of the 60 top dispensing pharmacies 26.7% completed the extensive self-audit; 13.3% declined and 60% did not respond. For the mandatory self-audit the audit pack was sent to 567 pharmacies. In total 63.1% of pharmacies responded. Out of these 67.9% had dispensed thalidomide during the self-audit period. The remaining 30.2% confirmed that they had not dispensed the medicinal product and were therefore exempt from completing the mandatory audit. The majority of PAFs covered by the extensive self-audit were for male patients 55.8% and women of non-childbearing potential (WNCBP) 41.6%. As expected only 2.6% were women of childbearing potential (WCBP). The mandatory self-audit shows similar results (52.8% male, 40.5% WNCBP, 3.8% WCBP). Overall, there was a high level of adherence from the audited pharmacies to the PPP requirements (>95%). Significantly, the results from both the audits demonstrated comparability.

Conclusion: Overall the results for the extensive self-audit and those of the mandatory self-audit were similar. The mandatory self-audit was successfully verified and qualified to evaluate the adherence to the implemented PPP for thalidomide and therefore the extensive audit is no longer required.

P042. Development and Validation of an Algorithm Based on Administrative Claims Data for the Surveillance of Suicide Attempts in Youth

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Introduction: Health databases are recognized as a leading tool for drug safety surveillance. However, it is largely recognized that their use is hampered by the validity of diagnostic codes recorded in medical billing claims. Population-based studies on suicide attempts so far published in the literature are subject to misclassification bias since very few have been able to ascertain non-hospitalized suicide attempts.

Aim: To develop and validate an algorithm for the ascertainment of non-hospitalized suicide attempts in youth through patterns of health care use recorded in administrative databases.

Methods: Algorithms, consisting of a sequence of outpatient medical services, diagnostic codes, location of service, and medical specialty, were developed *a priori* through clinical expertise and pattern recognition on 30 known cases of non-hospitalized suicide attempts treated at the two Montreal paediatric hospitals. Algorithms were validated in a sample of 100 known cases of suicide attempts and 100 cases of intentional injuries (i.e. non-suicide attempts), using hospital charts as ''gold standard''. Measures of sensitivity and specificity were obtained. Data-based algorithms were also derived through multivariate logistic regression and regression tree analysis.

Results: Using a billing at the emergency department followed by a diagnosis of trauma (injury or intoxication) within 2 days of ED visit was associated with a sensitivity and specificity of 98.1% and 14.6%, respectively. The addition of a medical visit billed by a psychiatrist or the diagnosis of a psychiatric condition within 2 days increased specificity to 97.6% but decreased sensitivity to 69.8%. Regression analysis slightly improved validity measures.

Conclusion: Over the past decade, suicide attempt in youth has been involved in several pharmacovigilance issues and is frequently considered as an adverse event of special interest in risk management plans. Algorithm selected depends on the objective of the study. Signal detection studies will favour algorithms with high sensitivity while epidemiologic studies, such as case-control studies, require methods with high specificity.

P044. Reports of Arrhythmia in Patients Taking the Non-Systemic Corticosteroid Mometasone

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Background: The WHO International Drug Monitoring Programme has coordinated the collection of spontaneous reports of suspected adverse drug reactions (ADRs) since 1968. Currently 107 countries contribute to the WHO Global Individual Case Safety Report (ICSR) database, VigiBase™, which is managed by the Uppsala Monitoring Centre (UMC) and today contains over 7 million ICSRs. Analysis of VigiBase data is performed in accordance with UMC's routine signal detection process. A signal of arrhythmia caused by mometasone was discovered while evaluating novel methods for signal detection in VigiBase.

Aim: Analyse VigiBase ICSRs of an association between mometasone use and subsequent development of arrhythmia.

Method: Clinical review of all ICSRs in VigiBase of arrhythmia possibly attributable to mometasone use.
Results: As of May 2012, VigiBase included 15 reports of arrhythmia and two reports of atrial arrhythmia in association with mometasone. One report was excluded from the analysis as it was a neonatal with congenital heart disease which left 16 reports. The reports originated from the United States, the United Kingdom, Sweden and Switzerland. Where reported, six of the cases were in males and eight in females, and patient age ranged from 12 to 79 years. Mometasone was the only drug suspected in thirteen cases and only three of these listed concomitant drugs. Mometasone was administered intranasally in thirteen cases with two reports of inhalation and one of topical use. Time to onset was reported in only three of the reports and ranged from the same day up to three months. A positive dechallenge from mometasone was recorded in nine cases and in four cases it was reported that the reaction recurred on rechallenge.
Discussion: The existing literature regarding corticosteroid use and arrhythmia is rather limited. The possibility of systemic reactions in association with intranasal, inhaled or topical corticosteroids is considered low but there has been one literature report of atrial flutter in association with fluticasone proprionate by the inhalation route[1] and case control studies have shown an increased risk of atrial flutter in association with oral corticosteroids.[2,3] A postulated mechanism by which corticosteroids can cause heart rate disorders involves potassium efflux in cardiac cells.[4]
Conclusion: Case reports in VigiBase suggest that there is a signal for the association of mometasone and arrhythmia. Most of the cases have mometasone as the sole suspected drug and a positive dechallenge, supporting a signal. Importantly, in four of the cases, the reaction recurred on rechallenge.

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P045. Interaction between Bexarotene and Aprepitant: The First Case of Death

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Background: Bexarotene, a Retinoid-X-Receptor (RXR)-specific ligand, has been approved in 2001 in France for the treatment of recurring or refractory cutaneous T-cell lymphoma (CTCL) such as in Sezary syndrome. Since aprepitant can alleviate chronic pruritus resulting from Sezary syndrome, by inhibiting the receptor of substance P increased on keratinocytes in Sezary patients, this drug has been combined with standard treatment since 2010, in a context of an off-labeled use. Being a substrate and inhibitor of cytochrome P450/3A4, drug-drug interactions may occur when aprepitant is administered with drugs metabolized by this enzyme such as bexarotene.
Aim: We report a case of severe global dehydration leading to death and observed after co-administration of bexarotene, alpha2a interferon and aprepitant.
Results: This case concerns a 65-year-old-male patient. He had been treated with bexarotene (300 mg/m^2/day) and alpha2a interferon (3 MUI 3 times/week) since November 2009 for an erythrodermic Sezary syndrome. An associated chronic pruritus, was also treated with aprepitant on September 2011 (80 mg/day). At the beginning of November 2011, he developed generalized asthenia, anorexia and aphagia, leading to a 15 kg weight loss in 3 weeks. A severe dehydration associated with hypernatremia (185 mmol/L) and an acute renal insufficiency were diagnosed. Despite symptomatic treatment, the patient died in the middle of December.
Discussion: Since bexarotene undergoes oxidative metabolization via the cytochrome P450 enzyme CYP3A4, bexarotene concentrations may have been increased following the inhibition of this enzyme by aprepitant, leading to renal impairment in our case. We did not find aprepitant-induced or concurrent usage with bexarotene in the international literature or in the French National Pharmacovigilance Database. However, acute renal failure during all-trans-retinoic acid (ATRA) and concurrent use of fluconazole (CYP450/3A4 inhibitor) treatment has already been reported. PPAR gamma and ligand-bound RXR can activate PPAR gamma/RXR heterodimer in the absence of PPAR gamma ligand. PPAR gamma expression in the proximal tubular cells of the kidneys suggests that sodium retention may be due to PPAR stimulation of proximal tubular Na transporters. As a RXR ligand, bexarotene can mimic PPAR ligand effect in sodium resorption.
Conclusion: Patients and physicians should be carefully monitored for side effects of bexarotene, particularly when it is used in association with other medications modulating cytochrome P-450 system, such as aprepitant.

P046. Improved Adverse Drug Interaction Signal Detection by Combining Clinical, Pharmacological, And Statistical Information

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Introduction: Drug interactions impose a substantial burden on clinical care, being responsible for about 20% of all adverse drug reactions.[1,2] Because far from all drug interactions and their possible effects are known at the time of marketing, effective post-marketing signal detection of adverse drug interactions is imperative. All currently available methods for first-pass screening in large collections of individual case safety reports (ICSRs) rely on statistical measures of disproportionality.[3-5] However, clinical information and pharmacological characteristics are essential in the clinical assessment, and previous research indicates that they may be of great value also in triages for automated first-pass filtering.[6]
Aim: To develop triages for adverse drug interaction surveillance, and to compare their performance in predicting adverse drug interaction signals to the performance of disproportionality analysis.

Methods: A broad set of variables were considered for inclusion into the triages, including cytochrome P450 (CYP) activity, explicit suspicions of drug interactions noted by the reporter, dose and treatment overlap, and a measure of interaction disproportionality. Their unique contributions in predicting signals of adverse drug interactions were determined through logistic regression. This was based on the reporting in the WHO Global ICSR Database, VigiBase, for a set of known adverse drug interactions and corresponding negative controls. The developed triages were compared to disproportionality analysis alone based on two separate gold standards derived from expert clinical assessment: prospective adverse drug interaction signals and adverse drug interactions known in the literature.
Results: The following were identified as valuable predictors of adverse drug interaction signals: plausible CYP metabolism; notes of suspected interaction by the reporter; and reports of unexpected therapeutic response, altered therapeutic effect with dose information, and altered therapeutic effect when only two drugs had been used. The new triages identified reporting patterns corresponding to both prospective signals of adverse drug interactions and already established ones. It performed better than disproportionality analysis alone relative to both gold standards. For example, at the level of specificity corresponding to the natural threshold for the considered disproportionality metric, the developed triages obtained a sensitivity that was between 1.3 and 2.0 times as high as that obtained by disproportionality analysis alone, across the two separate gold standards.
Conclusions: A range of predictors for adverse drug interaction signals have been identified. They substantially improve signal detection capacity compared to disproportionality analysis alone. The value of incorporating clinical and pharmacological information in first-pass screening is clear.

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P047. Prescribing Pattern of Glucose Lowering Drugs in the UK in the Last Decade: Focus on the Warnings About Rosiglitazone

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Introduction: In the last decade, new glucose lowering drugs (GLDs) were launched, but also several warnings regarding the safety of these drugs.[1,2] The cardiovascular safety of thiazolidinediones (TZD) has been questioned.[3] Several studies, mainly in the United States,[4,5] have assessed the prescription pattern of the glucose lowering drugs in a short period around the publication of the FDA safety alert of rosiglitazone in May 2007. Until now only few data are available regarding the prescription pattern of glucose lowering drugs in Europe[6] for a long period of time.
Aim: We analyzed the prescription pattern of GLDs from 2000 to November 2009 in the United Kingdom (UK) using The Health Improvement Network (THIN) database with special focus on the effects of the safety warnings about rosiglitazone issued in May 2007 and January 2008 by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA).
Methods: Annual prevalence and incidence of GLD prescription were measured. For TZD, the monthly prevalence and incidence of prescription were calculated from May 2006 to January 2009. The switching pattern around the FDA alert in May 2007 and the characteristics of subjects starting treatment with TZD before and after the alerts issued by the FDA (May 2007) and EMA (January 2008) were observed.
Results: The prevalence of prescriptions of GLD increased during the 10-year period, metformin increasing more than three times (2000: 6.9 (95% CI 6.8-7.0) per 1000; 2009: 22.7 per 1000) surpassing prevalence prescription of sulfonylureas after 2001. The prescription rates of TZD increased from 2000 to 2007, afterwards it decreased progressively. The prevalence of use of other therapies remained rather stable from 2000 to 2007 but it increased in the following years. The incidence of rosiglitazone use decreased sharply after May 2007 until August 2007 (0.8/1000 py in May 2007 and 0.2/1000 py in August 2007) and later it remained stable. At the end of the period (January 2009) the incidence of pioglitazone use was higher than that of rosiglitazone. After May 2007, rosiglitazone users were increasingly switched to pioglitazone. There was an increased proportion of new users of pioglitazone with cardiovascular risk after the alerts.
Conclusions: The prescription of GLD in the UK increased in the last decade, for TZDs, it changed after May 2007 as well as the characteristics of subjects treated with them.

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P048. Evaluation of QT-Interval Prolongation: A Multicenter Study to Detect Drugs More Frequently Associated in the Clinical Practice

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Introduction: QT interval prolongation induced by drugs is a major adverse event associated with morbidity and mortality, and is the most common cause of drug withdrawal from the market in recent years.[1,2] The aim of the study is to determine its prevalence in clinical practice and related drugs.

Materials/Methods: We included patients consecutively admitted to three hospitals. An electrocardiogram was performed at baseline, during and after drug treatment indicated. The QT interval between the Q-wave onset and end of the T wave in the electrocardiogram was quantified in milliseconds and corrected by Bazzet formula. It was felt that QTc interval prolongation showing a delta between admission and treatment more than 20 ms.

Results: Between January 2011 and April 2012, 1087 patients (538 men, 50%) were included. We analyzed a total of 3099 ECG (3 ECG per patient) and a total of 1948 laboratories. The average age was 59 years (8–99, SD 20), weight 72 kg (40–200, SD 15), height 167 cm (131–191, SD 9). The clinical history revealed a history of ischemic cardiomyopathy (9%), arrhythmia (10%), diabetes (10%), heart failure (7%), CNS diseases (6%), hypertrophic cardiomyopathy (5%), hypothyroidism (5%), and renal failure (3%). Prior to the start of drug treatment, patients had [mean (range, SD)]: Na 138 (119–156, 5), K 4 (2–7, 1), RR 799 (320–2200, 203), QT 379 (200–600, 52), QTc 427 (280–600, 30). After the start of drug treatment: Na 137 (115–157, 5), K 4 (2–6, 1), RR 803 (360–2400, 164), QT 385 (200–720, 45), QTc 432 (283–611, 34). After treatment ends: Na 138 (122–154, 5), K 4 (2–7, 1), RR 807 (520–2080, 136), QT 384 (280–800, 39), QTc 428 (320–730, 24). There were 219 detected cases (20%) with drug-induced QTc interval prolongation >20 ms. The most commonly used drugs in patients with prolonged QT interval were Amiodarone (10), Fentanil (8), Aciclovir (4), Diltiazem (4), Midazolam (4), Difenhidramine (2), Oseltamivir (2), Sevofluorane (2), Atracurium (1), Oxcabazepine (1). Clinical history of ischemic cardiomyopathy, diabetes, heart failure, CNS diseases and hypothyroidism were identified as risk factors.

Discussion: Drug-induced QT interval prolongation is a frequent event in clinical practice. Risk factors and related drugs should be recognized by medical professionals in order to reduce their frequency by proper control of prodisponentes factors and ECG and laboratory monitoring.

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P049. Evaluation of QT-Interval Prolongation: Detection of Most Frequently Associated Drugs in Clinical Oncology

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Introduction: QT interval prolongation induced by oncology drugs is a frequent adverse event.[1] Its prevalence and association with morbidity remains unknown.[2,3] The aim of the study is to determine its prevalence in clinical oncology practice, related drugs, and clinical characteristics.

Methods: 60 patients were included for chemotherapy administration in one oncology specialized university hospital. Electrocardiogram was performed at baseline, and after chemotherapy. The QT interval in the electrocardiogram was quantified in milliseconds and corrected (QTc) by Bazzet formula. QTc interval prolongation was defined as a delta between admission and treatment period greater than 20 ms or and absolute QTc value greater than 440 ms (males) or 460 ms (females).

Results: 198 chemotherapy cycles were studied in 60 patients (50% female; aged: 63.1 + 12.5 years). The mean ± SD baseline and post-treatment QTc were: 430.1 + 27.1 msec and 437.7 + 40.6 msec, respectively. The first mean ± SD baseline and post-treatment QTc were: 426.7 + 28.2 msec and 444.3 + 64.9 msec, respectively ($p = 0.056$). The mean QTc for the first post-treatment cycles was 15.7 msec greater in patients with not small cell lung carcinoma (NSCLC) (N = 24). In the total sample, 31.3% of the chemotherapy cycles show QTc prolongation (mostly).

Discusion: Drug-induced QT interval prolongation is a frequent event during chemotherapy infusion more frequently detected in patients with not small cells lung carcinoma. Risk factors and related drugs should be recognized by medical professionals in order to reduce their frequency by proper control of related factors. ECG and laboratory monitoring must be essential in clinical oncology in order to not add a new cause of morbidity such as QT interval prolongation.

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P050. Effectiveness of Proactive-Approach in a Pharmacovigilance Unit: Review and Analysis of 3348 Notifications Received

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Objectives: In Argentina, pharmacovigilance program was created in 1993 centered in the national regulatory agency with peripheral nodes. Our node has used a proactive approach since 2006, in addition to the registration of spontaneous reports. Notifications are incorporated into a database, and then sent to national regulatory agency.

Methods: The notifications are incorporated into a database (SQL), in addition to being sent to Regulatory Agency. We describe the notifications received (demographics and types of events reported; side effects, ineffectiveness or failure of quality)[1] and the result of the intervention of analysis, when it was required.

Results: From November 2004 to May 2012, 3348 notifications were received. There was no difference between sex, with a low proportion of pediatric patients (<3%) and high proportion of elderly (>60 years) patients (1346, 40%). Most notifications corresponded to adverse effects (3177, 95%), followed by cases of lack of efficacy (143, 4%) and quality failure (28, <1%). The degree of severity was mild in the majority (2385, 75%), followed by severe (510, 16%) and moderate (282, 9%). The largest categories of drugs involved in adverse effects were antimicrobials (29%), drugs for cardiovascular disorders (24%), drugs for CNS disorders (15%), antineoplastics (8%), NSAIDs (6%) and drugs for lung diseases (3%). Among all (3177) adverse event notifications, 521 (17%) were serious adverse events, including cases of 367 (72%) hospital admissions, 98 (19%) prolonging an existing hospitalization, 41 (8%) life-threatening diseases, 4 (<1%) deaths, and 1 (<1%) persistent incapacity. Among cases of lack of efficacy the most frequently involved were neurological drugs (28%), cardiovascular drugs (18%), antimicrobials (18%), and NSAIDs (11%). All samples of products involved in notifications of failure of efficacy or quality were sent to the National Institute of Medicines (INAME). Strikingly, all but one case were subjected to quantitative analysis and reported as "meets the specifications."

Conclusions: The presence of old people and groups involved in drug side effects is consistent with data from other pharmacovigilance studies.[2,3] The unit obtained a increase in the number of notifications received by adopting a proactive approach.[4,5] Possible causes of lack of notification by the health professionals seem to include ignorance, fear, lack of time, lack of incorporation of the drug, and lack of necessary data, among others. The proactive approach allows the systematic inculcation of side effects and effectiveness evaluation as part of the activity.

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P051. Development and Content Validation of a Patient-Reported Adverse Drug Event Questionnaire

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Background: Direct patient reporting of adverse drug events (ADEs) is considered important for the evaluation of the benefit-risk profile of a drug. Existing questionnaires have limited applicability because they are drug or ADE specific, not validated and/or do not ask for additional information regarding the nature of the experienced ADEs, e.g. causality, duration, severity.

Objectives: To develop a generic patient-reported questionnaire to identify and quantify the type and nature of experienced ADEs, and test its content validity.

Methods: Based on existing questionnaires and patient reported ADE information from the Lareb Intensive Monitoring Project, a draft list was created of commonly reported ADEs in lay-terms. ADEs were classified in body categories, and mapped to the Medical Dictionary for Regulatory Activities. Questions regarding the nature of the ADE were derived from existing questionnaires and the Naranjo scale. Readability and clarity of items and response options were tested in cognitive debriefing interviews with 25 patients who use chronic drugs for diabetes or asthma/chronic obstructive pulmonary disease. Interviews were recorded and transcribed verbatim. Identified problems were discussed by two researchers. The questionnaire was revised in an iterative process until no major problems were detected. In addition, 24 patients were asked to classify a random sample of ADEs into body categories.

Results: The questionnaire was revised 15 times, rephrasing questions and response options and improving lay-out. Based on the classification task, 39 changes were made with respect to the grouping or labeling of ADEs in body categories. The final questionnaire contains a checklist with 252 ADEs organized in 16 body categories, and including 15 questions per reported ADE.

Conclusions: We developed a novel generic patient-reported ADE questionnaire intended for clinical trials and post-marketing studies. We confirmed its content validity regarding questions, response options, and terminology of ADEs and body categories. Further validation studies are planned.

P052. Safety Issues Seem to Occur More Often in Highly Innovative Drugs

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Background: Truly innovative new drugs often answer unmet medical need. They are usually first-in-class and class-related safety issues may not be fully identified at time of approval. This may put these drugs at risk of showing safety events early post marketing.

Objectives: To assess whether safety issues of highly innovative drugs are identified more frequently and rapidly than of other drugs.

Methods: A retrospective cohort study was performed of new drugs approved in Europe between 1999 and 2011 excluding vaccines and diagnostics. Drugs were classified according to their innovation [Motola, BJCP 2006] as A) important, B) moderate, C) modest or merely pharmacological/technological innovations. Comparison was made between highly innovative (A) and all other drugs. Safety issues were identified based on dear doctor letters (DHPCs) issued by the Dutch Medicines Evaluation Board or withdrawals. Outcome variables were frequency and timing of a first DHPC or safety-related withdrawal. Kaplan-Meier survival analysis and Cox-regression to correct for possible confounders were used to analyze the data.

Results: Innovativeness was assessed for 119 new drugs; 144 drugs, approved after July '04 are still being classified. Of those 119 drugs 32 (27%) were rated grade A. DHPCs were issued for 14/32 (44%) with no withdrawals vs 16/87 (18%) with 2 withdrawals for other drugs ($p = 0.005$). In the 14 DHPCs for innovative drugs only 3 recommended to limit the indication and 2 added a contraindication. The probability of acquiring a DHPC for innovative drugs during 3 years follow up is 16% (95 CI 3%; 28%) vs 9% (95 CI 3%; 15%) for other drugs and during 12 years 46% (95 CI 28%, 65%) vs 20% (95 CI 11%, 29%), respectively (log-rank $p = 0.007$). Adjusted hazard ratio was 3.2 (95 CI 1.5; 7.1) with no identified significant confounders.

Conclusions: Our preliminary data indicate that important safety issues are more often identified for highly innovative drugs that were observed continuously from 3 through 12 years after approval. This underlines the importance of close monitoring of safety of these drugs after registration. As no withdrawals were observed and only few indications changed, their therapeutic benefit appeared unchallenged.

P053. An Evaluation of the Evidence of an Association between Montelukast and Suicide: A Publicity Exacerbated Signal?

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Background: In March 2008 the suicide of a 15-year-old boy captured media attention. It was suggested that the suicide might be linked to exposure to montelukast, and the FDA requested further investigation.

Objective: To examine available evidence of any association between montelukast and suicide-related adverse events (SRAEs) in children aged 2–17 years.

Methods: Individual Case Harm Reports (ICHRs) related to montelukast and SRAEs in children aged 2–17 years (up to February 2010) were extracted from a worldwide database of spontaneous reports of suspected adverse drug reactions, VigiBase, maintained by the Uppsala Monitoring Centre (UMC). ICHRs with death or hospitalisation as outcomes were selected, and the original reports were obtained from national centres by the UMC. An expert panel assessed causality in definite cases of suicide using WHO definitions. Evidence from published reviews of clinical trials, case studies, and ICHRs were subjected to causality assessment using a modified version of the Bradford Hill guidelines.

Results: We identified a total of 321 ICHRs, 96% originating from the US. Even though there were 9 prior cases of suicide, there were disproportionately more ICHRs following the media reports and the FDA's call for further investigation. Causality assessment of 48 of the total number of original cases, all associated with death or hospitalisation showed that none was certain or probable, 10 were possible, and 14 were unlikely; 24 were un-assessable owing to limited information. Investigations searching for evidence of SRAEs and montelukast in previous clinical trials showed that SRAEs were rare in patients taking montelukast and similar to those seen in controls. We found no published clinical trials designed to study SRAEs. Both published literature and ICHRs provided insufficient evidence to meet all seven modified Bradford-Hill guidelines.

Conclusion: Despite the high number of reports received after the media attention and FDA call, we found limited evidence to support the prior signal generated from a case reported in the mass media. The subset of ICHRs of SRAEs with death or hospitalisation as an outcome contained limited information and we identified no certain or probable cases of SRAEs with montelukast. Well-designed follow-up questionnaires of SRAEs are needed in order to capture relevant details specific for the event to make it possible to carry out a satisfactory analysis of a signal of such a rare event as suicide in the young.

P054. Positive Predictive Value for Upper Gastrointestinal Bleeding in Four European Healthcare Databases Using Different Coding Systems

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Background: Validation of upper gastrointestinal bleeding (UGIB) is warranted when using electronic healthcare record databases (DB).[1,2]

Aim: We evaluated the accuracy of codes and free text from various coding systems to identify patients with UGIB and the implications of misclassification on the relative risk estimate.

Methods: A validation study was conducted in the following databases of the EU-ADR network:[3] 1) IPCI (Netherlands); 2) HSD (Italy); 3) ARS Regional DB (Italy); and 4) Aarhus (Denmark). The first two are primary care DBs, the latter are administrative DBs. Three diagnosis coding systems were used: 1) International Classification of Diseases (ICD)-9th revision (HSD and ARS); 2) ICD-10th revision (Aarhus); and 3) International Classification of Primary Care (ICPC) [IPCI]. We identified patients with UGIB-specific codes (ICD-10: K25-29, K92.0, K92.1, K92.2; ICD-9: 531-535, 578; ICPC: D14-15, D85-86) or key words (IPCI and HSD). A random sample of 200 potential UGIB cases was selected from each DB (400 for IPCI) and reviewed manually by medically trained assessors. Positive predictive values (PPV) were calculated. Relative risks (RR) were calculated for drugs known to be associated with UGIB while using different thresholds for PPV.

Results: For IPCI, the PPV was 23% (95% CI: 17%-30%) and 25% (95% CI: 18%-31%) for free text and ICPC codes respectively. For HSD, the PPV was 92% (95% CI: 88%-97%) for codes and 50% (95% CI: 37%-63%) for free text only. The overall PPV for the ICD9-based system in ARS was 77% (95% CI: 71%-83%). The estimated PPV was 66% for the ICD10-based coding system (95% CI: 59%-73%). The impact of codes with low PPVs on estimation of RR was small.

Conclusions: There are differences are in the accuracy of automated case identification using various databases (hospitalisation claims vs medical records) that stem from differences in the coding systems and in the type of data collected. However, use of codes with lower PPV resulted in only small changes in the estimated relative risks of drugs known to be associated with UGIB.

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P055. What Can Electronic Healthcare Record Databases do for Paediatric Drug Safety Surveillance?

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Background: Traditional pharmacovigilance activities do not focus specifically on children and medicines in children are frequently prescribed off-label based on extrapolating experience from adults.[1] The EU-ADR Project aims to use information from various electronic healthcare record (EHR) databases to produce a computerised integrated system for early detection of drug safety signals.[2]

Objectives: To provide estimates of the number of drugs and incidence rates (IRs) of adverse events that can be monitored in children and adolescents in the EU-ADR network.

Methods: Demographic, clinical events and outpatient drug prescription/dispensing data were obtained for individuals 0 to 18 years of age from seven databases from Denmark, Italy, and the Netherlands. Data were analysed from 1996–2008. We estimated the number and types of drugs for which specific adverse events can be monitored as function of actual drug use, minimally detectable RR, and empirically-derived incidence rates for 10 events deemed to be important in pharmacovigilance.[3,4] The same was done for adverse events frequently reported in children, using IRs described in literature.

Results: The paediatric population comprised 4 838 146 individuals contributing 25 575 132 person-years (PYs) of follow-up during the study period. Within this population a total of 2170 drugs were prescribed, with a total drug exposure of 1 610 631 PYs. Eighteen of the 2170 drugs (0.8%) comprised half of total drug exposure while 90% of the total drug exposure in PYs was represented by 158 drugs (7.3%). For a relatively frequent event such as upper gastrointestinal bleeding (IR = 14.4/100 000 PYs), there were 39 drugs (comprising 66% of total exposure in PY) for which an association with a RR ≥4, if present, can be investigated. For a rare event such as anaphylactic shock, there were 8 drugs (comprising 35% of total exposure) for which an association of same magnitude can be investigated. Based on literature-derived IR, there was a higher number of drugs that can be monitored for the events febrile convulsions and suicide attempt at the same magnitude of risk.

Conclusion: Drug use in children is rare and shows little variation. Signal detection for the paediatric population seems especially promising for events with a high background incidence and for drugs with a large amount of exposure. Intercontinental collaboration will be necessary gain enough statistical power for paediatric drug safety detection.

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P056. The Effect of a Transitional Pharmaceutical Care Intervention on the Incidence and Nature of Post-Hospital Medication Discrepancies in Geriatrics

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Background: Inadequate documentation, communication and interpretation of the patients' medication record causes discrepancies.

Objective: To investigate the influence of a multicomponent transitional pharmaceutical care intervention on the incidence and nature of medication discrepancies after hospital discharge.

Methods: A prospective study with a pre-intervention/intervention design was conducted. Patients admitted to an acute care geriatric ward of a tertiary hospital in the Netherlands between August 2010 and February 2011 participated. The intervention consisted of oral patient counseling and a structured discharge medication overview for both patient and next healthcare provider. At one-week follow-up, discrepancies were assessed and divided into intentional and unintentional. Unintentional discrepancies were subdivided into patient-based and system-based and assessed on potential harmfulness. Intentional discrepancies were subdivided into patient-initiated and healthcare provider-initiated.

Results: 41 patients were included in the pre-intervention group; 44 in the intervention group. Discrepancies occurred in 13.6% of the prescriptions in the pre-intervention group vs 10.9% in the intervention group (table I), which were prescribed to 80.5% and 65.9% of the patients, respectively. The incidence of unintentional discrepancies remained equal, although they were mainly patient-based in the pre-intervention group, and mainly system-based in the intervention group. Furthermore, while the number of potentially harmful discrepancies did not differ significantly, they were experienced by fewer patients in the intervention group (18.2% vs 34.1%, adj. OR 0.20 (95% CI 0.05-0.71)). The incidence of intentional discrepancies decreased non-significantly from 10% to 7.5%.

Conclusion: Although the multicomponent transitional care intervention did not significantly decrease the incidence of medication discrepancies after hospital discharge, it did alter the nature of the discrepancies from mainly patient-based in the pre-intervention group to mainly system-based in the intervention group, with less patients experiencing potentially harmful discrepancies.

Table I.

	Pre-intervention group N = 580	Intervention group N = 611	RR (95% CI)
Incidence			
Total discrepancies (n)	13.6% (79)	10.9% (67)	0.81 (0.59-1.11)
Nature			
Intentional discrepancies (n)	10.0% (58)	7.5% (46)	0.75 (0.51-1.11)
Unintentional discrepancies (n)	3.6% (21)	3.4% (21)	0.95 (0.50-1.79)
Patient-based (n)	2.4% (14)	0.8% (5)	0.34 (0.11-1.00)
System-based (n)	1.2% (7)	2.6% (16)	2.17 (0.85-5.78)
Potentially harmful (n)	3.1% (18)	1.8% (11)	0.58 (0.26-1.28)

Discussion: The increase of system-based unintentional discrepancies in the intervention group was remarkable. An important explanation for this observation was that the next healthcare providers often incorrectly processed the information on the medication overview. Hence, in order to actually decrease the incidence of unintentional medication discrepancies, information to the next healthcare providers should be both unambiguous and correctly processed.

P057. Accuracy of Coding-Based Algorithms in Identification of Acute Myocardial Infarction from Multi-Country Electronic Healthcare Record Databases

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Background: Accuracy of outcome ascertainment is crucial to ensure validity when mining electronic healthcare records (EHR) databases for drug safety signal detection.[1-3]

Objective: To evaluate and compare the accuracy of various coding algorithms used to identify cases of acute myocardial infarction (AMI) from three European EHR databases.

Methods: We conducted a validation study in three databases of the EU-ADR network:[4] (1) IPCI (GP database, Netherlands); (2) HSD (GP database, Italy): and 3) Aarhus (claims, Denmark). We identified cases of AMI from GP medical records, primary hospital discharge diagnoses, and death registries using coding algorithms which employed different disease terminology schemes: (1) ICPC; (2) ICD9-CM; (3) ICD-10th revision. We also used free text using key words consistent with AMI. A random sample of 200 cases per database was obtained from all potential cases identified. Additional 200 cases identified by free text search were obtained in IPCI. Manual review of medical records and hospitalisation charts was performed using standardised questionnaire implemented as computerised data entry via custom-built software Chameleon,© locally installed in each database. Positive predictive values (PPV) were calculated overall and for each code and free text query.

Results: The study population comprised healthcare data from 4 034 232 individuals with 22 428 883 person-years (PYs) of follow-up during the period 1995–2011. Within this population, a total of 42 774 potential cases of AMI were identified. From the random sample of 800 potential cases of AMI selected for validation, 748 records were retrieved (93.5%) and reviewed. All ICD-10 codes used (I21.0, I21.1, I21.2, I21.3, I21.4, and I21.9) had 100% PPV. Overall the ICD9-CM codes had very good PPV, with 410.9/410.90, the most frequently occurring code having a PPV of 96.5% (95%CI 93.5-100.4). The ICPC code K75 had a PPV of

75% (67.4-82.6). Use of free text had a lower PPV: 60% (95% CI 17.1-102.9) in HSD and 19.7% (95%CI 12.9-26.5) in IPCI.

Conclusion: The results obtained in this study are consistent with the PPV estimates for ICD-9CM and ICD-10 cited in the literature. Strategies are necessary to further optimise the value of free text search in the identification of AMI in EHR databases.

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P058. The Prevalence and Determinants of Incorrect Dosage Prescribing in Patients with Impaired Renal Function Discharged from the Hospital

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Background: A reduction in glomerular filtration rate (GFR) decreases the elimination rate of medications that are primarily excreted by the kidneys. In order to prevent accumulation and subsequently exaggerated pharmacologic effects or adverse drug reactions, dosage adjustments are often required.

Objective: To analyze the prevalence and determinants of incorrect dosage prescribing in patients with renal insufficiency discharged from an academic hospital.

Methods: The study was conducted at a 1042-bed academic teaching hospital in the Netherlands. All patients, aged ≥18 years, with an estimated (e)GFR between 10–50 ml/min/1.73 m^2 by the MDRD, and discharged between January 2007 and July 2011 were included if they were prescribed one or more medications that required dosage adjustment according to the Dutch Guideline for Drug Dosing in Renal Failure in the last 24 hours before discharge. The prevalence of incorrect dosage prescribing was assessed using descriptive statistics. The influence of the determinants age, gender, automatic reporting of eGFR, severity of renal impairment, and length of hospital stay was analyzed through logistic regression.

Results: 1327 patients were included, which received 1722 prescriptions of 44 different medications that required dosage adjustment. Mean age of the studied population was 67 years, 52% was male. Required dosage adjustments were not performed in 40.1% of the prescriptions, which were prescribed to 46.1% of the patients. The prevalence of incorrect dosage prescribing was not influenced by age, gender, or length of hospital stay. Automatic reporting of eGFR resulted in less patients with incorrect dosage prescriptions (table I): OR 0.78 (95% CI 0.63-0.96). Furthermore, incorrect dosage prescriptions were more prevalent in patients with severe renal impairment (eGFR 10–29 mL/min/1.73 m^2), compared to patients with moderate renal impairment: OR 1.70 (95% CI 1.37-2.13).

Table I.

Characteristic	N (patients)	N patients with ≥1 incorrect prescriptions	OR (95% CI)
Total	1327	612 (46.1%)	
No automatic reporting of eGFR	655	323 (49.3%)	Ref
Automatic reporting of eGFR	672	289 (43.0%)	0.78 (0.63-0.96)
eGFR 30–50 ml/min/1.73 m^2	866	363 (41.9%)	Ref
eGFR 10–29 ml/min/1.73 m^2	461	249 (54.0%)	1.63 (1.30-2.04)

Discussion: Although automatic reporting of eGFR decreases the frequency of incorrect dosage prescribing, the prevalence remains high at 43%. Incorrect dosage prescribing at discharge negatively affects patient safety by potentially causing adverse drug events. Therefore, ceaseless attention for appropriate dosage prescribing in patients with reduced renal function remains indispensable in order to achieve a further reduction in inappropriate prescribing.

Conclusion: Especially in patients with severe renal impairment required dosage adjustments are often not performed at hospital discharge. Automatic reporting of eGFR decreases the frequency of incorrect dosage prescribing.

P059. Dysphonia as a Previously Unreported Side Effect of Bevacizumab Treatment in Patients with Metastatic Breast Cancer (MBC)

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Introduction: Bevacizumab is a humanized monoclonal antibody directed against vascular endothelial growth factor A and has been approved for the treatment of several metastatic tumours. There is considerable heterogeneity in the response to treatment with bevacizumab, both in effectiveness and in toxicity. Here we describe a previously unreported side effect in patients with MBC treated with bevacizumab.

Methods: In a teaching hospital in the Netherlands (from September 2009 to July 2011), 32 consecutive patients with MBC treated with chemotherapy and bevacizumab were registered in a retrospective database. TNM stage, comorbidities, concomitant medication, prior treatment for the primary tumour, date of metastatic disease, prior treatment for metastatic disease and toxicities were recorded. The WHO global individual case safety report database, VigiBase, contains summaries of suspected spontaneous case reports summated by health care professionals and patients to national pharmacovigilance centres. As of May 2010, VigiBase contained >5 million case reports. We

searched the VigiBase extraction of December 2011 for dysphonia. Reporting odds ratios (ROR) were calculated for the occurrence of dysphonia compared with other side effects for bevacizumab and paclitaxel.
Results: In total, 9/32 patients (28%) reported dysphonia during treatment with bevacizumab and 5/9 patients underwent ENT examination. In several patients marked oedema of the vocal cords and/or chronic laryngitis were found. As of December 2011, 6 880 361 reports were available in VigiBase, of which 16 239 were related to dysphonia. For bevacizumab there were 51 reports for dysphonia and 46 041 reports for other adverse effects. Corresponding figures for all other drugs were 22 108 reports for dysphonia and 25 151 628 reports for other adverse effects: ROR of 1.26 (95% CI: 0.95-1.66). For paclitaxel there were 45 reports for dysphonia and 85 988 reports for other adverse effects. Corresponding figures for all other drugs were 22 114 reports for dysphonia and 25 111 681 reports for other adverse effects: ROR of 0.59 (95% CI: 0.44-0.80)), meaning that the risk on angioedema is significantly higher in bevacizumab users compared with paclitaxel users.
Conclusion: Dysphonia is a previously unreported side effect in patients with MBC treated with bevacizumab and paclitaxel.

P060. Triage and Evaluation of Potential Safety Signals Identified from Electronic Healthcare Record Databases

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Background: There is huge potential for mining electronic healthcare records (EHR) databases to augment current systems in pharmacovigilance.[1-3] Like any signal detection system, there is a need to establish 'rules' how to trigger an alert, when to consider a signal likely enough to be true to warrant follow-up or even to require immediate health policy intervention.[4,5]
Objectives: To describe the process of prioritisation of drug-adverse event associations derived from signal detection using EHR databases in the EU-ADR Project.
Methods: Association measures between drug use and acute myocardial infarction (AMI) were generated by first applying various statistical methods on healthcare data from seven databases of the EU-ADR network.[6] Association estimates were ranked based on the best performing method (Longitudinal Gamma Poisson Shrinker). Matched case-control and self-controlled case series methods were additionally conducted to deal with temporality and confounding effect, while the LEOPARD method was applied to specifically detect protopathic bias. Consistency of the association among drugs of the same class and the number of excess cases attributable to the drug exposure were further assessed to prioritize the list of potential signals. Finally, signal filtering and signal substantiation were done using different bioinformatics workflows to determine the novelty and plausibility of the identified signals.
Results: Demographic, clinical and prescription/dispensing data in three European Countries were obtained from 21 171 291 individuals with 154 474 063 person-years of follow-up within the period 1995–2011. Overall, 163 potential signals for AMI were identified based on statistical association. Of these, 72 signals were flagged by LEOPARD as likely due to protopathic bias. Further signal refinement to reduce possible confounding decreased the number of signals to 39. Nine signals remained after applying the criteria for novelty and plausibility.
Conclusion: We propose a prioritisation strategy for drug safety signal detection using EHR by taking into account, in addition to statistical association, also public health relevance, novelty, and plausibility. This strategy needs to be further tested using other EHR data sources and other adverse events.

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P061. Evaluating the Effectiveness of Health Canada's Health Product Public Advisories: A Comparative Study of Health Literacy Burden and Usability

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Background: Health Canada is developing best practices to evaluate the effectiveness of risk communications through studies that measure reach, usability and/or impact of health risk communications. One such study considered the health literacy burden of Health Canada's Public Advisories (PAs) to the general public on issues that concern the health of Canadians. Health literacy is defined as a person's ability to access, understand, evaluate and communicate information to

promote, maintain and improve health in various life-course settings.[1] In May 2010, the Department launched a new Health Canada Advisory template. The design took into account advice from its Expert Advisory Committee on the Vigilance of Health Products and aligned with formats adopted by international regulators. Formatting revisions included: important messages first, boxed text, key bullets and enhanced use of plain language.

Study Objective: 1) To examine the health literacy burden and usability of PAs pre and post format improvements; 2) to determine which health literacy assessment method(s) best measure the health literacy burden of PAs.

Methods: The Suitability Assessment of Materials (SAM)[2] test to evaluate health related information for adults and 7 readability tests[3] (using different mathematical formulas counting syllables, words and sentences to predict reading difficulty) were run by 3 independent evaluators on 46 PAs (14 pre and 32 post improvement). These tests provided adequacy scores for various health literacy elements (SAM) and scholastic grade level ratings (readability).

Results: PAs with the improved format scored slightly better (18% on average) on the SAM test. The majority of the 46 PAs scored high for reading grade level (college/university); well above many Canadian's health literacy capacities.[1] All study readability tests gave reliable results which were independent of the evaluator when cut-off criteria were pre-determined.

Conclusion: Improvements to Health Canada's PA format had a moderate positive effect on reducing the health literacy burden. Future improvements focusing on plain language would be expected to further improve usability of the health risk information presented. Simple methods like the SAM and readability formulas can be used to reliably evaluate the health literacy burden of health product risk communications targeting the general public.

Manufacturers and regulators should consider using SAM and readability tests to periodically evaluate the effectiveness of their risk communications in terms of the general public's ability to read, understand and use the information to make informed health decisions.

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P062. The Antituberculosis Adverse Drug Reactions Prevalence in Morocco

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Introduction: The therapeutic strategy of tuberculosis drugs is well standardized, it includes four first-line antibiotics, which have individually and associated frequent adverse effects.[1,2]

The objective of this work was to evaluate the adverse drug reactions prevalence of antituberculosis drugs collected at the National Pharmacovigilance Centre for the past 5 years.

Material and Methods: It was a retrospective study of antituberculosis adverse drug reactions collected from 2007 to 2011. All cases from spontaneous or active reports were collected. The statistical method has been made from our database center by SPSS 10.0 software.

Results: In our database 16 001 adverse drug reactions were collected from which 466 were related to antituberculosis drugs (2.91%) versus 0.40% ($p < 0.001$) in the international database of Uppsala Monitoring Centre. The mean age of our patients was 43.20 ± 15.60 years with a sex ratio of 0.72. In the 466 adverse drug reactions, 310 were attributed to Isoniazid (66.63%), 281 to Rifampicin (60.48%), 200 to Pyrazinamide (43.07%) and 90 to Ethambutol (19.23%). Liver damages accounted for 60.63%, general disorders (17.17%) and skin damages (12.31%). Of the 466 adverse drug reactions of antituberculosis drugs, 113 were serious (24.24%) versus 12.85% of all drugs in our national database ($p < 0.001$).

Conclusion: The adverse drug reactions prevalence of antituberculosis drugs in Morocco was 7.2 times higher than in the international database, this requires more vigilance in the patients care.

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P063. Utilisation and Tolerability of Aliskiren: Final Results of a Prescription Event-Monitoring Study

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Background: The renin inhibitor aliskiren (Rasilez®) is licensed for essential hypertension and was launched in the UK in Aug 2007.[1] In clinical trials diarrhoea was a common ADR but angioedema (a known ADR with other Renin Angiotensin System drugs), occurred rarely. As aliskiren is first in its class, a Prescription Event Monitoring (PEM) study was performed.

Objectives: To describe the utilisation characteristics and tolerability of aliskiren in patients in England under real-life primary care conditions.

Method: This study used an observational single exposure cohort design. Exposure data were collected from dispensed prescriptions issued by General Practitioners (GPs) from February 2008 to November 2010. Outcome data (demographic, utilisation, and adverse events) were collected by sending questionnaires to GPs 6 months after each patient's first prescription. Summary descriptive statistics were calculated. Percentages presented exclude missing data.

Results: The evaluable final cohort consisted of 6385 patients. Median age 68 years (IQR 59–76), 44.2% (2821/6385) male, Indications: hypertension in 93.3% (5958/6385), chronic renal failure in 1.4% (90/6385) and diabetes mellitus in 1.1% (68/6385) Starting dose 150 mg as per SPC in 89.7% (5389/6007). Aliskiren reported effective in 77.4% (3888/5024). There were 362 ADRs reported in 258 patients. Commonest specified ADRs: diarrhoea (7.2%, 26/362) and malaise (6.4% 23/362). Angioneurotic oedema and oedema face had 2 reports each (both 0.6%, 2/362). Aliskiren stopped in 31.0% (1858/5995). There were 2388 reasons for stopping (RFS) in 1829 patients. Commonest RFS: not effective (16.6%, 397/2388), diarrhoea (5.2%, 123/2388). Angioedema was RFS 5 times (0.2% of RFS). There were 100 deaths during the study (1.6% of cohort). Where cause of death was specified, the majority were cardiovascular in nature, (44.7%, 34/76) followed by neoplasms (18.4%, 14/76).

Conclusion: Aliskiren was prescribed for hypertension and at the recommended starting dose, in the vast majority of patients. Off-label

use was infrequent, but there was evidence of aliskiren being prescribed as part of the management of chronic conditions including diabetes mellitus and chronic renal failure. Aliskiren was reported to have been effective in the majority, and it was well tolerated. Angioedema was both uncommon and uncommonly a RFS. Diarrhoea that was uncommonly a RFS in clinical trials, was a common RFS in this cohort.

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P064. Lenalidomide's Risk Management Plan in Argentina

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Introduction: The risk management plan (RMP) for drug products with lenalidomide is mandatory because of the serious potential risk of teratogenesis. The RMP consists of encouraging physicians to report adverse drug reactions (ADRs), the prescribing information and the Pregnancy Prevention Program (PPP) for all patients with lenalidomide. The PPP was designed according to the experience of the thalidomide pharmacovigilance plan and it includes: educational material for physicians and patients with precautions to prevent pregnancies (contraception measures and pregnancy tests), neutropenia and thrombocytopenia (laboratory tests); controlled distribution system; informed consent (females with or without childbearing potencial and males). Marketing Authorisation Holders (MAH) send a patient registry to the ANMAT Pharmacovigilance Department (PD) periodically. Since October 2008 three drug products with lenalidomide have been approved in Argentina and all of them submitted a RMP, only two products are on the market currently. During postmarketing, new safety information raised from controlled clinical trials that showed a higher rate of second primary (new) malignancies among patients who were treated with lenalidomide compared with those who were not. EMA and FDA advised doctors about the risk of new cancers and the prescribing information was updated in accordance.[1,2] ANMAT warned physicians about this risk and request the MAH to update the prescribing information of products with lenalidomide.

Aim: To evaluate and describe the information collected through the lenalidomide's RMP in Argentina during October 2008–December 2011.

Methods: PD's database completed with the MAH's registry of all patients consuming lenalidomide. PD's data base with the reported ADRs.

Results: The number of patients with lenalidomide was: 2008: 54; 2009: 213; 2010: 350; 2011: 577. Table I shows the distribution of gender and females with childbearing potencial. The most frequent indications were multiple myeloma, myelodisplasia and myelodisplasia 5q. PD received 9 ADRs reports: hematological toxicity (6), extramedullary myeloma (1), ocular angioedema (1), stroke (1). Causality: probable (7), possible (1), not yet described (1); serious (7), non serious (2). Neither teratogenesis nor second primary malignancies were reported.

Conclusions: There was an increasing use of lenalidomide through the studied period. The objective of the RMP was reached as no cases of teratogenesis were detected. The update of the new safety information was required promptly for the prescribing information. While there was a high percentage of compliance in the presentation of the patient registry periodic reports, it is necessary to enhance the reports of ADRs.

Table I. Total number of patients with lenalidomide, distribution of gender and women with gestation capacity during October 2008–December 2011

Year (October–December)	Men	Women	
		Without childbearing potential	With childbearing potential
2008	36 (66.7%)	18 (33.3%)	0 (0.0%)
2009	108 (50.7%)	100 (47.0%)	5 (2.3%)
2010	170 (48.6%)	169 (48.3%)	11 (3.1%)
2011	285 (49.4%)	280 (48.5%)	12 (2.1%)

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P065. Pharmacovigilance of Traditional Chinese Medicine Drugs in China

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Introduction: Traditional Chinese Medicine (TCM) has been playing a very important role in health protection and disease control for thousands of years in China, is still widely used in and increasingly out of China. A vast body of TCM 'materia medica' has accumulated through history. However, the production, composition and toxicity of medicinal products used in TCM are totally different from those of modern medicine. TCMs are not free of adverse drug reactions (ADRs).[1] Since the numbers of TCM users are increasing world-wide, the TCM drug safety monitoring and risk management have become a priority task for the Chinese State Food and Drug Administration (SFDA).

Aim: To review the current status of the TCM pharmacovigilance in China and summarize the risk factors associated with TCM.

Methods: We performed a retrospective study on the ADR reports from 1988–2011 in the Database of National ADR Monitoring Center with descriptive statistics methods and analyzed the common risk factors of TCM ADR.

Results: The National ADR Monitoring Center received a total of over 4 000 000 reports by the end of 2011. Among the reports received each year, about 10–15% of the ADR reports are related to TCM drugs, which were mainly formulated products. Overall, Traditional Chinese Medicine drugs represent 13.8% of total case reports, involving more than 2400 products. The majority are formulated products (99.7%)

with less than 0.4% from crude drugs. Unexpected and serious TCM drug ADR reports represent 12.2% of total unexpected and serious reports.[2] In our practice, we summarized the major TCM risk factors as (1) risk factors arising from the drugs, e.g. the place of origin and collection, processing, storage, manufacturing, constituents, defects in the product information, counterfeiting and adulteration; (2) risk factors arising from clinical use, such as failure to follow theoretical guidance, failure to adhere to prescription instruction, inappropriate combination with Western medicines,or related to individual patient conditions; (3) risk factors related to individual patient's condition.

Conclusion: The TCM safety monitoring and risk management in Chinahas have made tremendous progress in the last two decades and is still in the process of developing.[3-5] The management and control of risk factors associated with TCM drugs requires the raise of the awareness, focused basic scientific research, better quality control in manufacturing, enforcement of voluntary and on active monitoring/surveillance, standardization of clinical practice, introduction of the concept of pharmacovigilance as well as international communication and cooperation.[6]

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P066. Predicting Drug-Induced Stevens Johnson Syndrome Using Quantitative Structure-Activity Relationship Models Based on Individual Case Safety Reports

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Introduction: For some adverse drug reactions (ADRs), such as Stevens Johnson Syndrome (SJS), causative drugs often incorporate certain chemical features.[1] Large collections of individual case safety reports (ICSRs) provide vast resources of information on suspected ADRs, and could therefore possibly be utilised to infer chemical features likely to be linked to a certain ADR. We investigated the usefulness of ICSRs for building Quantitative Structure-Activity Relationship (QSAR) models that can be used to predict an individual drug's SJS-causing potential and discover SJS-specific chemical alerts.

Aim: To identify chemical features associated with SJS, and to investigate the predictive performance of QSAR models for SJS.

Methods: A reference set of drugs was constructed from VigiBase, the WHO Global ICSR database. Reporting correlation with SJS was defined through shrinkage regression to avoid confounding due to concomitant medication.[2] Negative controls were conservatively defined as either (i) drugs with zero reports with SJS and at least 1000 reports in total, or (ii) drugs with zero reports where the drug was solely suspected to cause SJS, in combination with robust lower-than-expected reporting with SJS.[3] The reference set was cleaned of mixtures and inorganic compounds,[4] and chemical descriptors for the remaining drugs were calculated. QSAR models were derived using k-nearest-neighbours and random forest approaches. Models' predictive power was assessed using a five-fold external cross-validation scheme. Chemical descriptors with significant contribution to models were examined for mechanistic association with SJS.

Results: The final reference set contained 194 drugs correlated with SJS and 170 negative controls. The derived QSAR models attained 65–72% specificity and 67–78% sensitivity in external cross-validation. Statistically significant descriptors included the number of hydrogen atoms, polarity, and presence of amine and sulfur groups. They were consistent with the substructures frequently found in SJS-linked drugs such as sulfonyl arylamines, sulphur-adjacent beta-lactams, tetracyclines, and fluoroquinolones. The reference set clearly discriminated between sulfonamides in general and sulfonyl arylamines in particular: 5 of 34 among the former were negative controls, compared to 0 of 21 among the latter. This fits with the established pathway for arylamine-induced immunogenicity.[5]

Conclusions: QSAR models for SJS displayed high predictive accuracy and identified distinct chemical profiles linked to SJS. These models have value in predicting the potential of any substance to cause SJS using only molecular structure as input. This might both prevent harmful re-exposure of patients and aid the development of safer drugs.

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P067. Paediatric Acute Liver Injury: Signal Detection Using Multiple Healthcare Databases from the EU-ADR Network

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Introduction: Data mining in spontaneous reporting databases has shown that drug-induced acute liver injury (ALI) is infrequently reported in children,[1] but such system still has limitations in terms of signal detection. The EU-ADR project aimed to develop and validate a computerised system combining data from multiple European electronic healthcare records (EHR) for early detection of drug safety signals.[2]

Aims: To identify drugs potentially associated with ALI in children and adolescents using EHR data.

Methods: We extracted data on ALI cases and prescribed/dispensed drugs for individuals 0–18 years old registered with seven European population-based medical records/claims databases of the EU-ADR network during the years 1996–2008. Based on the estimated background incidence rate of ALI, power = 80%, alpha = 5% and the number of person-years (PYs) of drug exposure by ATC classification, we calculated the minimal drug exposure required to detect a signal concerning paediatric ALI.[3] Using the Longitudinal Gamma Poisson Shrinker (LGPS) method,[4] we defined as threshold for potential signals in EU-ADR a value of relative risk (RR_{LGPS}) ≥2 and a lower 95% CI of RRLGPS >1 for each drug associated with at least three events of ALI. We discriminated among potentially relevant new signals and already known signals either in adults or in children by data mining of published literature as well as product labels.

Results: Overall 4 838 146 children 0–18 years old contributed 25 575 132 PYs of follow-up time to the EU-ADR database network. Within this population, 1015 events of ALI were identified. The IR of paediatric ALI was estimated to be 3.96 (3.73–4.21)/100 000 PYs. The total amount of drug exposure that is required to detect a weak, moderate and strong association with paediatric ALI (RR≥ 2.0, 4.0 and 6.0) was 202 733 PYs, and 31 041 PYs, and 13 860 PYs, respectively. Among drugs associated with at least three cases, 20 drugs were found to be potential signals for ALI. Except for the anti-asthmatic agent flunisolide, these signals are known to be hepatotoxic in adults.

Conclusions: Combining multiple EHR databases increases the power for drug safety signal detection in children. Signals identified by this system include drugs known to be associated with ALI in adults and may further be utilised to characterise ALI in the paediatric population.

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P068. Establishing Electronic Adverse Drug Reaction Reporting in UK Primary Care Clinical IT Systems

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Spontaneous Adverse Drug Reaction reporting schemes, such as the UK's Yellow Card Scheme, are recognised to be subject to under-reporting.[1-3] Efforts to increase ADR reporting may improve the potential for earlier detection of drug safety issues, and allow earlier regulatory action to protect public health.

Surveys investigating reasons for health professionals failing to report include a lack of time, difficulty in accessing a reporting form or access to the Yellow Card website.[3]

General Practitioners (GPs) are considered to be the cornerstoneof Yellow Card reporting, and are the single largest reporter group. However it is of concern that although overall Yellow Card reporting is increasing each year, a decreasing trend has been seen in the number of reports received from GPs.

Electronic reporting has been used by the Medicines and Healthcare products Regulatory Agency (MHRA) as a method for improving access to reporting forms. This also reduces the need for data entry, postage costs, whilst also making data available for signal detection more quickly as the data can be loaded automatically into the MHRA's pharmacovigilance database. Recently the system has been expanded to enable Yellow Card messages based on the ICH E2B(R2) standard to be received from external IT systems.

Reporting directly from clinical IT systems improves accessibility of reporting and reduces reporting effort through automatic information population from patient records into the form. ADR reporting can also be triggered within the system by specific events such as medication withdrawal.

In England, electronic Yellow Card reporting has been developed into a primary care system SystmOne (from TPP). The software is used by GPs and nurses in 15% of the primary care setting. Introduction lead to a 43.8% increase (1437 reports) from GPs in 2011 compared to 2010.

Based on this development, an information standard for electronic Yellow Card reporting (ISB 1582[4]) has been developed for the UK National Health Service (NHS). The standard defines an electronic message for ADR reporting and a set of triggers resulting in a prompt to submit a Yellow Card.

Implementation in the majority of primary care IT systems is being pursued through the GP Systems of Choice (GPSoC), a scheme through which the NHS funds the provision of GP clinical IT systems in England. Reporting at levels seen from SystmOne across all other GPSoC systems are anticipated to result in a significant increase in GP reporting for the UK.

Table I. Total number of Yellow Card reports received from GPs between 2007 and 2011 and those received directly from SystemOne

Year	Yellow Cards received from GPs	SystemOne GP Yellow Cards (% of total GP Yellow Cards)
2007	3794	-
2008	3504	-
2009	2594	-
2010	2290	92 (4.0%)
2011	3279	1437 (43.8%)

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P069. Representativeness of Diabetes Patients Participating in a Web-Based Adverse Drug Reaction Monitoring System

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Introduction: Lareb Intensive Monitoring, LIM, is a non-interventional observational cohort method which follows first-time users of certain drugs during a certain period of time and collects information about adverse drug reactions, ADRs. In order for LIM to be a useful pharmacovigilance tool, it is important to know whether the LIM population is comparable to the whole population using the drug.

Aim: The aim of this study to compare the LIM diabetes population with an external diabetes reference population on characteristics that may influence the patient's susceptibility for ADRs.

Methods: In this study, a LIM diabetes population was compared to a reference diabetes population derived from The Groningen Initiative to ANalyse Type 2 diabetes Treatment project (GIANTT). Comparisons were made regarding age, gender, BMI and polypharmacy, as well as diabetes medication used and disease/treatment duration.

Results: LIM patients were more often men (58.5% vs 50.8%) and in general younger (59.1 vs 64.7 years) and the population had a higher percentage of de novo treated patients (55.5% vs 53.2%), a shorter diabetes treatment duration (3.7 vs 5.5 years) and used less co-medication than patients in the reference population.

Conclusions: This study shows that diabetes patients participating in a web-based monitoring system differ from a reference population. The observed differences might lead to an underestimation of ADRs but it is not clear whether this would also influence the type or time-course of the ADRs reported. When interpreting results from LIM studies, this allows for generalisation toward the general population.

P070. Pharmacovigilance of Herbal Medicines in Morocco: Experience of Twelve Years, Opportunities and Challenges

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The use of herbal medicines (HM) is on the rise among the global population. The influence of religious, sociocultural, and socioeconomic issues, traditional practices, and belief in the use of HM is evident, particularly in Chinese, Indian, and African societies. This is the case in Morocco where HM, as with all medicines and around the world, have been shown to have adverse effects, which are related to a variety of causes, essentially in relation to self-medication, quality of raw materials, misidentification, incorrect dosing, and particular conditions of use. Furthermore, HM may affect pharmacokinetic and pharmacodynamic properties of conventional drugs when used concomitantly and thus cause herb-drug interactions with potential adverse effects. The safety of HM is monitored through the Moroccan pharmacovigilance center via the Pharmacovigilance of Herbal Medicines or Phytovigilance Unit, implemented in 2000.

The objective of this communication is to discuss the Moroccan experience in terms of pharmacovigilance of herbal medicines which probably can be an example to many countries, as well as to discuss opportunities for increasing quantity and quality of HM reports and challenges which are faced in the assessment of HM safety.

Since its inception, the activities of the Unit continue to grow with an adaptation of the reporting form, a continued increase in reported cases (with a total of 2128 reports during twelve years) which is 10% of all notifications, for all health products, the same monitoring as conventional drugs both at national and international levels, regular awareness for all partners of the phytovigilance system, training in the field, publications, scientific studies, alerts and a response to any request for information on the rational use, adverse effects and interactions in relation to HM.

We have recruited a PhD scientist specialized in Aromatic and Medicinal Plants for pharmacovigilance of HM activities. Our Unit also works in tandem with the Poison Control Center, with whom we share the same building. We also use the Poison Control Center database as an important source for HM adverse effects (Sometimes up to 50% of HM reports). This activity has contributed to the development of pharmacovigilance of HM in Morocco.

The pharmacovigilance tools such as causality assessment have been developed for conventional drugs and these can't be applied to HM raw materials and the need for an adequate regulatory framework for HM, to effectively protect consumers and patients, present the main challenges for HM in Morocco.

P071. Management of Medication Error Reports Associated with the Use of Paracetamol Solution for Infusion at the French Health Products Safety

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In the framework of the objectives set by the Public Health Act aimed at reducing drug-related adverse events (enacted in 2004), the French National Drug and Health Products Safety Agency (ANSM) has set up in 2005 a dedicated unit to collect and manage, in a single location, reports of medication errors or potential errors related to the packaging, labelling or names of medicinal products, and perform the follow up of those likely to present a risk to Public Health. The ''Medication errors' Guichet'' enables healthcare professionals to report directly medication errors without adverse reaction or near misses in addition of reports collected from the Pharmacovigilance System.

In this context, some serious dosing errors have been collected with the intravenous formulation of paracetamol (acetaminophen) leading to severe liver injury or death. Most of cases of overdose were reported in the paediatric population weighing ≤10 kg and were due to confusion between mg and mL resulting in the administration of a 10 times higher dose than the prescribed dose, the strength of the medicinal product being 10 mg/mL.

Therefore, the ANSM decided in accordance to the European pharmacovigilance working party to set up risk minimisation measures including a DHPC (communication to healthcare professionals) which highlight the risk of medication error and inform the changes in the SmPC and PIL for preparation and administration for patients.

P072. The Follow-Up Activity in Vaccine Post-Marketing Surveillance in Italy

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Introduction: Spontaneous ADRs reports are an important tool in the post-marketing surveillance; often the reported data are not enough complete to allow the case assessment. In particular the evaluation of adverse events following immunization (AEFI) requires the availability of several details and for this reason a follow-up including detailed medical history and any missing data is necessary at least for serious cases.[1] Different methods are used to increase follow up rates, including targeted letters to reporters.[2]

The follow-up activities in Italy are in charge of the Local Responsible of Pharmacovigilance (LRP) by law. However, often it is complemented by a request coming from the Agency.

Objective: To describe results of the follow up activities performed in case of serious vaccine(s) reports during the timeframe September 2011 to April 2012.

Methods: Spontaneous reports are collected in Italy in the Pharmacovigilance database. Firstly the serious reports are checked with respect to completeness of data. If there are lacking information, a formal request is sent by fax to the LRP who can contact directly the reporter to obtain the follow-up data. From January 2012 it was decided to closely monitor the ratio between the request sent/received follow up, and in the absence of a response, the LRP was contacted by telephone to know the reasons for not sending the required information.

Results: 200 serious spontaneous reports concerning vaccines were included in the National Pharmacovigilance Network from September 2011 to April 2012.

As of 20 May 2012, aresponse to follow up was available for 149 cases (74,5%), while it was requested but not yet received in 42 cases (21%). In 9 cases (4,5%) report were already complete not requiring any additional request.

Among the 149 cases with a response to follow-up, the additional information was available within one month in 119 cases (80%) of which 54 cases within the first week. In eleven cases the follow-up was received within 60 days, while only for 19 cases in a period >60 days. Of course for cases requiring a clinical re-assessment after months or an update of the outcome, more than one follow-ups could be necessary.

Conclusions: Our intention is to monitoring for a longer period also this activity, but preliminary results referred to the months from September 2011 to April 2012 show very positive results due to multiple collaborative interventions within the national pharmacovigilance network at local, regional and central level.

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P073. Italian Programme for the Performance Monitoring of Regional Pharmacovigilance Centres

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In Italy, the Regional Pharmacovigilance Centres (RPCs) represent a strategic component for the proper functioning of the National pharmacovigilance system as well as a vital connecting node between the central and local structures. Eight RPCs are operating in the following regions: Lombardia, Veneto, Liguria, Emilia-Romagna, Toscana, Campania, Basilicata and Sicilia.

These centers are Regional structures with defined roles and responsibilities:[1]

- Evaluation of reports coming from a Region, with reference to quality of data and coding (medications and adverse reactions);
- Support the local responsible for pharmacovigilance (LRPs);
- Causality assessment and listedness evaluation;
- Support LRPs in feedback and training activities directed to reporters;
- Contribute to signal analysis on drugs and vaccines in collaboration with the Italian Medicines Agency (AIFA).

So far no systematic attempts to evaluate the activities of the pharmacovigilance centers are known. In contrast, several analysis to assess the quality of reports are published.[2-4]

In April 2012, the AIFA started a program to monitor the performance of RPCs. Several indicators were selected with the aim to use robust measures to assess the effectiveness and efficiency of the system. The choice of indicators was based on the following criteria: i) quickly measurable parameters; ii) dependent on the specific objectives or tasks of a RPCs; iii) applicable to all RPCs.

Through the use of such common indicators it will possible to make comparisons amongst different RPCs and, following the first data collection, future audits will also enable to assess progress over time. Overall, 33 different indicators were identified and included in a data collection form. The indicators, which can be both qualitative and quantitative, are divided into five distinct sections relating to: i) organization or the RPCs (e.g. personnel, infrastructures); ii) spontaneous reports (e.g. descriptive analysis over years; quality of reports; SOPs); iii) drug information and training (e.g. feedback to reporters, courses, periodic report); iv) cooperation and networking (e.g. regional projects); v) budget. A sixth section has been included as free text and is dedicated to comments/critiques/proposals from the RPCs.

The audit include a first step in which the data collection form is sent to the RPCs. Then, a 1-day visit to RPCs is organized to discuss and analyze available data and to look into the process for the management of reports (and related pharmacovigilance activity) at the RPCs. A report with a full analysis of data collected is expected to be published.

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P074. Programme for Funding Active Pharmacovigilance Projects in the Italian Regions

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In 2007 the National law provided for a programme for active pharmacovigilance to be set up in the 21 Italian Regions in collaboration with the Italian Medicines Agency (AIFA). More than seventy million Euros per year were allocated from 2007 to 2009. A specific agreement is signed between the Italian State and the Regions identifying research areas of interest and the distribution of funds. The AIFA is involved in the following steps: i) definition of guidelines for research areas; ii) approval of the projects submitted by the Regions; iii) management of the agreements between AIFA and Regions; iv) monitoring of the projects; v) publish the list of projects funded.

The guidelines included initiatives aimed at improving the knowledge on the benefit-risk profile of drugs when used in the post-marketing phase. Five areas of interests have been identified: i) studies of adverse drug reactions (ADRs) either on the basis of analyses of spontaneous reports or conduction of epidemiological studies; ii) evaluation of drug use and promotion of drug appropriateness; iii) drug information and training interventions directed to professionals to stimulate spontaneous reporting; iv) strengthening the pharmacovigilance activities of ethical committees in the context of clinical trials; v) set up and/or maintenance of Regional Centres.

The distribution of funds between the Regions entails three *tranches* based on the resident populations: 30% of the available fund is given directly to the Regions to improve PhV activity at local level, 60% is granted for regional projects submitted within the five areas of interest identified, 10% is dedicated to multiregional projects with national relevance.

The monitoring of projects implies interim and final reports on single projects as well as audits with Regional structures.

In the beginning of 2012 has been concluded the activity for funding projects with resources available for years 2007–2009. Overall, 200 new projects have been funded; About 80% of projects falls in the areas of studies of ADRs and evaluation of drug use; The majority of projects funded in 2007 (61%) come from Northern Regions, the remaining 39% are equally distributed between Central and Southern Regions. In 2008 and 2009 the distribution was balanced amongst Italian areas being 30% North, 30% Central, 40% South respectively. Eleven multiregional projects with national relevance have been funded and six new Regional Centres have been established.

Active pharmacovigilance projects are strategic to increase the National capacity on pharmacovigilance as well as to promote the ADR reporting.

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P075. Patient's Benefit & Risk Preferences for Drugs to Treat Type II Diabetes Mellitus

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Background: In the summer of 2011 the use of pioglitazone was banned in some European countries. Other countries did not take such strong measures as the risk of bladder cancer – an increase from 4 to 6 cases per 10 000 patient years – was considered small and of uncertain nature. It is unknown how type II diabetes mellitus (T2DM) patients value such serious but small drug risks in the context of other benefits and adverse drug effects (ADEs) of antihyperglycemic agents (AHA).

Objectives: Weighing of short-term glucose regulating and long-term cardiovascular benefits and risks in the context of symptomatic ADEs and small but serious risks.

Methods: A stated choice survey was administered to 315 T2DM patients, aged 60 to 75. Patients were recruited through their community pharmacies. In total 18 choice sets (fictional drugs) were constructed with drug attributes with varying levels: HbA1c control, risk of cardiovascular disease, weight, risk of gastrointestinal symptoms, and risk of hypoglycaemic episodes. In addition, all fictional drugs had either the baseline or increased level of risk of bladder cancer. Patients were presented with 6 choice sets each and asked to indicate which of the two they preferred. Analysis was done using conditional multinomial logit.

Results: Response was 226 (72%), with mean age 67 (SD: 4.5) years and 48% women. Self-reported HbA1c was 6.8% (SD: 1.1), mean duration of diabetes 9.1 years (SD: 8.1) and mean BMI 29.0 (SD: 4.4). 51 (23%) patients had experienced adverse drug effects (ADEs) from their current AHA. Patients prioritised attributes in the following order. Long-term GI problems (OR: 0.16, $p<0.001$) > frequent hypoglycaemia (OR: 0.24, $p<0.001$) > weight increase (OR: 0.39, $p<0.001$) > CV risk increase (OR: 0.47, $p=0.004$) > less frequent hypoglycaemia (OR: 0.50, $p=0.020$) were seen as negative attributes and CV risk reduction (OR: 1.74, $p=0.028$) as positive. HbA1c and other levels of attributes were not statistically significant including the risk of bladder cancer (OR: 0.98, $p=0.97$).

Conclusions: Patients weigh heavily ADEs that influence their daily life. Control of glucose and a small increased risk of cancer are not as important.

P076. Agreement in Balancing Benefit and Risk of New Drugs Between Patients, Doctors and Regulators

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Background: Regulators approve new drugs based on an assessment of their benefit risk balance at a population level as determined in clinical trials. Subsequently, these results have to be translated by doctors for individual patients, who then have to integrate these drugs into their daily life. Little information exists on (dis)agreement in perception of benefits and risks of antihyperglycemic agents (AHA) between these stakeholders.
Objectives: Compare the perception on benefit risk balance of new AHA by regulators, doctors and type II diabetes mellitus (T2DM) patients.
Methods: A stated choice survey was administered to 79 Dutch Medicines Evaluation Board assessors, 845 doctors and 315 T2DM patients. 18 choice sets were made comparing 2 fictional new AHA varying on the following drug characteristics: HbA1c control (main surrogate efficacy marker for AHA), effect on the risk of cardiovascular (CV) disease, weight, gastrointestinal complaints, hypoglycemic episodes and risk of bladder cancer. Regulators were presented 18 choice sets, while 3 groups of patients and doctors answered 6 choice sets each. They were asked each time which AHA they preferred. Analysis was done with multinomial conditional logit.
Results: 226 (72%) T2DM patients, 175 (21%) doctors and 52 (66%) regulators responded.
Long-term GI problems (OR: Regulator; 0.24, $p<0.001$; Doctor; 0.20, $p<0.001$; Patient; 0.16, $p<0.001$) and CV risk increase (OR: R; 0.49, $p=0.016$; D; 0.37, $p<0.001$; P; 0.47, $p=0.004$) were seen as negative attributes and CV risk reduction (OR: R; 1.98, $p=0.020$; D; 4.40, <0.001; P; 1.74, $p=0.028$) as positive by all groups. Additionally, doctors and patients regarded frequent attacks of hypoglycaemia (OR: D; 0.16, $p<0.001$; P; 0.24, $p<0.001$) and weight increase (OR: D; 0.39, $p=0.025$; P; 0.39, $p<0.001$) as negative attributes. Doctors regarded large HbA1c reduction (OR: 3.24, $p=0.016$) as positive attribute. Risk of bladder cancer and other drug characteristics levels did not significantly affect stakeholders drug preference.
Conclusions: CV risk reduction, and not glucose control is considered the most beneficial characteristic by all groups. Doctors and patients have generally similar preferences for new AHA. Assessors were less sensitive to weight increase and incidence of hypoglycemia.

P077. Old Medication New Combination: 1 Tablet Once a Day in HIV Treatment

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Introduction: Treatment of HIV has evolved over the last 30 yrs with a dramatic reduction in morbidity and mortality. Successful treatment depends on strict adherence to medication. It is well recognised that multiple complicated dosing regimes and adverse effects are associated with poor adherence.
Aim: We decided to investigate whether there are any unexpected side effects from changing treatment regimes from separate tablets to a 1 tablet Atripla once a day regime.
Methods: A retrospective case notes analysis and pharmacy record of 145 sets of notes was undertaken. We included all patients prescribed Atripla between 2008 and 2010.
Results: 26 patients were excluded due to inadequate information. Out of 119 cases 102 were switched from individual components (tenofovir, emtricitabine and efavirenz) to Atripla and 17 started Atripla de novo. 26.4% of patients (27 of 102) experienced adverse effects when changed from multiple treatments to Atripla compared to 53% (9 of 17) of patients in the de novo group. Full details of the adverse effect profile will be presented.

Table I.

Adverse effects	Multiple to Atripla adverse effects (n = 27)	*De novo* Atripla adverse effects (n = 9)
CNS	14 (51.8%)	9 (100%)
Skin	11 (40.7%)	5 (55.5%)
Other	3 (11.1%)	5 (55.5%)

Conclusion: There were no unexpected side effects in either group. The group of patients taking multiple components for a minimum of 48 wks did not report any adverse effects before switching to Atripla. Of the 36 patients (27 + 9) from both groups that experienced adverse effects none were treatment limiting and all patients continued with the new regime. This study shows that single dose combination therapy is a safe option for treatment of HIV.

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P078. Determinants of Impact of Drug Safety Warnings. A Retrospective Analysis of Direct Healthcare Professional Communications

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Introduction: Throughout the post-marketing lifecycle of a drug serious safety issues may emerge, which can cause hospitalization, disability, or even death of patients. Communication of such risks is mainly taking place by sending Direct Healthcare Professional Communications (DHPCs) or 'Dear Doctor Letters' to healthcare professionals. In the present study we analyze whether several drug- and DHPC-related characteristics explain the differences in impact of DHPCs.
Methods: DHPCs issued in the Netherlands (2001–2007) and monthly dispensing data (2000–2008) were obtained. We performed a multiple linear regression analysis to examine the explanatory power of the following drug and DHPC characteristics: time to DHPC, trend in use (before DHPC), degree of innovation, type of required prescriber, first or repeated DHPC, timing of DHPC, and type of serious safety issue. The outcome variable was defined as the relative change in new drug use, post DHPC. The explained variance was indicated by the adjusted R^2.
Results: We identified 58 DHPCs for 46 drugs for which DHPC-specific standardized changes in new drug use were calculated. Twenty (34.5%) DHPCs resulted in a mean long-term decrease in use of 26.7% (95% CI: -15% to -38%). A significant effect was found for drugs with a declining use prior to the DHPC ($p<0.05$). DHPCs for specialist in-

itiated drugs had less impact than GP initiated drugs ($p<0.05$). The DHPCs' impact marginally increased during the study period ($p=0.056$). Seriousness of the safety issue was relevant, both risk of death and disability led to lower use (both $p<0.05$). The remaining characteristics had no significant impact, the characteristics explained 34% (adjusted $R^2=0.337$) of the variation in DHPC effect size.

Comment: Declining use prior to the DHPC, non-specialist drugs, the type of safety issue, and DHPCs issued later in the study period increased the DHPCs impact on drug use. These results should be considered when additional measures are considered to improve impact of DHPCs to prevent future safety issues.

P080. Progressive Multifocal Leukoencephalopathy After Chemotherapies: A Case Report

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The progressive multifocal leukoencephalopathy (PML) is a demyelinating disorder of the white matter of the central nervous system observed during the deep cell immunosuppression.[1] This disease is due to an opportunist infection by the JC virus. It could be favored by the use of monoclonal antibodies, in particular after a treatment by natalizumab upper to 6 months.

We report here the case of a man who developed hemiplegia with frontal syndrome and cognitive troubles after various lines of chemotherapies. A PML was diagnosed.

The patient was a 66-year-old man, followed up for an IgG Kappa myeloma since 2004 with complex care: allograft, then diverse protocols of chemotherapies including thalidomide (2006 to 2007), lenalidomide (2007 to 2009), bendamustine (2009 to 2011) and finally bortezomib (September 2011).

In December 2011, he began to lose his left visual field. At the beginning of January 2012, after a fall, he had difficulties to hold his walking frame with his left hand. A hemiplegia is individualized at the middle of January, leading to a hospitalization in Neurology department. Then, his state declined with frontal syndrome and cognitive troubles. The examinations of scanner imaging showed bilateral damage making discuss an ischemic origin but with a negative etiologic assessment.

In February 2012, the patient was hospitalized in Emergency department for seizures of the right hemibody. Biological examinations were normal, electroencephalogram showed diffuse pseudoperiodic slow activities. The images of the scanner evoked a PML: junctional hypodense left lesion and very irregular, badly defined right parietal lesion, unusual for an ischemic sequel. These images associated with the progressive constitution, and a severe immunosuppression directed to the diagnosis of PML, confirmed by a positive PCR for the JC virus. The patient died 2 months after the diagnosis.

Few cases of PML are described with monoclonal antibodies, in particular natalizumab[2] and more rarely with rituximab. Disease progression and death are not inevitable. Indeed, the mortality associated with natalizumab-related PML was 19%.

At our knowledge, our case is the first case report with bortezomib. Previous chemotherapies may probably be a risk factor of PML. Early diagnosis and active efforts to accelerate immune restoration could allow to improve the forecast in potential future other cases.

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P081. The Ribavirin Pregnancy Registry: Challenges and Lessons Learned

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Introduction: Ribavirin, is an anti-viral administered with interferon and recently approved protease inhibitors, boceprevir and telaprevir, for hepatitis C virus (HCV) infection. Ribavirin is classified as a potential human teratogen (FDA Pregnancy Category X) based on animal data; in addition, there is also indication of persistence in the human male reproductive tract resulting in the potential for fetal bioavailability.[1-3] The 12-day multiple dose half-life suggests pre-pregnancy doses may lead to fetal exposure. Since 2003, all 7 manufacturers marketing ribavirin in the US have jointly conducted the Ribavirin Pregnancy Registry (RPR) to monitor for signals of teratogenicity and estimate the birth defect rate among ribavirin-exposed pregnancies compared to the general population. Characteristics of ribavirin metabolism and pregnancy-exposed population present unique methodological challenges for RPR.

Aim: To identify challenges in monitoring ribavirin-exposed pregnancies and associated methods implemented by RPR.

Methods: Six key issues were reviewed: 1) lost to follow-up (LTFU); 2) induced abortions (IAB) based on fear of birth defects; 3) awareness strategies promoting enrollment without encouraging use in pregnancy; 4) importance of male exposures; 5) enrollment challenges in a population aging beyond child-bearing years; 6) ribavirin's long half-life. Practices implemented and lessons learned over RPR's 9 years were evaluated. Linear enrollment projection models were developed based on historical enrollment rates.

Results: To address pharmacokinetic issues, RPR enrolls pregnant women exposed to ribavirin during pregnancy or 6 months prior to conception either directly, by taking ribavirin, or indirectly, through her male sexual partner. Outcomes are stratified by trimester of earliest exposure including the pre-conception period and exposure type. Reaching the enrollment target of 300 pregnancies (158 live births) in each exposure type (direct or indirect) is projected to take 20 and 16 years from Registry inception, respectively (table I). Frequent evaluation of awareness effectiveness, with manufacturer and Scientific Advisory Board input, guides outreach to promote enrollment and avoid improper messaging suggesting unsubstantiated safety or risk in pregnancy. IAB rates and reasons are reviewed annually; approximately half attributing IAB to ribavirin exposure. LTFU is highest among manufacturer-initiated enrollments followed by health care providers and lowest among patient-initiated enrollments.

Conclusions: This complicated registry has overcome many challenges; however, it continues to suffer from low enrollment. Although no safety signals have emerged, enrollment is too low to draw conclusions.

Table I. Selected Characteristics of RPR, Dec 2003- Feb 2012

Enrollment and Outcomes	Overall	Exposure type	
		Direct	Indirect
Pregnancies	230	103	127
Maternal Age (years)[a]	30.0	29.6	30.3
Live Births[b]	147/231 (64%)	64/104 (62%)	83/127 (65%)
Induced Abortions (IAB)	51/231 (22%)	26/104 (25%)	25/127 (20%)
IAB Related to Ribavirin	25/51 (49%)	13/26 (50%)	12/25% (48%)
Projected Year of Completion		2023	2019
LTFU	113/343 (33%)	51/154 (33%)	62/189 (33%)
Patient Reports	18/125 (14%)	9/52 (17%)	9/73 (12%)
HCP Reports	37/139 (27%)	21/73 (29%)	16/66 (24%)
Manufacturer Reports	58/79 (73%)	21/29 (72%)	37/50 (74%)

a Mean maternal age at the time of enrollment.

b Live births as a percentage of all pregnancy outcomes; includes one set of twins in direct exposure group.

HCP = Healthcare provider; **IAB** = Induced abortion

Efforts are ongoing to meet enrollment targets and address the potential for teratogenicity following paternal or maternal exposure to ribavirin.

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P082. Characteristics and Contribution of Consumer Reports of Adverse Drug Reactions: Experience from Denmark during the Last Decade

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Introduction: Consumers can provide first hand information about their experience with drugs and possible Adverse Drug Reactions (ADRs). Since 2003 consumers have been able to submit reports of possible ADRs directly to the Danish Health and Medicines Authority (DHMA).

Aim: To characterize the ADR reports from consumers and to compare consumer reports with reports received from other groups.

Methods: Consumer reports received by DHMA between 1 January 2003 and 31 December 2011 were analyzed and compared with the reports received from doctors, pharmacists and other health care professionals (eg. nurses) received in the same period regarding various characteristics. We analyzed characteristics of the consumers, e.g. age and sex and characteristics of the reports e.g. numbers and types of ADRs and drugs reported, outcome, seriousness and timeliness of reports.

Results: A total of 24 900 ADR reports corresponding to 61 884 ADRs were analyzed. 19% of the reports were reported by the consumers.

Concerning the characteristics of the consumers we found broad similarities except for ADR reports from pharmacists, where the consumer was 10 years older in average age than in the other groups. The average number of ADRs included in the reports was 3.7 for consumers and approximately 2 for the other groups. The number of different substances included in each ADR report, were nearly the same (1.05–1.21).

The suspected drugs most often reported differed between types of reporters. Vaccines were the most often reported suspect drug by doctors, whereas the most commonly reported drug for consumers was thyroid therapy. Other healthcare professionals submitted most reports regarding immunosuppressants and asthma medications were the most often reported drug by pharmacists.

Nervous system disorders was the most frequently involved System Organ Class for consumers for which the ADRs were most frequently reported for consumers and general disorder and administration site conditions for the other groups.

The share of ADRs reports classified as serious by consumers was 22% and differed from those classified as serious by doctors (48%), pharmacist (25%) and other health care professionals (72%). The distribution of the criteria of seriousness differed between groups.

Conclusion: This analysis showed that there are a number of similarities but also differences between consumer reports and reports received from other sources. The present study indicates that consumer reports may contribute with important information. Consumer reporting should be considered a valuable complement to traditional ADR reporting by health care professionals.

P083. Communication Strategy with an Interactive Game to Promote Pharmacovigilance Education in Workers at University Hospital Fundación Santa Fe De Bogota

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Background: Pharmacovigilance's education is complex in the hospital environment mainly because the impossibility of bringing together colleagues in the same time and place. In this experience we decided to use an innovator strategy in order to facilitate a full comprehension of the rational use of medicines and pharmacovigilance.

Objectives: To develop a new communication strategy to facilitate pharmacovigilance knowledge in employees.

Methods: The Hospital assembled a multidisciplinary team with four pharmacists, a nurse and three doctors, supported by an advertising agency. Characters were designed alluding to the three professions mentioned, were determined the messages to communicate. It defined communication channels to reach the employees.
Results: The Hospital designed and implemented a communication campaign that included: 1. An interactive game located in the intranet available (What do you Know About pharmacovigilance?) In this game the participants answer different questions about pharmacovigilance and rational use of medicines. 30 questions were designed to appear randomly. The game starts with a drawing of a patient, with the right answers remains at 100% the patient's life, but failing responses in 50% decreases the patient's life, with two wrong answers in a row the patient dies. The game features sound similar to an electrocardiogram machine, which is accelerated according to incorrect responses and normalizes with correct answers. After the results (correct or incorrect) it will present a sentence with the teachings of positive feedback. 2. 12 posters with messages that were located in nursing stations. 3. Messages related to rational use of medicines through email. 4. Publications with similar messages and approach to patients in written bulletins for two months.
As a result of the campaign the reporting of medication related events in the first quarter of 2012 increased by 84% over the same quarter of previous year.
Conclusions: The implementation of striking and innovator strategies that allow access at anytime, anywhere, it helps to socialize the basic concepts of pharmacovigilance and indirectly favor the volume of reports of events related to medications.
To play the game please go to http://www.fsfb.org.co/juego/index.html, access code 16866

P084. Adverse Drug Reactions (ADRs) Characterization, University Hospital Fundación Santa Fe De Bogotá (HUFSFB), Colombia (2008 to 2011)

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Introduction: The ADRs occurrence profile in patients help to determining risk groups. This study evaluates the ADRs from 2008 to 2011 in the HUFSFB high complexity. Some similar studies have been conducted in Colombia but with traces in shorter time and lower case volumes.
Objectives: To characterize ADRs occurred in patients HUFSFB during January 2008 to December 2011.
Methods: According with reports received in the HUFSFB pharmacovigilance program during the study period, we analyzed the report, patients and the particular reaction variables, and also was determined causality, the type of reaction, and the drug associated and among others.
Results: *Characteristics of the report*: We received and analyzed a total of 461 ADRs; reporting channels used were the telephone (55%) followed by physical report (33%). In 48% of cases the reporting was anonymous, 21% were performed by nurses, 17% pharmacists and 12% doctors and 62% of ADRs were received in the ward.
Characteristics of patients: 53% of ADRs occurred in women, the most affected age groups were age between 45 to 64 years and 65 years and older with 27% of cases for each of these groups.
RAM features: 56% of ADRs had a slight impact outcome and 43% moderate, only reaction had a serious outcome (0.22%). 51% of the reactions were classify as a possible consequence of the medication and 38% as probable. 64% of ADRs were type A and 32% type B. The most common clinical manifestation was phlebitis (31%), followed by rash (9%). According to ATC medication group was more reactions with J (63%), followed by L (11%). The highest incidence of medication reactions was clarithromycin (28%).
Discussion and Conclusions: According to the Report characteristics, the telephone channel is the most commonly used probably by the easily access.
The results on the characteristics of patients show concordance with similar studies in feminine gender, been the most at risk to suffer reactions, and the age groups most affected are elderly patients.
Also consistent is the fact that the drug groups with higher incidence of ADRs are antibiotics and oncologic agents, however striking the high incidence of chemical phlebitis type reactions associated with the use of Clarithromycin IV, so that the HUFSFB strategies were designed to reduce these cases.

P085. Accuracy of a Post-Market Registry in Providing Post-Market Surveillance for Implantable Medical Devices

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Introduction: Post-marketing safety surveillance for implantable medical devices poses challenges. Manufacturers rely on passive complaint systems to detect safety issues. Post-market surveillance for drug safety utilizes expected and observed proportional reporting ratios and or expected event rates in statistical surveillance for safety signals. Many devices enter use without clinical data. Passive systems generate rates of reported events but require a known benchmark of good performance for a similar device to have meaning or generate an expected rate of events. Implantable devices frequently have a lag period of months or years before an event related to device design or performance occurs and may have total complaints numbering in the hundreds over the product lifecycle, rendering statistical evaluation or aggregate assessment untimely or inaccurate. Some form of active post-market surveillance is useful in understanding safety performance of newly introduced implantable devices. The validity of a patient registry in providing a timely and effective method for active post-market surveillance is presented for synthetic mesh for hernia repair.
Method: The International Hernia Mesh Registry is an international patient registry longitudinally tracking patient reported outcomes after surgical repair with a synthetic mesh using a validated quality of life tool specific for hernia repair. IHMR collects quality of life data pre-operativey as a baseline and post-operatively at 1, 6, 12 and 24 months. Clinical outcomes are reported based on 30 day follow up and as needed visits. Validation is sought for reported adverse events via a customer quality system and self-reported poor quality of life outcomes result in referral for clinical evaluation and reporting. Information from these systems is presented for a mesh device for umbilical hernia repair for which an independent study was also conducted.
Results: Spontaneous complaints: 44 recurrences/163 442 PVP sold; a rate of .2/10 000 IHMR: 14 reported recurrences/164 cases with 12 month data (3 of 167 dropped out) 9 validated and two false positive, three not validated; recurrence rate of 5.5%. Investigator initiated study 148 patients; recurrence rate of 4%.
Conclusion: Well designed observational registry can provide an accurate tool for active post-market surveillance.

P086. Therapeutic Failure of Human Menopausal Gonadotrophin in Treatment of Female Infertility: A Signal Arising from Spontaneously Reported Case Series

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Therapeutic failure as a type of adverse drug reaction (Type F ADR) has been introduced in 2000 by Hartigan-Go and Wong[1] due to the fact that reporting of drug inefficacy can produce important signals in identifying substandard and counterfeit medicinal products. Croatian Agency for Medicinal Products and Medical Devices has received a series of 9 cases of therapeutic failure related to the purified menotrophin (human menopausal gonadotrophin, HMG – Menopur®) administration. Cases were received from a gynecologist within a timeframe of 3 months during 2011. According to the reporting physician, common denominator for all cases were inadequate number and morphology of follicles and a higher rate of drug inefficacy than usually observed in spite of higher doses of Menopur® administered.

Additional data was collected through follow-up with physicians. After the follow-up, excluded factors potentially accounting for therapeutic failure were: *i) medical* (inappropriate medication for the disease, underdosing, poor patient compliance), *ii) pharmacological* (inappropriate route of administration, drug interactions, antimicrobial resistance, tolerance) and *iii) medication error* (errors in planning, errors in the execution of correctly planned actions).[1] In addition, a pharmaceutical quality check was performed for the suspected batches of Menopur® (batches CE0562 and CE0187B). SE-HPLC results for batch CE0562 revealed that the content of human luteinising hormone (LH) which equalled 45.2 IU/vial in 75 IU vials was outside of the specified limits (60,0–93,8 IU/vial), as well as LH confidence interval (2,5%–217,7%) outside the limits (p = 0,95; CI: 64%–156%). Test results for the batch CE187B were within the specification.

Regulatory action undertaken by HALMED was to withdraw the defect series from the market and to perform additional non-routine potency tests with every new series of Menopur® which is to be placed on the market.

The usual context of therapeutic failure is related to deterioration or prolongation of patient's pathological state which warrants prolonged hospitalisation and increased costs. Furthermore, in persons undergoing treatment for infertility, psychosocial consequences for the patient have to be considered. Timely recognising of Type F ADRs by the healthcare professionals and immediate reporting to the regulatory authority is necessary to trigger regulatory action which results in patient protection and ultimately reduced healthcare costs. Continuing education on the importance of reporting Type F ADRs and raising awareness among all the stakeholders within the health system is necessary to achieve this objective.

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P087. Prevalence Study of Adverse Events Associated with the Use of Medicinal Plants at the National Institute of Oncology Rabat

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Objective: To assess the prevalence of adverse effects (AEs) associated with the use of herbal medicines (HM) in an oncology ward.

Material and Method: We conducted a survey of 1234 patients during four months at the National Institute of Oncology (INO) in Rabat and more precisely within the inpatient and day hospital of INO. This survey is based on the use of a 10-item questionnaire in order to gather the necessary information about the patient and the HM used by the latter.

Results and Discussion: Among the 1234 patients enrolled in this survey, 35% used medicinal plants. 98.5% of them did not inform their physicians about the consumption of HM concomitantly with chemotherapy. Demographic data show that the sex ratio of this group is 0.6 in favor of women. 16% of these patients experienced at least one adverse drug event, from which 68% have been reported in women. The tubule-interstitial nephritis, was the most common serious ADR (15.7%) reported followed by liver damage (12.9%), diarrhea (5.7%), vomiting, constipation, and rectal bleeding with a frequency of 4.3% each.The most frequently HM used were, *Nigella sativa L.* and *Aristolochia longa L.*

Conclusion: Herbal medicine is one of the most commonly used complementary and alternative therapies used by patient with cancer in Morocco. The frequent concurrent use emphasizes the need for clinicians to include questions on complementary and alternative medicine in routine history taking and for further studies on possible herb–drug interactions among the cancer patient.

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P088. Effects of Clopidogrel with Proton Pump Inhibitors on Cardiovascular Events in Patients with Type 2 Diabetes Mellitus after Bare-Metal Stent

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Introduction: Recent studies have suggested that proton pump inhibitors (PPIs) might reduce the inhibitory effect of clopidogrel on platelet aggregation.[1] Diabetes remains a major risk factor for restenosis after both bare-metal stents (BMSs) and DESs.[2,3] It is still unknown whether diabetic patients were at risk after BMS from treatment with PPIs.

Aim: The objective was to evaluate the clinical outcomes of PPIs in type 2 diabetic patients within 1 year of receiving BMSs.

Methods: This retrospective cohort study was performed in 6107 Taiwanese type 2 diabetic patients (3779 men; 2328 women) who received BMSs between March 1, 2001 and December 31, 2005. Patients were classified into Clopidogre with PPI (n = 352) or without TZD groups (n = 5755) using medication records within 3 months of the index hospitalization. Follow-up data were available through December 31, 2008. Clinical outcome measurements included CABG, and repeat revascularization within 1 year after the index date of hospitalization. Cox proportional hazards model and other analyses were performed for the study.

Results: For the Clopidogrel with PPI and without TZD groups, the mean ages were 67.5 + 10.0 and 65.4 + 10.2 years, respectively. With or

without PPIs medication, there were no significant differences in the adjusted hazard ratios of CABG (HR = 0.76; 95% CI = 0.34–1.69), or repeat revascularization for diabetic patients who received BMSs (HR = 1.07; 95% CI = 0.86–1.33).

Conclusions: Clopidogrel with PPI did not increase the risk in Taiwanese type 2 diabetes patients who received BMSs.

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P089. Global Patient Safety Surveillance on Free-text Information from ICSRs: To be or Not to Be?

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Background: Well documented Individual Case Safety Reports (ICSRs) including case narratives are fundamental for thorough clinical assessments.[1-3] According to the new European pharmacovigilance legislation, the European Medicines Agency (EMA) ''shall make available to WHO Collaborating Centre all suspected adverse reaction reports occurring in the EU''. However, referring to EU personal data protection legislation, certain data fields, including case narratives, will not be made available to other parties of the global pharmacovigilance community.[4,5] Consequently, the concerns about confidentiality measures versus informative case data[6] may become a fact for global patient safety surveillance.

Objective: To evaluate the extent of narratives available in VigiBase, the WHO global ICSR database, and exemplify valuable information from narratives adding to the structured information.

Methods: In order to estimate the frequency of narratives in VigiBase, reports with a substantially long text-string in the E2B(R2) field 'narrativeincludeclinical' (narrative) were extracted.

The additional contributions of free-text information to standard E2B data fields were assessed in 50 case reports, selected by translatable language and by reporter type. The E2B free-text fields 'primarysource reaction' (reaction), 'drugadditional' (drug), and 'resultstestsprocedures' (tests) were also evaluated for information not otherwise presented in structured form.

Results: 11% (n = 708 315) of the 6.2 million ICSRs collected in VigiBase at the time of study met the inclusion criteria for substantial narratives, out of which 60% originated from Europe. 89 of the 104 active member countries had at least one report with a substantial narrative; 18 of the 28 countries reporting in INTDIS format and 71 of the 75 reporting in E2B.

Within the evaluated selection of 50 ICSRs, VigiBase entry dates ranged from year 2004 to 2011. Variables occurring in free-text but not in the assigned structured fields included relevant medical history, drug indication, concomitant drugs, dose, onset date of ADR, lab-findings, causality assessment on the national centre level and re-/dechallenge.

Information not reportable in structured E2B fields occurring in free-text included ADR severity, location, intervention, genetic disposition, number of administered doses and pathogen underlying infections.

Conclusion: More than every tenth ICSR in VigiBase have substantial narratives, of which the majority originated from European countries. This study shows that VigiBase currently contains valuable information for effective patient safety surveillance, despite the limited selection of reports reviewed. VigiBase is the global ICSR database; the continued availability of free-text information in ICSRs would ensure the maximum efficacy for its intended purpose.

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P090. Appetite-Suppressant Drugs Surveillance: Importance and Proposal of Prospective Vigilance

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In recent years obesity has become a significant and progressive public health problem in industrialized and some developing countries.[1,2] Despite the proved efficacy of exercise and diet, most affected individuals need additional treatment (behavioral, pharmacological, or even surgery). The adverse effects of anorexic drugs limit their utility and, in several cases, have resulted in withdrawal from the market. In addition, their efficacy in terms of long-term control of overweight is limited since the effect requires continuous administration, which is usually unacceptable. This is further complicated by the frequent use without medical control or in pharmaceutical preparations of uncontrolled or even illicit origin. These drugs induce weight loss through increased satiety and reduced hunger at the CNS level, accompanied by variable degrees of sympathetic stimulation.[3,4] Whilst there is an urgent need to develop additional drugs,[5,6] an increased use of currently available drugs can be anticipated for the coming years, thus requiring further efforts to assess risks in relation to new alternatives. Many drugs entered to the market in recent years have been withdrawn due to side effects probably shared by older agents, such as amphetamines and related drugs (though molecular substitutions in some derivatives, such as phentermine reduce the risks). To prospectively assess safety of currently used anorexic agents in Argentina, one pharmacovigilance center began by reviewing side effects notified to the National System of Pharmacovigilance as well as reports registered in Vigibase, to have basal values before beginning an active surveillance of anorexic side effects. In Argentina, since 2004, only 34 reports are registered, mainly involving centrally acting drugs (phenylpropanolamine: 1; mazindol: 12; sibutramine: 20; one additional case corresponds to orlistat); none of these reports was serious. The analysis of the Uppsala database by the more

frequent System Organ Class reports retrieved 1849 cases for phenylpropanolamine (since 1979); 9386 for sibutramine (since 2000), 366 for mazindol (since 1974) and 18 004 for phentermine; most reports were not serious though several fatal cases were present. Even the most frequently reported drug (phentermine) is still marketed in several anti-obesity products in developed countries, including the US. Since these drugs are sometimes used for long times and improperly controlled, a proactive approach, with strong involvement of producers, as well as a reassessment of risks and benefits of both, new and currently marketed drugs, seems needed to cope with the overweight epidemics and associated diseases.

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P091. The Impact of Uncertain Causality on Benefit-Risk Assessment: Insights from a Hierarchical Complexity Model

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In benefit-risk assessment, it is crucial to consider the likelihood of a causal link between a drug and any negative, unintended, effect for which it is implicated. This is particularly true in the post-marketing setting, where signals of causality are uncertain by nature. With a prospect of increasing transparency and consistency, quantitative methods to support benefit-risk assessment are currently attracting a lot of interest. However, thus far the aspect of causality has not been explicitly incorporated into such methods.

Benefit-risk assessments are often required to inform a subsequent decision. It could be e.g. a policy decision regarding initial or sustained licensing of a drug, or an individual treatment decision. The close link between benefit-risk assessment and decision-making is further emphasised by the use of decision analysis in some form in many of the proposed methods for quantitative benefit-risk assessment. I propose to make use of this link to define a hierarchical complexity model for benefit-risk assessment based on the decision-theoretic concepts 'decision under certainty', 'decision under risk', and 'decision under uncertainty'. The purpose of this model is to put into perspective the complexity of benefit-risk assessments facing uncertain causality.

At the bottom of the hierarchy are hypothetical situations where the outcome following a given drug is equal for all and known with certainty. However, such assessments need not be straightforward, as one cannot avoid fundamental clinical judgments when comparing the outcomes of different treatment alternatives. The second level contains – still hypothetical – situations where a drug is allowed several different possible outcomes, each with a supposedly known probability. At the third level these probabilities are allowed to be uncertain. This corresponds reasonably well to situations where all considered effects are well studied so that all causal links are established. On the contrary, the fourth and final level permits also causal links to be uncertain.

Because uncertainty regarding causality is sometimes inevitable, quantitative approaches to benefit-risk assessment should be able to accommodate it, the complexity notwithstanding. Conceptually, a probabilistic decision-analytical approach to benefit-risk assessment offers a framework in which this is possible. A reasonable modelling strategy is to explicitly separate the uncertainty with respect to the probability of a causal link between a drug and an adverse effect from the uncertainty with respect to the size of the association between the two. In this setting one can transparently study the potential impact of uncertain causality on benefit-risk assessment.

P092. Key Leading Factors for Great Performance in Pharmacovigilance

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Background: The statement 'no chain is stronger than its weakest link' is clearly valid and the implementation of quality management practices in pharmacovigilance needs to be put high on the agenda. Therefore, the Performance Maximizer® as a model, which illustrates the nature of successful human performance by describing all of the factors, has been adapted to Pharmacovigilance System considering its known basic principles. The model indicates the four conditions that Pharmacovigilance staff should *know what to do*, *be able to do it*, *be equipped to do it*, *want to do it* and experience interactions that support great performance in their job duties.

Objective: The presented model aims to elucidate possible effects of these four conditions on the quality of pharmacovigilance with revealing already existing identified skills, missing parts that need to be recovered and potential development points.

Method: Under this respect, overall requirements were determined in accordance with Pharmacovigilance system and the factors that improve pharmacovigilance process and enhance the quality of pharmacovigilance have been specified for each condition. After implementation of the model and related factors, the results are observed via surveys.

Results: ''Be able to do it'' facilitate to understand who is the qualified personnel to carry out pharmacovigilance work with questioning the person-specific characteristic feature. For the proper conduct of pharmacovigilance, importance of equipments and resources in parallel with technological development and awareness of current regulations, guidelines are indicated by ''Equipped to do it''. As described in ''Want to do it'' pharmacovigilance staff should have the ultimate beneficiaries of our work in mind – the patients are the ones who are harmed if we do not do our job properly. Finally ''Know what to do it'' emphasizes that gaining knowledge about objectives, goals, values and strategy help a staff become more effective and productive. Sharing best practices, which should enable information exchange and possibilities to learn from each other's experiences, is the one of the major factor that supports the achievement and provides enthusiasm.

Conclusion: Excellence and great performance in pharmacovigilance is based on the four conditions which are statistically significant predictors of the model. The model is implemented that all people could

examine themselves in accordance with pharmacovigilance and assess the pharmacovigilance systems in order to contribute great performance and enhance the quality. Herewith understanding and tackling these are an essential prerequisite for future development of the quality and practice of pharmacovigilance.

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P093. Risk Minimization Tools in Turkey Compared by EMA RMP and FDA REMS

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Background: Risk is a choice rather than a fate. Minimising and/or mitigating risks to public health are absolutely necessary for ''real world'' use of medicinal products, and the development of more effective risk minimisation tools is a priority. In the current regulatory environment, risk management and minimisation tool preference may differ from one health authority to another, which creates a challenge for pharmaceutical companies since their tool selection approach is often based on a ''global'' concept with regional adaptation thereof.

Objective: Aim is to review the risk minimisation tools applied for drugs in Turkey, compare with EMA and FDA activities to have a closer look across the countries and discuss the practical aspects of the national implementation.

Method: The risk management tools that are applied in Turkey for various International Nonproprietary Names (INNs) were analysed in order to identify the characteristics of product (active substance, Anatomic Therapeutic Chemical (ATC) classification, safety concerns) and compared with the additional Risk Minimisation Activities (RMAs) based on the European Public Assessment Reports (EPARs) of EMA and with the Risk Evaluation and Mitigation Strategies (REMS) of FDA to highlight the implementation and effectiveness of these tools.

Results: Although the new legislation on risk management in Turkey came into force in May 2011, a variety of INNs required RMAs. RMAs are applied for either the new chemical entities (NCE) approved or with experience in the market. We identified that that most frequent RMA is the provision of educational material; antineoplastic and immunomodulating agents most often had RMA which is similar to EMA. It is pointed out that out of these 90 INNs with RMAs only 10 of them (bosentan, dronedarone, eltrombopag, fingolimod, lenalidomide, natalizumab, nilotinib, rivaroxaban, thalidomide, ustekinumab) have both additional RMAs in EPARs and REMS. There are only approved REMS for 6 INNs with RMAs (bupropion, erythropoiesis-stimulating agents [ESAs], icodextrin, isotretinoin, rosiglizatone, varenicline). On the other hand for 5 INNs with RMAs (canakinumab, daptomycin, deferasirox, ranibizumab, tigecycline), it is observed that there are only additional RMAs in EPARs but not approved REMS.

Conclusion: The risk minimisation tools (RMTs) are at risk of being another ''cosmetic'' intervention and measuring RMA effectiveness is essential. All RMTs applied in Turkey is presented by a comprehensive assessment and discussed by comparison with activities of other international health authorities. The risk minimisation activities seem to be either similar or unique/innovative; transparency and collaboration with marketing authorisation holders are identified.

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P094. Adverse Events Related to Vancomycin Use in a University Hospital in Brazil

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Introduction: Vancomycin is indicated to patients who have not responded to treatment with other antibiotics in serious infections caused by organisms susceptible to it and resistant to other antimicrobials, such as methicillin-resistant Staphylococcus aureus.[1] However, over the last five years, many adverse events have been reported with this medicine in the University Hospital of the University of São Paulo (HU/USP), such as nephrotoxicity and toxicity related to infusion.[2] Some critical patients, for example surgical patients with sepsis and severe trauma are generally susceptible to renal failure due to the severity of the underlying disease.[3]

Aim: To analyze adverse events caused by vancomycin.

Methods: We conducted a retrospective observational quantitative and qualify study of medical records of patients who had confirmed adverse events occurred with vancomycin in the period from January 2007 to May 2012, at the HU/USP - Brazil. All notifications related to vancomycin were evaluated in the following items: age and sex of patients, type of adverse event and ward where occurred.

Results: In this period of time it was confirmed 37 adverse events with vancomycin. Of these cases reported, 75.7% (n = 28) accounted for adults (14 female and 14 male patients). The mean age was 56.4 years. Among these adults, 57.1% were hospitalized at the medical clinic, 21.4% at the surgical clinic and 17.9% at ICU.

The other remaining 24.3% (n = 9) of reports occurred in pediatric patients and the age ranged from 7 days to 15 years old. These events occurred more frequently in pediatric ICU (n = 8) followed by the emergency pediatric department (n = 1). The skin events (70.3%) were the most prevalent, comprising signs such as itching, rash, swelling, and Steven-Johnson's syndrome. Secondly, it was notified renal events (13.5%), for instance acute renal failure, interstitial nephritis and parenchymal injury. Thirdly, there were events involved the therapeutic ineffectiveness (10.8%), and hematological and intestinal, with the same frequency (2.7%).

Conclusions: In this study, the events were the most frequent skin followed by renal, hematological and intestinal and they occurred more frequently in adult patients admitted to the medical clinic.

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P095. Adverse Drug Reaction not yet Described in the Scientific Literature (Case Report): Facial Hyperpigmentation Due to Use of Polymyxin B

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Introduction: Polymyxin B has been used for treatment of surgical infectious complications, especially osteomyelitis caused by *Acinetobacter baumannii*.[1] Osteomyelitis is a condition which refers to an infection of the bone and it may be caused by different factors; these include underlying health conditions, injury to the bone or an infection that spread from the blood and causes damage to the bone.[2,3]

Aim: To report an adverse reaction not described in the scientific literature with the medicine polymyxin B injection.

Description: It was an observational study of the patient KMK, female, 70 years old, who has insulin dependent diabetes mellitus and labyrinthitis. She was admitted to the University Hospital of the University of São Paulo (HU/USP) for repair the distal left femur fracture and underwent reoperations due to various infectious complications in the surgical site. Thus, it was prescribed polymyxin B at a dosage of 350 000 IU, intravenous 12/12 h (started on the 17th February 2012) for *Acinetobacter baumannii* revealed in bone fragment (11th February 2012).

Results: After 7 days of treatment (24th February 2012) with polymyxin B, the patient presented with dermatitis, especially in the face. Further, in the patient's medical report it was described as hyperpigmentation from 28th February 2012. To treat this condition, it was prescribed betamethasone cream twice a day and the replaced by hydrocortisone cream twice a day. The diagnostic hypothesis of hyperpigmentation is related to the use of polymyxin B. There was no interruption during the hospitalization period. On March 30th 2012, she was discharged from the hospital with prescription of polymyxin B and teicoplanin. The patient remains with hyperpigmentation on her face, with injury, and she has been assisted at our ambulatory. Antibiotic therapy is planned to last more six months.

Conclusions: We can infer that it was the first time that such adverse drug reaction was described. It is very important to alert the scientific community to the possibility of hyperpigmentation caused the use of polymyxin B. Further studies are needed to elucidate the mechanism that triggers this process of hyperpigmentation as well as the adoption of measures for the detection, control and treatment.

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P096. Profile of Adverse Events at a Brazilian University Hospital

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Introduction: The University Hospital of São Paulo of the University of São Paulo (HU/USP) is part of the Sentinel Network, a program managed by the National Agency of Sanitary Surveillance in Brazil (ANVISA). Institutions shall notify the ANVISA and in case of alert returns with a signal for the whole country.[1]

Aim: To analyze the adverse drug events (ADEs) on between the adult and pediatric groups, from January 2012 to May 2012, reported to the Pharmacy Service of the HU/USP.

Methods: We included only those ADEs detected by a multidisciplinary team of HU/USP and notified by Pharmacovigilance to ANVISA, during the period of study. We compiled the following data: age, sex, ward, classification of the medicine according to the *Anatomical Therapeutical Chemical* (ATC) in the first level and the adverse drug reaction was classified according to the *Adverse Reaction Terminology* from the World Health Organization (WHO-ART).

Results: During this period were reported 47 ADEs, 59.6% male and 40.4 female. Most reported ADEs occurred in adults (70.2%, n = 33) with a mean age of 43 years old. In this group 33.3% (n = 11) of events occurred at surgical ward, followed by 21.2% at medical ward, 15.2% at ICU and 9.1% at surgical center. According to the ATC, it was observed that the ADEs were directly linked to the medicines classified as General antiinfective for systemic use (51.5%) and nervous system drugs (42.4%). Using the WHO-ART, the most frequent adverse event was skin (48.5%) followed by general disorders (24.2%).

Pediatric patients accounted for 29.8% (n = 14) of ADEs and age ranging from 7 days to 15 years old. Most of ADEs was detected in the pediatric ICU (42.9%), followed by the Emergency Service (21.4%), pediatric ward and neonatology ICU both with 14.3% and pediatric ward with 7.1%. According to ATC, 85.7% of ADEs were related to General anti-infective for systemic. The ADEs with skin represents 42.9% of pediatric patients.

Conclusions: The present study shows that adults hospitalized at surgical, medical and ICU had a higher frequency in the occurrence of event adverse. For pediatric patients the frequency was higher in pediatric ICU or at the emergency room. Both groups showed that the anti-infective drugs are the main causes of adverse event and skin reactions were more significant.

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P097. Pharmacogenetics in Pharmacovigilance for Biologic Therapeutic Medicine

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Summary: An increasing number of new recombinant biotechnology derived agents have recently been introduced as treatment options for many disease conditions and revolutionized therapy in oncology, rheumatology, and dermatology during the past twenty years. However, considerable variability occurs in patients in response to these

therapies. Pharmacogenetic, the study of how individual genetic variation affects the response to medicines is promising to be extremely useful in predicting efficacy, toxicity and safety in drug discovery, drug development and post-market surveillance program. Pharmacogenetics has not only been applied to old vanguard Disease Modifying Antirheumatoid Drugs (DMARD), like methotrexate, but has also been applied to the newer, more expensive biologic agents. Application of pharmacogentics might make personalized approach in biologic therapy a reality with much promise for patient safety.

Objective: To review the application of pharmacogentics in identifying suitable sub-population for the treatment to insure efficacy and safety in the current state of art biologic therapy.

Description: Genetic factors contribute to the phenotype of drug response. Advancement in the sequencing and mapping of the human genome,[1] coupled with single nucleotide polymorphism (SNP)-based high-throughput genotyping methods[2] have been pivotal to making a wide range of pharmacogenetic efficacy and safety studies possible. A recent breakthrough in applying pharmacogenetic to biotechnological therapy showed that genotype 1 hepatitis C patients carrying certain genetic variant alleles near the IL28B gene are more likely than others,[3] to achieve sustained virological response after the treatment with Pegylated interferon-alpha-2a or pegylated interferon-alpha-2b combined with ribavirin. Oncologic drugs such as Trastuzumab[4] and Rituximab[5] have also shown similar promise for prospective application of pharmacogentics in modern biologic therapy.

Results: Pharmacogenetic analysis can be used to differentiate phenotypic heterogeneity, to segment populations that seem to be responsive or unresponsive to a medicine, or to accurately define individuals who might be at higher personal risk of an adverse event.

Conclusion: Pharmacogenetics is increasingly seen as holding potential for tailoring prescription to defined sub-populations and individuals, based on genetic make-up. In order to obtain clinically and practically robust pharmacogenetic testing, Health Canada has established guidelines for submission of pharmacogenomics Information[6] to facilitate the identification and testing of potentiate candidate drugs for which predictive genotyping could be undertaken before drug therapy is initiated.

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P098. Sudden Stroke After Sclerotherapy of Varicose Veins by Lauromacrogol: A Case Report

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Sclerotherapy is a minimally invasive treatment used to treat varicose veins. The procedure consists in an injection of a sclerotic agent directly into the varicose vein. In France, lauromacrogol 400 (Aetoxisclerol®) is the reference medication thanks to its local anaesthetic properties. Lauromacrogol, as a sclerotic agent, induces the development of a thrombus into the superficial varicose vein and an endothelium fibrosis which is dose-dependent. The risk of local and systemic complications is low.

Here, we report the case of a patient who suddenly developed neurological symptoms just after sclerotherapy.

A 70-year-old man with history of hypertension, chronic lymphoid leukaemia (that has remained stable for 2 years) and superficial vein thrombosis (left great saphenous vein) received an injection of lauromacrogol 3% into the right great saphenous vein. A few minutes after the injection, he developed a left-sided brachio-facial hemiparesia associated with a hypertensive crisis (180 mmHg pression maxima). After 15 minutes, symptoms resolved but a discomfort persisted.

During the night, the patient reported a left lower-limb paralysis, frontal headache, nausea, photophonophobia and was admitted the day after in the Neurologic Department of the Hospital for suspicion of stroke. A neurological examination revealed dysphonia, discret facial paralysis and mild left upper-limb weakness. The etiological investigation was in favour of a cerebrovascular accident and the brain MRI revealed acute occipital ischemic lesions. The evolution in the unit was positive, the patient was discharged after 10 days.

We have no information about the way lauromacrogol was injected (volume, liquid or foam…).

In the literature, some cases of patients who develop neurological symptoms after sclerotherapy such as scotomas, migraine attack or stroke have been reported.[1] Moreover, a study[2] pointed out that foam-induced microembolism is a common phenomenon during foam sclerotherapy. This microembolism can be detectable in the left atrium and ventricule in patients with right-to-left shunt. Concerning our patient, a transoesophageal echocardiogram has been planned to research a Patent Foramen Ovale (PFO).

In France, sclerotic agents are under surveillance. A national study pointed out the risk of systemic adverse effects and the French drug agency (ANSM) added some recommendations for patients with neurological history and patients with a known PFO.

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P099. Individual Case Safety Reports and VigiBase: The Vital Importance of Quality

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The WHO Global Individual Case Safety Report (ICSR) database, VigiBase™, is the source of worldwide post-marketing case safety reports. Currently more than 100 countries contribute to VigiBase submitting ICSRs collected at their national pharmacovigilance centres (NCs). VigiBase data is accessible to all NCs participating in the WHO Medicines Safety Programme and is a vital source of information for countries with limited data resources. VigiBase is maintained by the

Uppsala Monitoring Centre (UMC) and periodic analysis of VigiBase is performed, in accordance with UMC's current routine signal detection process, to find previously unrecognized patient safety concerns.

ICSRs constitute a key resource for the early identification of patient safety issues in relation to medicines, thus the quality of ICSR databases is crucial. The consequence of poor quality data is the risk of drawing wrong or delayed conclusions about a patient safety concern, which could lead to patients being harmed unnecessarily.

A fundamental requirement for the quality of an ICSR database is that the data is up to date. To ascertain high quality data in VigiBase, WHO programme members are expected to transmit all post-marketing ICSRs, complete and irrespective of origin, regularly and preferably more frequently than once a month. As underreporting is a major problem in post-marketing reporting systems,[1,2] each report is valuable and the quality of it essential. With the exception of confidential patient and reporter details, preferably no information should be left out when transmitting an ICSR, if available on the original report.

Certain information is needed for a valid ICSR and inclusion in VigiBase, e.g. case identification number, report dates, a patient, one reaction/event and one suspect drug. Further information is crucial for making a valid medical assessment. For instance, missing information on the time interval between drug start and reaction onset prevents confirmation of any time relationship between drug and reaction/event hindering causality assessment, especially if also missing information on dechallenge/rechallenge. Lack of details on patient age, sex, medical history or drug indication may result in incorrect conclusions about a patient; confounding factors should always be considered. Importantly, the case narrative includes information not captured elsewhere on the report and may be crucial for assessment of the case.

High quality data and completeness of information are critical factors for VigiBase serving as the source of worldwide ICSRs and UMC's core mission of assessing new patient safety issues on behalf of the WHO.

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P100. Adverse Drug Reactions as a Cause of Admission: Results from a Multidisciplinary Proactive Pharmacovigilance Program in an Internal Medicine Ward

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Background: Adverse drug reactions (ADR) are a major cause of morbidity and mortality worldwide. Several studies suggest that between 1.69 and 10% of hospitals admissions are due to ADR.

Objective: To determine the prevalence of adverse drug reactions as a reason for admission to an Internal Medicine ward in a University Hospital in Buenos Aires, Argentina.

Method: We assessed every patient admitted between August 2010 and February 2012 to determine if an ADR has been the cause of admission. Within 24 hours of admission the patient was interviewed and examined by a staff physician who was part of the pharmacovigilance team and a pharmacist. If after reviewing patient history and complementary studies an ADR was suspected causality was analyzed according to WHO criteria.

Results: Over 18 months there were 1045 admissions. Mean age was 67.9 years old (66.7–69.1), female sex 55.6%. Mean ADL score was 4.8 ± 0.1. Mean Charlson score was 4.11 ± 0.08. Comorbities included hypertensión 47%, Dyslipidemia 30%. Cancer 18.4%, Renal Transplant 12.3%, Diabetes 15.1%, Congestive Heart Failure 11.6%. Coronary Artery Disease 11.2% Peptic Ulcer/Gastritis 10.9% Chronic Obstructive Pulmonary Diesease 10% Stroke 6.8% and depresión 6.3%. The mean number of medications per patient was 5.2 ± 0.1 and aproximately 11% of the patients were receiving alternative medicines. There were 111 (10.6%) of probable ADR as a reason for admisión. The most frequent manifestations of ADR were gastrointestinal bleeding (19.8%), acute renal failure (14.4%), diarrhea (9.9%), hyponatremia (6.3%), altered sensorium (5.4%), febrile neutropenia (4.5%), hypoglucemia (3.6%), seisures (2.7%), bleeding-epistaxis, hematuria, hemoptisis (2.7%). The drugs most frequently reported in probable adverse events were aspirin (16.2%), non-steroidal antinflammatory agens (15.3%), steroids (10.8%), antibiotics (9.9%), vitamin K antagonists (8.1%), hydrochlorotiazide (6.3%), mycophenolate (6.3%), opiods (4.5%), benzodiazepines (3.6%). The risk of being admitted because of ADR augmented among patients who have initiated a drug within the last month (OR 9.64; 95% CI 6.06-15.35) and took more than 5 medications (OR 1.98; 95% CI 1.26-3,09).

Conclusion: In our population ADR are responsible of 1 out of 10 admissions. Patients who initiated a drug within one month had a higher risk of being admitted because of an ADR.

P101. Identifying Gaps and Priorities in Pharmacological Prevention of Cardiovascular Disease: Insights from a Proactive Pharmacovigilance Registry

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Background: Cardiovascular disease is the leading cause of death in Argentina. Therefore, the implementation of strategies for primary (PP) and secondary prevention (SP) is essential. Aspirin has been questioned in PP mainly because of the risk of bleeding. On the other hand, in SP where the benefit has been clearly established underutilization has been reported.

Aim: To determine through the analysis of a proactive pharmacovigilance registry the pattern of use of antiplatelet agents and statins in cardiovascular prevention.

Methods: Patients who were admitted by the Department of Internal Medicine, University Hospital CEMIC Las Heras were evaluated.

Demographic data, comorbidities and medications were asked. Coronary artery disease (CAD) was defined as a history reported by the patient or documented in the medical history of unstable angina, myocardial infarction, chronic stable angina, coronary angioplasty or coronary artery bypass grafting. The presence of cerebrovascular disease (CVD) (stroke or transient ischemic attack) was defined by history or the questioning of the patient.

Results: We analyzed a total of 1045 patients (67.9 ± 0.6 years, male: 44.4%) of whom 183 patients had a history of CAD or CVD (17.5%) and 10 patients (1.0%) peripheral vascular disease alone. Of the 852 without such antecedents 130 took aspirin as PP. Fourteen of these patients had a higher aspirin dose to 100 mg/day. Patients who were receiving aspirin for PP were older (76 ± 1 vs 64. ± 1; $p < 0.0001$) and had a higher prevalence of arterial hypertension (64.6% vs 37.7%; $p < 0.0001$), diabetes mellitus (24.6% vs 8.9%; $p < 0.0001$) and dyslipidemia (40.8% vs 22.0%; $p < 0.0001$). Of these patients, 10 were admitted for bleeding associated with aspirin and 3 were taking 325 mg/day.

Of the 183 patients with a history of CAD or CVD only 113 (61.7%) received antiplatelet therapy. In this group, 6 of 113 patients had bleeding. The seventy (38.3%) patients not receiving antiplatelet therapy had no clinically significant differences with patients if they received. In SP, only 80 (43.7%) were taking a statin.

Conclusion: In our population the use of aspirin in PP was not without risk. In almost 1/3 of these patients who bled the dose was higher than recommended.We observed a significant underutilization of antiplatelet agents and statins in SP that reached 38% and 56%, respectively.

P102. Hospital Pharmacists' Attitudes Concerning Antibiotic Resistance: A Pilot Study

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Background: The World Health Organization has defined antimicrobial resistance as one of the main concerns of public health for the next years.[1] It is important that international community embrace efforts to reduce the tendency of the rise of resistance and to diminish prevalence of resistant pathogens.[2] The increasing rate of antimicrobial pathogens along with the lower number of new drugs entering the market, if there is no intervention, can be the source of the increasing rates of morbidity and mortality due to bacterial resistance.[3]

Aim: This study sought to evaluate a questionnaire' reproducibility and internal consistency about attitudes and knowledge of pharmacists working in hospital pharmacy concerning antibiotic use and bacterial resistance.

Methods: The study covered a group of pharmacists working in hospital environment, situated in the North Health Region Administration (ARS-Norte), comprising five geographical districts. Questionnaires were distributed to each health professional in two different moments, separated by two to four weeks. Attitudes were evaluated using a Visual Analogic Scale (VAS), with answers being scored between zero (totally agree) to 20 (totally disagree). It was calculated the Cronbach's Alpha (to study internal consistency) and the Correlation Intraclass Coefficient (ICC) for reproducibility evaluation.

Results: The pilot-study comprised a sample of 29 pharmacists. Questionnaire evaluated 17 attitudes and knowledge about antibiotic resistance and dispensing practice of pharmacists. Attitudes were grouped in four dimensions: perception of the problem, attribution of responsibilities, confidence and factors associated to dispensing habits. The evaluated attitudes demonstrated good ICC for each question and the value of the Cronbach's alpha (reliability) was 0.925.

Conclusion: Questionnaire revealed to be reproducible and consistent, allowing its use on the evaluation of attitudes and knowledge of hospital pharmacists. Designed questionnaire demonstrated to be valid, allowing to detect some differences between hospital pharmacists' attitudes related to dispensing practice and antibiotic resistances. This study is a preliminary phase of an intervention designed with the results obtained by questionnaires' analysis on attitudes, knowledge and practices s of hospital pharmacists, aiming to improve antibiotic use by these health professionals.

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P103. Adverse Drug Reactions as a Reason for Admission to an Internal Medicine Ward among the Oldest Old

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Background: The significant burden of adverse drug reactions among elderly patients has been reported.

Aim: Describe the burden of adverse drug reactions (ADR) among the oldest old (80 years-old or older) and indentify drugs that may increase the risk of being admitted to an Internal Medicine ward.

Method: We assessed every patient admitted to our Internal Medicine ward in a University Hospital in Buenos Aires, Argentina between August 2010 and February 2012 to determine if an ADR has been the cause of admission.Within 24 hours of admission the patient was interviewed and examined by a staff physician who was part of the pharmacovigilance team and a pharmacist. If after reviewing patient history and complementary studies an ADR was suspected causality was analyzed according to WHO criteria. In addition Proportional Reporting Ratio (PRR) was calculated to identify drugs that may predispose patients for being admitted to an Internal Medicine ward.

Results: Over 18 months 362 patients whot fulfilled the definition of oldest old were admitted to our Internal Medicine Ward. Mean age

was 86.4 years-old (80–101), female sex: 230 (63,5%). 91% lived in their homes. Almost half of the patients had Activities of Daily Living Score of 5 or 6. The main comorbities included dementia (32%), hypertension (61%), dyslipidemia (23%), cancer (15%) and diabetes (17%). The mean number of medications per patient was 6 (0–15).

There were 40 (11%) of probable ADR as a reason for admision. The drugs with high PRR for the risk of admission were: the combination of enalapril and hydrochlorotiazide, prometazine, vitamin E, anastrozole and modafinil.

Conclusion: The prevalence of ADR as a reason for admission to an Internal Medicine ward is high among the oldest old. The identification of high risk drugs in this population may help to design safer therapeutic strategies and prevent harm.

P104. Usability of Dose Information on Compiled ICSRs by the Example of Olanzapine and Weight Increase

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Background: Dose information compiled in large collections of ICSRs, such as the global WHO ICSR database VigiBase,[1] has the potential of providing new or complementary data on patient safety problems, e.g. reported daily doses (rDDs) for the suspected drug of an ADR. In order to use existing dose information from ICSRs, it is essential to have knowledge on how well reported data correlates to established references from the literature.

Objective: To explore rDD variations of compiled olanzapine ICSRs in VigiBase.

Method: All ICSRs with olanzapine recorded as the suspected or interacting drug reported up until February 2011 were retrieved from VigiBase. rDDs were calculated for aggregated olanzapine reports based on the information reported in the structured dose fields. Complementary dose information from the field 'reported drug name', was also used. ICSRs generating more than one rDD were accounted for more than once. The WHO Defined Daily Dose (DDD)[2] was used as a reference for our dose result.

Results: A total of 2581 ICSRs where olanzapine was the suspected drug were identified and included in this study. The most frequently reported ADR for olanzapine was the MedDRA preferred term (PT) 'Weight increased', which accounted for 14% (n = 355) of the ICSRs and generated 618 rDDs. The most frequently reported daily doses for olanzapine were 5, 10 and 20 mg, the median rDD being equal to the DDD at 10 mg. The median rDD for 'Weight increased'' had an elevated median rDD at 15 mg.

Conclusion: This study demonstrated that compiled ICSRs allow for exploration of dose variations in reported drugs. The elevated median rDD for olanzapine reported with weight increase exemplified a variation within the drug, which may generate a hypothesis of dose dependency of the ADR. Second-generation antipsychotic drugs have been provided evidence for clinically significant metabolic effects capable of inducing weight gain.[3] The relationship between the daily dose and the metabolic effects has nevertheless been questioned.[4] Our findings suggest that compiled dose data from ICSRs could contribute with complementary information regarding the dose relationship of olanzapine-induced weight increase.

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P105. Understanding the Antibiotic Prescribing Physician Behavior in Hospital Care: A Systematic Review of Qualitative Studies

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Background: Misprescription of antibiotics has been associated with high levels of antibiotic resistance,[1,2] raising worldwide concerns and demanding a thorough understanding of physicians' prescribing behavior.[3-5]

Aim: To explore and identify factors, attitudes and knowledge that influence antibiotic prescription in hospital care.

Methods: We systematically searched PubMed scientific database for qualitative studies published between January 1987 and December 2011, on attitudes, knowledge and perceptions of hospital care physicians towards antibiotic prescription, using search terms and their synonyms. Data extracted included methods used in each study and the factors that influence physician behavior on antibiotic prescribing process.

Results: Fourteen articles were selected for the review. Of these, some were focused on physicians (n = 7) or also in patients and/or other healthcare providers (n = 7). The targeted pathologies/clinical conditions of the patients were stated in ten studies and included: respiratory tract infections (n = 5), cesarean sections (n = 2), urinary tract infection (n = 1), surgical site infections (n = 1) and diarrhea and respiratory tract infection (n = 1). Concerning the type of patient, emergency patients and pregnant women were studied in two papers each. Adults, pediatric patients and institutionalized elderly patients were the object of one article each. The articles reviewed used different methods of data collection, namely, interviews (n = 8), questionnaires (n = 4) and focus group discussions (n = 2). The method of analysis was defined in nine studies and comprises mainly thematic analysis (n = 3) and grounded theory (n = 3) and in the others authors used two or more specific methodologies. Complacency, fear, ignorance or indifference, were the physicians' intrinsic factors most frequently associated with misprescription of antibiotics. Concerning external factors to the physician, we observed that some aspects of the patient (signs and symptoms), some specifications of the healthcare system (patient volume or implemented policies/ guidelines) and the influence of others healthcare providers were also described as being associated with misuse of antibiotics.

Discussion: Our finds reveals that: (i) antibiotic prescribing is influenced by all players involved in this process, namely physicians, other healthcare providers, healthcare system, patients and public in general; (ii) the results expresses a relationship between some identified factors that suggest the existence of synergic relationships between them.

Conclusion: A better understanding about the factors that influence antibiotic prescribing process, clarifying how they influence the decision

making, is fundamental to define strategies to effectively tackle the development of antibiotic resistance.

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P106. The Two Pharmacos: Vigilance and Genetics: A Powerful Partnership to Improve Drug Safety

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Adverse drug reactions (ADRs) cause significant morbidity and mortality. 95% of all ADRs are never reported. We built a national pharmacovigilance and pharmacogenomic network in Canada to carefully and completely characterize ADRs in children and find genomic solutions to the lack of predictability of severe reactions. Clinicians who conduct surveillance are employed by the Network and identify children who have suffered ADRs and matched controls from inpatient, outpatient and emergency departments at 13 major paediatric tertiary care hospitals in Canada. Drug biotransformation genes are analyzed to determine their role in the development of specific ADRs and to identify novel predictive genomic markers. Identified biomarkers are validated with functional and pharmacokinetic studies. As of March 2012, 4702 ADR cases and 46 890 matched controls have been enrolled. Relevant biomarkers for three serious ADRs have been identified: anthracycline-induced cardiotoxicity, cisplatin-induced hearing loss and maternal codeine use and infant death. This work has lead to two drug label changes by national and international regulators. Ongoing studies include vincristine-induced neurotoxicity, drug-induced Stevens Johnson syndrome and others. Active surveillance networks can be effective strategies for both complete ADR reporting and drug safety biomarker research. The network was designed to capture a broad range of ADR cases and target the surveillance of specific drugs or ADRs of principal concern. The identification of genetic markers is essential for developing diagnostic tests to predict children who are at higher risk of developing ADRs. Ultimately, this will lead to the modification of treatment for susceptible individuals, and therefore, a reduction in the incidence of severe ADRs.

P107. Choice of Denominator in Case-Population Studies: Event Rates for Registration for Liver Transplantation after NSAID Exposure, SALT Study, France

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Background: One of the concerns in case-population studies is the definition of the relevant exposure.

Objective: To evaluate and compare the effect of denominator options on population event rates in France using different source of denominators on the French part of the SALT (Study of Acute Liver Transplant) study.

Methods: SALT is a case-population study of acute liver failure (ALF) registered for transplantation, exposed to non-steroidal anti-inflammatory drugs (NSAIDs) or non-overdose paracetamol within 30 days before initial symptoms, from 2005–2007. Population exposure was computed from Intercontinental Medical Services (IMS) data and from the French national healthcare insurance system data, as number of defined daily doses (DDD) sold or dispensed, and number of exposed patients.

Results: Ten cases exposed to NSAIDs and 49 cases exposed to non-overdose paracetamol were identified in France. Three-year NSAID sales ranged from 0.04 (niflumic acid) to 0.5 (ibuprofen) billion DDDs, and reached 2.5 billion DDDs for all NSAIDs. Three-year mean per-person exposure ranged from 13.1 (niflumic acid) to 43.2 DDDs (ketoprofen), 60.5 DDDs for any NSAIDs. Numbers of users ranged from 2 (niflumic acid) to 13 million users (ibuprofen), 26.6 for all NSAIDs pooled. ALF rates per billion DDDs ranged from 0 to 26 for individual NSAIDs, 4.6 all NSAIDs pooled. They were inversely correlated with average per-patient exposure (log-log regression, $R^2 = 0.935$, $p = 0.0016$). ALF rates per million users ranged from 0.31 to 0.49, 0.41 all NSAIDs pooled, with no effect of mean per-patient exposure ($R^2 = 0.01$, $p = 0.9$). Whether measured per DDD or per user, the event rate with paracetamol was 3 to 5 times higher than with NSAIDs.

Conclusion: The risk of ALF with NSAID seems to be user-dependent rather than exposure-dependent. Choosing the wrong denominator might give erroneous results.

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P108. Benfluorex and Pregnancy: A Case-Control Study in EFEMERIS Database

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Benfluorex (Mediator®) is an anorectic agent marketed in France since 1976 as an adjuvant drug for diabetic patients with overweight. Following benfluorex withdrawal, fully presented and discussed in media, several women who had taken benfluorex before or during pregnancy have questioned the Midi-Pyrenees Centre of Pharmacovigilance to know if benfluorex intake could be associated to malformations (mainly cardiovascular) for the newborn. No clinical data have been published yet on benfluorex and pregnancy.

Objective: Determine the relationship between benfluorex exposure in utero and malformation.

Method: We performed a case-control study in EFEMERIS, a French prescription database including pregnant women. EFEMERIS is a database including prescribed and delivered drugs during pregnancy (data from Caisse Primaire d'Assurance Maladie of Haute-Garonne) and outcomes (data from Maternal and Infant Protection Service and from Antenatal diagnostic Centre). At the time of the present study, 40 355 women who were delivered from July 1st 2004 to June 30th 2008 inHaute-Garonne and registered into the French Health Insurance Service were included into EFEMERIS database. Benfluorex prescriptions during organogenesis were compared between children with congenital anomalies (cases) and children without congenital anomalies (controls).

Results: During the study period, 59 women registered in EFEMERIS had at least one prescription of benfluorex during pregnancy including 52 during the two first months. Seven women only had an associated prescription for a hypoglycemic medication. From the group with congenital anomalies (943 cases), two babies (0.2%) have been exposed to benfluorex during the two first months of pregnancy versus 50 (0.1%) among the 39 412 controls (OR = 1.6 [0.4–6.7], p = 0.5 after adjustment on mother age). Malformations in benfluorex exposed babies concerned one urinary tract malformation and one heart defect (ventricular septal defect).

Conclusion: Benfluorex was a fenfluramine derivative and several animal studies have reported an increased risk of malformations after in utero exposure to amphetamines. Data on human (case reports and retrospective study) have suggested a potential association between cardiovascular malformations and in utero exposure to amphetamine during organogenesis.

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P109. Preventability of "Serious" Adverse Drug Reactions Induced by Oral Protein Kinase Inhibitors (PKIs)

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Introduction: Results from the EMIR study, performed in 2007 in France, showed that incidence of adverse drug reactions (ADRs) who required hospital admission was the highest with vitamin K antagonists (VKA) and then antineoplastic drugs. Currently, several antineoplastic drugs, orally administered, as Protein Kinase Inhibitors (PKI) could be taken at home (ambulatory care). Using data of spontaneous reporting in France, we described in a previous study "serious" ADRs, specifically cutaneous, with oral PKI. In general, for all drugs, 50% of ADR were "preventable". In this study, we aimed to assess preventability of "serious" ADRs related to oral PKI.

Methods: We used the French Pharmacovigilance Database to select "serious" ADRs reported from 1st January 2008 to 31st December 2009 with 8 oral PKI: sorafenib, imatinib, erlotinib, sunitinib, dasatinib, lapatinib, nilotinib and everolimus. A "serious" ADR was defined as any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/incapacity or is life threatening. We used the French ADR preventability scale in this study.[1]

Results: This study carried out on 265 declarations: 68 for sorafenib, 64 for imatinib, 44 for erlotinib, 43 for sunitinib, 33 for dasatinib, 6 for lapatinib, 4 for nilotinib and 3 for everolimus. Most of ADRs were "unpreventable" (65%) because prescription was unavoidable. Thirty one percent were "unevaluable" (31%) because reports were poorly documented (medical history, dosage, 1st or 2nd intention, concomitant drugs). No ADR was "preventable" but 10 were "potentially preventable" (4%): aspergillosis, bleeding, pancreatitis, acute pulmonary edema, hepatic ADR, anal fissure and cutaneous ADR. Few ADRs were "potentially preventable" because recommendations of SPC (Summary of Product Characteristics) were not respected (drug interactions, indication, age or dosage) and risk factors existed (concomitant pathologies, previous ADRs with a PKI, exposition to radiotherapy, alcohol, tobacco).

Conclusion: The French ADRs Preventability Scale is a useful tool to assess preventability of antineoplastic drug-induced ADRs. However, some items are difficult to score, especially with antineoplastic drugs. Most of ADRs with oral PKI drugs were "unpreventable". Respect of SPC could avoid occurrence of some ADRs.

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P110. Comparison of Adverse Drug Reactions in Children between Prescription and OTC Drugs

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Introduction: In France, drugs are registered in 2 categories. Some drugs are only delivered with a prescription and the other ones, also called "over the counter" (OTC) drugs, may be sold directly to a consumer without a prescription from a healthcare professional. Prescription drugs have a higher toxicity or teratogenicity than OTC drugs. However, recently, some "serious" adverse drug reactions (ADRs) have also been reported with OTC drugs as cough and cold medicines. Our study compared ADRs occurred in children with nonprescription and prescription drugs and registered in the French Pharmacovigilance Database.

Methods: We used the French Pharmacovigilance Database (FPVD) to select ADR occurred in children (0–18 years) and registered between January 2009 and December 2010 by the Midi-Pyrenees Pharmacovigilance Center. We compared gender and age of children, drugs, ADR and ADR seriousness between prescription and OTC drugs.

Results: A total of 232 ADR reports were included. It involved 296 suspected drugs divided into 245 prescription drugs, mainly anti-infective agents (44.1%) and 51 OTC drugs, mainly analgesics (53.1%). ADRs in girls were more frequently occurred with OTC drugs than with prescription drugs (62.7% versus 45.7%, p = 0.030). Age (0–2, 3–9 and 10–18 years) was not significantly associated with the status of drug (prescription/OTC drugs; p = 0.465). Frequencies of ''serious'' ADRs was comparable in both groups (56.9% versus 54.3%; p = 0.737). General disorders (n = 87; 22.1%), dermatological (n = 59; 15%) and neurological (n = 53; 13.5%) ADRs were the most frequent in both groups. Neurological ADRs were significantly more frequently reported with OTC drugs than with prescription drugs (24.7% versus 13.3%; p = 0.017).

Conclusion: Most of ADRs in children were ''serious''. ADRs with prescription and OTC drugs in children were different for gender of patients and nature of ADRs. ADRs with OTC drugs were more frequently neurological and more reported in females than ADRs with prescription drugs.

P111. Characterization of Spontaneous Reporting of Drug-Induced Hepatic Disorders Associated with Alcohol Consumption: Data from the VigiBase™

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Introduction: Ethanol is considered to be a risk factor for drug-induced liver injury (DILI) and one of the Roussel Uclaf Causality Assessment Model's criteria specifically used for liver adverse drug reactions (ADRs).[1] The effects of ethanol on risk of paracetamol-induced hepatotoxicity are well characterized. However, in idiosyncratic DILI they are less delineated.[2]

Aim: To characterize the reporting of drug-induced hepatic disorders associated with ethanol consumption (Et-DILI).

Methods: VigiBase™, the World Health Organization (WHO) individual case safety reports database, was screened for reports of ethanol suspected to be involved in DILI. Criteria used for the retrieval of reports from the VigiBase™ were standardised MedDRA query (SMQ) on drug-induced hepatic disorders, ethanol consumption, and time period from the database establishment until December 31, 2011. Et-DILI reports were characterized for the following features: type of hepatic reaction, suspected drug, the patient's gender, age, and the reporting country. Drugs were classified according to Anatomical Therapeutic Chemical (ATC) classification. SPSS 16 software (Chicago, Ill) was used for statistical analysis.

Results: As of December 31, 2011, 19 countries submitted 602 Et-DILI reports with 1055 ADRs for 321 different drugs or their combinations. The largest percentage of reports was reported by the US (77.7%). There were significantly more reports for males 60.0% (361) than females 36.4% (219) [p < 0.001]. Males predominated in all age groups. The highest reporting frequency was observed for patients aged 40–49 years (95 males vs. 52 females). The majority of cases were related to hepatotoxicity of paracetamol used alone or as a multicomponent product (33.1% and 14.5%, respectively), followed by oxycodone (10.6%), diazepam (4.3%) alprazolam (4.2%), cocaine (4.2%), and warfarin (4.0%). Out of the 64 reported preferred terms of hepatic disorders, the most common were aspartate aminotransferase increased (17.1%), hepatic failure (16.6%), alanine aminotransferase increased (15.9%), hepatic function abnormal (10.5%), and liver function test abnormal (9.3%). Fatal outcome was reported in 18.3% (110) cases involving 16.3% (59) males and 23.3% (51) females.

Conclusions: Hepatic disorders were recorded for concomitant use of ethanol with a number of different drug classes, among which the most frequent were drugs affecting the nervous system. Males were more prevalent, but females were more likely to develop fatal outcome. The causative role of ethanol in the onset of idiosyncratic DILI has yet to be investigated.

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P112. Potential Risks from Counterfeit Conventional & Herbal Products Used for Erectile Dysfunction

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Background: The production of counterfeit drugs is a growing problem that may poses risks to the public worldwide.[1,2] In UAE one of common counterfeited class of medicines are erectile dysfunction drugs; phosphodiesterase type 5 inhibitors (PDE-5 inhibitors).

Objective: This study assessed quality and safety of conventional drugs and herbs that may contain undeclared ingredients of PDE-5 inhibitors.

Methods: 70 samples were collected from 2003 till April 2012. Detection of PDE-5 inhibitors in these products was performed by high performance thin layer chromatography and ultraviolet absorption scanning. Adverse Drug Reactions (ADRs) were monitored by patients voluntary reporting. Labels and claims of the products were also evaluated.

Results: 66/70 (94.3%) samples were confirmed to be counterfeit containing sildenafil and tadalafil. 17 products were imitations of originals (11 Viagra, 2 Cialis, 3 Levitra & 1 Snafi). 13 herbal products labelled for improving sexual potency (4 Satibo, 5 VigRx for Men; 3 Tongkat Ali). 34 were other herbs and 3 were unknown. Out of 17 imitations of conventional products 16 (94.1%) showed manufacturer name, origin and batch number. 11/12 (91.7%) of herbs labelled for improving potency and 21/34 (61.8%) other herbs contained only manufacturer and origin details. 17/34 (50%) samples of other herbs had only batch number. No details appeared on unknown formulations. Four types of adulteration were found: sildenafil (75.7%, n = 50/66), tadalafil (16.7%, n = 11/66), tadalafil & sildenafil (6.1%, n = 4/66), tadalafil & caffeine (1.5%, n = 1/66). The identified quantity of sildenafil & tadalafil ranged (9–145 mg) and (5.43–25 mg) respectively. ADRs were evaluated from 4 patients. 3 patients (75%) reported hypoglycaemic symptoms as two patients used herbs contained sildenafil and one patient used fake Viagra. One patient (25%) suffered severe hypotension due to use of fake Levitra. Low rate of ADRs reporting is due to fact that patients are reluctant to disclose ADRs.

Discussion: Counterfeit drugs do not meet quality standards. The herbal products are widely distributed in non-regulated outlets and are freely available to purchase without restrictions.[3,4] Adulteration of herbal supplements with PDE-5 inhibitors is common.[2-4] Many

herbal products labels do not mention standardized ingredients nor information on manufacturers or origins.[2]

Conclusion: Adulterations of these medicines with PDE-5 inhibitors could be serious.[2] Effective pharmacovigilance system is needed and professionals and public should be alerted to this threat.

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P113. Spontaneous Reporting of Drug-Induced Osteoporosis or Osteomalacia: Review of the French Pharmacovigilance Database

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Introduction: Long-term exposure to some drugs like corticosteroids can induce osteoporosis or other bone disorders.[1] The aim of this study was to identify drugs and risk factors more frequently involved in the development of these adverse drug reactions (ADR) in clinical practice.

Methods: In the French National Pharmacovigilance database, we identified spontaneous case reports of drug-induced bone disorders, according to the System and Organ Classification of MedDRA 14.0 dictionary and registered until the 15th of September 2011. In these reports, we analyzed suspected drugs, main features of cases, differences between osteomalacia and osteoporosis and association or not to corticosteroids.

Results: We found 256 cases (217 osteoporosis and 39 osteomalacia). 60.2% were female. Median age was 64 years (8 months – 95 years) and mean body mass index was: $21.8 \pm 0.7\ Kg/m^2$ ($n = 54$). There was no other risk factor in 63.7% of cases. The main ADRs reported were osteomalacia (15.2%) and osteoporosis (84.8%). Mean latency period to both ADRs was 1077.2 ± 107.1 days, clearly longer in the osteomalacia reports (1933.2 ± 395.5 days) than in the osteoporosis reports (859.7 ± 84.0 days). Nearly half (46.5%) of the reports analysed did not include corticosteroids. Absence of corticosteroids was more frequent in osteomalacia than in osteoporosis reports (92.3% versus 38.2%). Fracture was reported in 47.7 of cases (41.0% with osteomalacia versus 48.8% with osteoporosis). The mean of suspected drugs included in each report was 2.6 ± 0.1. Apart from corticosteroids, the more common suspected drugs were anti-retroviral! (23.4%), antiepileptic (5.6%), immunosuppressant (3.4%), proton pump inhibitors and other drugs for acid related disorders (3.2%) and antithrombotic (3.2%) drugs.

Conclusions: In a high number of cases, osteomalacia or osteoporosis were not associated with corticosteroids. Anti-retroviral and anti-epileptics drugs were the most frequent non-corticosteroid drugs involved. The possibility of development of bone disorders should be kept in mind during long-term treatment with these drugs.

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P114. Individual Case Reports' (ICRs) Causality Assessment in Elderly: Why Not to Try the Inversion of Proof?

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Background: Ageing is the process of the body's organ systems' progressive deterioration, leading to a frailty and increased susceptibility to illnesses. Adverse drug reactions (ADRs) have been shown to be more frequent in the elderly, and an important cause of hospitalizations, morbidity and mortality. In the developed world, older people are often treated with one or more drugs. However, the importance of ageing with its multiple acute or chronic conditions is that these can also be adverse drug reactions, and they hinder identification of drug-related harms in ICRs. In inversion of proof – a legal method aiming to protect the weakest part – the accused has to demonstrate innocence. The precautionary principle implies that lack of full scientific certainty isn't a reason for postponing protective measures when serious damages are possible.

Aim: To propose inverting causality assessment into a non-causality process, which at baseline assumes that in elderly patients taking one or several drugs, the adverse effect is quite likely to be drug-related and one has to demonstrate it isn't (inversion of proof).

Method: In elderly, a given effect should be always considered as drug-related if:

a) The drug(s) has been administered before the suspected adverse effect;
b) There are conclusive reports of this effect for the drug or combination of drugs, relying as conclusive information provided in Sumaries of Product Information and well-demonstrated case reports, OR the effect is pharmacologically or clinically possible, including idiosyncratic mechanisms.

Unless:

1. Other factors have been demonstrated as a (common) cause of the suspect adverse effects;
2. The adverse reaction did improve despite the fact that the drug was continued or a *specific* antagonist was administered.

This method should be further tested in clinical practice.

Discussion: In older people, the use of ADRs' causality scales or algorithms such as Naranjo's scale or WHO method (questions' set with the aim of probing the drug causality), usually ranges ADRs in a lower score (*possible*) because experimental facts, such as re-challenge or laboratory or diagnosing probes, are often not feasible in clinical practice, and de-challenge's outcomes are often slowed by decreased drug metabolism or total body clearance, due to impaired hepatic, cardiac and kidney functions related to elderly.

Conclusion: In the elderly at high risk for ADRs, the inversion of proof applied in event causality assessment could help to identify ADRs more effectively and promote decisions in favor of patients following the precautionary principle.

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P115. Four Cases of Serious and Atypical Infections in Patients with B-Lymphopenia After Treatment by Rituximab or Ocrelizumab

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Rituximab and ocrelizumab, monoclonal antibodies directed against the surface protein CD20 of *pre*-B and mature B-lymphocytes, induce depletion both in normal and malignant lymphocytes. Studies on rituximab in patients treated for rheumatoid arthritis showed a temporary depletion in B-lymphocytes with a mean time of re-population by B-lymphocytes of 8 months after rituximab course.[1] We describe four cases of long-term profound lymphopenia after discontinuation of rituximab spontaneously reported to our regional pharmacovigilance centre by the same department of rheumatology.

Case 1: A 69-year-old woman, treated by tocilizumab for rheumatoid arthritis, was hospitalized for a *Cytomegalovirus* colitis with perforation of the small intestine and an *Epstein-Barr* lymphoma. The signs appeared in a context of B-lymphopenia, eleven months after discontinuation of a treatment by rituximab. The B-lymphocyte count was normal before rituximab treatment, dropped during treatment, and remained low after rituximab discontinuation.

Case 2: A 79-year-old man had been treated by four courses of rituximab for rheumatoid arthritis. Ten months after discontinuation of rituximab for immunodepression, he still had major B-lymphopenia and developed septic shock secondary to a *Listeria monocytogenes* meningitis and a *cytomegalovirus* infection while on treatment by tocilizumab. The total lymphocyte counts were nevertheless normal before and during rituximab treatment as well as at the time of infection.

Case 3: An immunodepressed 49-year-old woman, treated by prednisone for rheumatoid arthritis, developed a herpes zoster complicated by meningo-radiculitis. During previous treatment by rituximab, she had a moderate lymphopenia and a major B-lymphopenia. At the time of infection, more than two years after discontinuation of rituximab, she had lymphopenia, B-alymphocytosis and moderate hypogammaglobulinemia.

Case 4: A 48-year-old woman, treated by tocilizumab for rheumatoid arthritis, developed acute hepatitis E five years after discontinuation of a treatment by ocrelizumab. At the time of infection, the patient had moderate lymphopenia and major B-lymphopenia.

These infections that occurred late after discontinuation of rituximab would involve a persistent B-lymphopenia induced by rituximab. This highlights the problem of the identification of adverse effects that occurred at distance of the exposure, while patients are treated by other medicines. A follow-up of subpopulations of lymphocytes when a treatment by rituximab is initiated could help to better assess the causal link between these infections and rituximab and to guide the choice of future drug treatments for patients.

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P116. Impact of the First of CONSORT Recommendations for Reporting Adverse Effects in Published Clinical Trials

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Background: The CONSORT (*Con*solidated *S*tandards *o*f *R*eporting *T*rials) statement, published in 1996, was conceived as an effort to standardize and improve published reports of randomized controlled trials (RCTs), throughout a checklist flow diagram. In 2001, an item about reporting adverse events was added. An extension of CONSORT statement,[1] which focuses on adverse event reporting, encourages authors to use the term "harms" instead of "safety", and presented a set of ten recommendations for the proper reporting of harms in RCTs. Most of RCTs collect data both on efficacy and adverse events; the first recommendation for studies collecting data on harms and benefits is that the title or abstract should so state this clearly. This article, published in November 2004, found that in the Cochrane Central Register of Controlled Trials only 337 references included the term "harm" compared with 55 374 for efficacy and 23 415 for safety. Besides, out of the 337 references only 3 trial reports and 2 abstracts contained the word "harm" in their titles, most of the articles referred to self harm or harm reduction.

Aim: To compare the frequency of use of words "harm" and "safety" in titles and abstracts of published clinical trials references in PubMed, after the publication of CONSORT guidelines(from 2005 to May 2012).

Method: A systematic search was performed in PubMed for the terms "harm" and "safety" (title/abstract, limits Humans, Clinical Trial, Randomized Controlled Trial, in English) from January 1st 2005 to May 31st 2012.

Results: From 2005 to May 2012, the search with the term "safety" retrieved 25 606 results, most of them were clinical trials. For the same period, the search with the term "harm" yielded 500 results. Out of 500 references, 72 reported results of clinical trials (including non-pharmacological therapeutics, such as surgery or kinesiology practices), 3 had the term "harm" in the title (1 about chiropraxis), and 69 in the abstract; out of these 69 articles, the term searched was part of "Number needed to harm" in 21 abstracts.

Conclusion: "Safety", a reassuring term, is widely used in clinical trials reports. CONSORT's first recommendation for reporting harms in clinical trials have had little impact. Regulatory requirements should be implemented in the editorial process in order to modify the way of reporting of harms in clinical trials, and therefore contribute to change the physicians' and general perception of drug-related harms in clinical research and in clinical practice.

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P117. Number of Drugs Usually Taken by Hospital Inpatients before Admission and Adverse Drug Reactions (ADRs) Identified as Cause of Hospitalization

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Background: Polypharmacy in clinical practice is used as therapeutic approach scientifically based for refractory conditions or resistant infections, or, on the other hand it can be the expression of non-rational addition of symptomatic treatments and/or ''therapeutic fall'', a kind of medication error aiming to pharmacologically treat symptoms of ADRs. Polypharmacy can cause harmful interactions, which can manifest when the interacting drug is added or when a concomitant physiological imbalance decreases drug clearance or impair metabolization. The higher is the number of drug taken by the patient, the higher is the likelihood of ADRs.

Aim: To assess how many drugs were usually taken before his/her admission by patients hospitalized in a University Hospital.

Methods: A sample of 200 clinical charts of patient hospitalized in the Clinical Medicine Service was reviewed in order to assess the number of drugs usually taken before admission. Except some fixed anti-infective combinations (trimetroprim-sulphamethoxazol, amoxicilin-clavulanic acid), active principles contained in the same pharmaceutical product were considered as separate drugs, ADRs as cause of hospitalization had been previously assessed and matched with the number of drugs.

Results: 62.5% of patients were treated with 3–8 drugs. Patients with no treatment (8%) were younger; most of them had discontinued ARV treatment and one was a case of diabetes type I. ADRs were most likely to be identified in patients treated with 4–6 drugs. Hospitalization has been assessed as drug-related in 29 patients (14.5%), 27 taking 2 or more drugs.

Table I.

No. of drugs	Admissions [(n) %]	ADRs as cause of admission [(n) %]	Sex (age range)
0	(15) 8%		9 men (26–69); 7 women (39–89)
1	(21) 10.5%	(2) 6.9%	9 men (60–95); 12 (40–97)
2	(31) 15.5%	(2) 6.9%	14 men (55–91); 17 women (55–84)
3	(22) 11%	(5) 17.24%	10 men (39–84); 12 women (45–91)
4	(32) 16%	(8) 27.59%	15 men (38–86); 17 women (46–93)
5	(22) 11%	(0) 0%	12 men (49–75); 10 women (53–88)
6	(25) 12.5%	(6) 20.69%	13 men (58–82); 12 women (66–93)
7	(14) 7%	(1) 3.45%	6 men (43–79); 8 women (70–95)
8	(10) 5%	(4) 13.80%	5 men (29–84); 5 women (55–90)
9	(5) 2.5%	(2) 6.9%	1 man (80); 4 women (71–85)
10	(1) 0.5%	(0) 0%	1 man (51); 0
11	(0) 0%	(0) 0%	0; 0
12	(1) 0.5%	(1) 3.45%	0; 1 woman (68-year-old)
13	(1) 0,5%	(0) 0%	1 man (43-year-old); 0

Discussion: These results have a limited value because they arose from the study of a reduced sample. Drugs were reported by patients and relatives, therefore memory bias are possible.

Conclusions: In this sample, a high percentage of patientshospitalized were under polypharmacy before admission. ADRs as cause of hospitalization can be related with the number of drugs taken by patients. A more rational therapeutic approach should carefully analyze every drug prescribed in order to assess its benefit/harm for each individual patient, in order to avoid unnecessary or potentially harmful drugs, and their possible interactions.

P118. Breast Cancer Risk in Relation to Use of Combined and Progestogen-Only Contraceptives: Results from a UK Record-Linkage Study

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Introduction: A collaborative re-analysis of breast cancer and hormonal contraceptives,[1,2] including data on about 53 000 women with breast cancer from 54 epidemiological studies, found a small but definite increase in risk among current users of combined oral contraceptives (RR in current versus never users = 1.24, 1.15–1.33) which gradually declined after ceasing use such that women who had ceased use more than 10 years previously were no longer at any increased risk. Corresponding findings with respect to use of injectable and oral progestogen-only preparations from that collaboration suggested broadly similar patterns of risk, but the relatively small numbers of women included in those studies (all conducted prior to 1996) prevented any reliable conclusions regarding the specific effects of such preparations. Information on the risk of breast cancer associated with more contemporary combined oral contraceptive formulations, including triphasic pills, is relatively sparse.

Aim: To describe the risks of breast cancer associated with recent use of specific types of hormonal contraceptives.

Methods: The relationship between recorded prescribing information on specific types of hormonal contraceptives and the subsequent incidence of breast cancer was analysed using data from the General Practice Research Database[3] (GPRD), a large computerised database containing anonymised patient records for about 6 million people in the United Kingdom registered with a National Health Service primary care physician (general practitioner). Data were extracted from the database in the form of a nested case-control study on around 6000 women with breast cancer, aged 20–49 at diagnosis, and around 12 000 matched control women. Odds ratios for breast cancer according to use of hormonal contraceptives were estimated using conditional logistic regression.

Results: Among controls about 14% were current or recent users of any type of combined oral contraceptive, about 6% were current or recent users of progestogen-only oral contraceptives, and about 2% were current or recent users of injectable depot preparations. Results will be presented according to age, patterns of contraceptive use and the specific type of preparations used.

Conclusions: The findings will be discussed in the light of relevant previously published data.

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P119. Drug Utilization Patterns and Prevalence of Adverse Drug Reactions of Antibiotics at a Tertiary Care Hospital in North India

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Background: Drug utilization research was defined by the World Health Organization (WHO) in 1977 as ''the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences''.[1] WHO defines an adverse drug reaction (ADR) as ''one which is noxious and unintended, and which occurs in doses normally used in human for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological functions.[2]''

Objectives/Aims: To study the pattern of antimicrobial prescription in OPD of the Otolaryngology department and to detect, document, assess and report the suspected ADRs due to antibiotic use and preparation of guidelines to minimize the incidence of ADRs.

Methods: Prospective study conducted at the TMMC&RC on a sample size of 3200 patients, who visited the ENT OPD over a period of 12 months. Only 2600 patients were included in the study. Adverse drug reaction forms were given to ENT specialist prior to study and ADR reports were accepted from all the healthcare professionals of ENT specialty. The causality relationship between suspected drug and reaction was established by using WHO and Naranjo's causality assessment scales. The protocol of the study was approved by the Research and Bioethical Committee of the hospital.

Results: Out of 3200 patients, only 2600 patients were included in the study, 60% (n = 1560) were males and 40% (n = 1040) were female. Maximum no. of patients were in the age group 16–35 years 60% (n = 1560) while the geriatric group 76–85 years comprised the lowest 1.9% (n = 50). 55% (n = 1430) of patients were diagnosed with ear, 30% (n = 764) with throat and 15% (n = 296) with nose disorders. The most frequently prescribed antibacterials were β-Lactams 74.58% (n = 2148) followed by Aminoglycosides 9.72% (n = 280). Only 194 (7.46%) patients suffered from adverse drug reaction. Diarrhea was found most (135 cases) than allergic reactions (36 cases). Ototoxicity and nephrotoxicity found in 11 and 6 cases respectively (table I).

Conclusion: Our study showed that antimicrobials were mostly prescribed in patients of ear diseases while it was least in Nose disorders. Diarrhea was the most common adverse drug reaction found. Minimizing unnecessary antibiotic use by even a small percentage could significantly reduce the immediate and direct risks of drug-related adverse events in individual patients.

Table I (relates to abstract no. P119).

Drug Class	Allergic reactions (36)	GI (Diarrhea) (135) & Others (6)	Ototoxicity [dizziness, decrease in hearing] (11) & Nephrotoxicity (6)
β-Lactams	Rashes (21) Urticaria (5)	75	Interstitial nephritis (3)
Quinolones	Rashes (5)	5	dizziness (2), Interstitial nephritis (1)
Aminoglycoside	Rashes (2)		decrease in hearing (9) & acute tubular necrosis (2)
Macrolide	Rashes (3)	Diarrhea (30), Vertigo (1)	
Nitroimidazoles		Diarrhea (25), Metallic taste (5)	

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P120. Drug Interaction Signal - Serotonin Syndrome Associated with Donepezil and Serotonin Reuptake Inhibitors

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Background: The WHO Adverse Drug Reaction (ADR) Database, VigiBase™, contains over 7 million Individual Case Safety Reports (ICSRs) collected since 1968 and currently augmented by 107 countries. VigiBase is managed by the Uppsala Monitoring Centre (UMC) and a routine detection process is used to identify and assess potential signals. These signals usually associate one drug with one ADR but a potential signal for a drug interaction has been identified.

Aim: To analyse VigiBase ICSRs for an interaction between donepezil and Serotonin Reuptake Inhibitors (SRIs) leading to serotonin syndrome.

Method: Clinical review of all ICSRs in VigiBase where serotonin syndrome is possibly associated with use of donepezil in combination with a Selective Serotonin Reuptake Inhibitor (SSRI), Serotonin and Noradrenalin Reuptake Inhibitor (SNRI) or Serotonin Antagonist and Reuptake Inhibitor (SARI).

Results: 13 reports from six countries were included after removal of probable duplicates. In four cases donepezil was added to pre-existing SRI treatment and in five cases the SRI was added to pre-existing donepezil treatment. In three of the four cases where donepezil was added, the reporters suspected an interaction between donepezil and the SRI. Time to onset was listed in four of the 13 cases ranging from one to 15 days.

Discussion: In vitro studies on rats and mice showed changes in serotonin levels by donepezil[1,2] and the metabolism of donepezil may be

inhibited by inhibitors of CYP3A4 and 2D6 such as fluoxetine[3] so an increased risk of serotonin syndrome with donepezil is plausible. Most of the patients are elderly and Alzheimer's disease has itself been shown to affect serotonin receptors[4] but in at least two ICSRs it appears likely that addition of donepezil to SRI treatment triggered the serotonin syndrome reaction.

Conclusion: Donepezil may have an effect on serotonin levels and this is potentially clinically important when combined with an SRI. The reaction could be due to age, the disease or either of the drugs alone, in particular the SRI, however cases with short time to onset after addition of one drug to pre-existing treatment with the other indicate an interaction between donepezil and SRIs. This is particularly suggestive in cases where donepezil was added to pre-existing SRI treatment and the reporters also suspected an interaction. As many patients are taking multiple medications, interactions between drugs should be considered when identifying and assessing possible signals. A process to identify drug interactions specifically is being developed by the UMC.

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P121. Are Risk Management Systems Appropriately Designed?

M.L. Mease
Quintiles

In the US, AEs result in more than 770 000 injuries and deaths each year and national hospital expenses to treat patients who suffer AEs during hospitalization are estimated at $1.56–5.6 billion annually.[1] In the European Union, AEs kill some 197 000 citizens per year, incurring €79 billion in costs.[2]

AEs can be idiosyncratic, some of which are mitigatable, or preventable. Idiosyncratic AEs are rare and unpredictable and thought to have an underlying genetic etiology.[3] Because of their unknown nature, there is often little control over this type of AE. Most interventions are directed at lessening the severity of idiosyncratic AE outcomes. In contrast, avoidance of preventable AEs is fully controllable. A recent meta-analysis of 16 studies on outpatients with 48 797 emergency room visits found that among both outpatients and inpatients, around half of adverse drug reactions are preventable.

News stories of and system reactions to high profile AEs give the impression and create a culture that we should not expect AEs. As a result, the system has reacted and created risk management mechanisms to control the occurrence of AEs. Although well intentioned, most risk management strategies cannot prevent AEs yet they continue to be required and cost significant industry and regulatory resources. Are the current risk management systems designed to manage risks or designed to avoid risks altogether?

If AEs that are fully controllable occur, can healthcare systems really be amended to eliminate all of them? Huge numbers of prescriptions continue to be dispensed, and many patients take four or more drugs, a known risk factor for AEs.[4] Against this backdrop, what do we understand by an 'acceptable number of adverse events compatible with patient safety? Or should we focus our attempts on AEs associated with human error so that these are reduced to an absolute minimum? We will present an outline of key contributors to the imperfect system – including payers, physicians and patients – examine the conflicting pressures, and make proposals for a system with a realistic and achievable benefit-risk targets which recognizes that the individual patient is the level at which benefit-risk treatment decisions must be made.

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P122. Design and Validation of a Questionnaire in Spanish in Order to Measure Pharmacovigilance Report Competences (Knowledge, Abilities and Attitudes)

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Introduction: The pharmacovigilance system collects adverse events registered by physicians in their clinical practice. However, there is a low index of reports in this regard. There are various publications at international level oriented to determine causes for this low notification of the said report. In this respect, it would be valuable to count with an instrument that would diagnose the situation prevailing for México.[1-3]

Aim: To develop and validate a questionnaire in order to identify competences for the report by physicians of Adverse Reactions for the Pharmacovigilance System, in Spanish, that is valid, reliable and sensible.

Material and Methods: A questionnaire was developed that included 30 questions related to the reporting of adverse reactions. Repeated versions were amended and tested progressively.[4] The definitive version of the questionnaire was applied to 124 physician subjects (table I) that responded to the final questions selected, and their answers were tabulated and categorized for a final statistical validation.[5,6] Alfa of Cronbach and "t" student tests were applied for the validation and test-posttest application.

Results: Demographics are presented in table I. The internal consistency test was valid. The different answers and scores were calculated, where the final global average in points for responses for the

Table I. Demographic characteristics of the pilot group tested for validation purposes

Item	Outcome	Range	SD
N	124		
Male/Female	63/61		
Age (years)	44.35	26/65	±10.50
Experience (years as professional)	16.4	1/35	±9.85
No. of patients/day	17.54	3/40	±7.36

pilot group studied was 100.72 (total possible: 150), that, translated to percentage, resulted in 67% (SD ±8) of answers optimally completed. A further test for validation was performed on 250 complementary physicians with an educational intervention and before-after (the intervention) questionnaire application, that resulted in a positive, statistically significant outcome. Cronbach test was favorable in a significant fashion for final selected questionnaire.

Conclusions: The questionnaire meets the objectives for which it was designed, and proved to be valid, reliable and sensible, reflecting the state of knowledge, abilities and attitudes of the physicians tested. This questionnaire will be used for testing wide audience competences aimed towards pharmacovigilance reporting by practicing physicians. Sponsored by a scholarship from CONACYT México. Escuela Superior de Medicina, División de Postgrado e Investigación, IPN. Doctorate in Medical Investigation.

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P123. Frequency, Types, Severity, Preventability and Costs of Adverse Drug Reactions at a Tertiary Care Hospital Over a 9-Month Period

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Background: Prior to this study, there were no pharmacovigilance centres or any other ADR monitoring framework available in any of the leading hospitals of the Indian state of Jammu and Kashmir including SKIMS.

Objective/Aim: To assess the frequency, preventability, types, severity, causality and costs of drug-related adverse effects in Kashmiri patients at a tertiary care hospital namely, SKIMS.

Methods: A prospective, observational, cohort, ADR monitoring study was conducted on adult patients admitted in Internal Medicine IPD, presenting to the Internal Medicine OPD and those visiting the Accident and Emergency Department of a tertiary care hospital namely, SKIMS, during a 270-day period. A total of 5482 patients belonging to both the sexes were screened and monitored on a daily basis for the occurrence of any ADRs. WHO definition[1] of ADRs was used and causality of suspected ADRs was determined using Naranjo's algorithm[2] whereas severity was assessed using modified Hartwig's Scale[3] and preventability was determined using Hallas methodology.[4]

Table I. Demographic characteristics of the study patients

Characteristics	No. of patients with ADR/No. of patients visiting the hospital	No. (%) [n = 121] of ADR-related admissions	ADRs occurring during hospital stay
Male	132/3283 (4.02%)*	21 (0.63%)*	111 (3.38%)*
Female	210/2199 (9.54%)*	47 (2.13%)*	163 (7.41%)*
Adult	187/3985 (4.69%)*	38 (0.95%)*	149 (3.73%)*
Elderly (>65 yrs)	155/1497 (10.35%)*	30 (2.00%)*	125 (8.35%)*
Total	**342/5482 (6.23%)**	**68 (1.24%)**	**274 (5.07%)**

*$p < 0.0001$ on Student's t-test/Chi-squared (χ^2) test (level = statistically highly significant)

Cost of ADRs was calculated as per the protocols suggested by Lagnaoui et al.[5] and Nicholas et al.[6] (extension in hospital stay).

Results: ADRs accounted for 6.23% of adult Kashmiri patients visiting a tertiary care hospital, SKIMS, either for referral or hospitalization, with the majority (81.57%) of these ADRs being preventable; 23.68% of patients had mild ADRs, 69.29% had ADRs of moderate severity, and 7.01% had severe ADRs. The 4 classes of drugs most frequently suspected in admissions due to ADRs were anti-infective agents (40.92%) including anti-tubercular drugs (13.15%), steroids (14.03%), anti-coagulants (8.77%), and NSAIDs (7.89%). Increasing age and female gender were identified as risk factors. The total cost to the hospital due to hospitalization of patients presenting with ADRs over the 9-month period in the internal medicine IPD was USD 22469.

Conclusion/Discussion: The present work is the maiden pharmacovigilance study conducted on Kashmiri patients, especially at a tertiary care teaching hospital like SKIMS that has provided baseline information about the prevalence of ADRs and their distribution among different age groups, genders, organ systems affected, and therapeutic classes of medicines. The data collected will be useful in future for more extensive ADR monitoring on Kashmiri patients and will also be useful in framing policies toward the rational use of drugs. This study led to the establishment of a full-fledged pharmacovigilance centre and initiation of pharmaceutical care services at the study hospital.

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P124. Development of Pharmacovigilance Networking System in Thailand

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Objectives: To develop the models of effective pharmacovigilance networking system at 4 regional sites and 2 provincial sites in Thailand i.e, Region 7 (Phuket, Phangnga, Ranong, Krabi and Trang), Region 8 (Songkhla, Satun, Pattani, Yala and Narathiwat), Region 12 (Khon Kaen, Maha Sarakham, Roi Et, Kalasin), Region 15 (Chiang Mai, Lamphun, Lampang, Mae Hong Son), Chiang Rai province and Phrae province.

Methods: The project was conducted from May 2010 to July 2011. Situation analysis of each site was implemented and activities were developed according to their situation analysis.

Results: In the beginning of the study, each system had varied in terms of their active stakeholders, competencies of personnel, strengths and weaknesses. Most of pharmacovigilance activities were restrictively implemented in hospitals, and emphasized ADR monitoring more than other drug-related problems i.e, medication error, etc. To develop the effective model, all sites had the main activities towards strengthening the existed networks in order to be more community-based. It started by involving participants from government agencies to private hospital, drugstores, clinics and other stakeholders in the network. Some extended the scope of surveillance to other health products i.e, herbal medicines, food, cosmetics, etc. Advisory groups, committees or working groups (both formal and informal) were appointed to carry out risk management measures, as well as to monitor the progress.

In addition, communication tools such as websites were elaborated to enhance their activities. Human resources were also continuously developed by training or managing knowledge by conducting root cause analysis or communities of practice.

Conclusions: The effective model of pharmacovigilance networking system should be that having coverage of all related-members equipped with qualified personnel, monitoring and evaluating system and supporting tools for knowledge and learning.

P125. Telling Patients About ADR Promotes Positive Attitudes

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Background: Adverse events are temporally associated with the use of a pharmaceutical product, but are not necessarily caused by it. The patient however can consider any associated event as caused by the drug and this can determine a certain reaction going up to the interruption of treatment.

Patients' education on possible adverse reactions may help in this matter and is widely accepted as part of the patient's right to respect and self-determination. No data about patients' communication on ADR are available in DR Congo.

Objective: To assess attitudes of the patients vis-à-vis adverse reaction depending on whether or not they were told about possible ADR by the prescriber.

Methodology: A survey was conducted in July 2009, among 250 students of the University of Kinshasa who had been treated as outpatients at the University Hospital 2 weeks ago. A questionnaire about what drug they took what AE they felt and how they managed them, and whether the Doctor told them about AE was given to them.

Table I. Attitudes of the 250 patients when AE occurred

Attitude	Percentage	
	Patients told about AE (N = 85)	Patients not told about AE (N = 165)
Going on with the treatment	41.2%	27.3%
Calling back the Doctor	31.8%	15.8%
Treatment interruption	21.2%	40.6%
Taking advice from neighbours and family members	3.5%	10.9%
Taking advice from a Pharmacist	0.0%	1.8%
No answer	2.4%	3.6%
Total	**100.0**	**100.0**

Results: Only 85 of the 250 patients (34%) were told about AE. The attitudes of the patients when AE occured, are presented in table I.

Patients who were told about AE were more likely to have "positive" reactions i.e. to go on with the treatment or call back their Doctor when AE occurred. The ones who were not told about AE were more likely to have possibly risky attitudes by stopping the treatment or taking advice from non-medical persons.

Conclusion: Patients education on AE promotes better attitudes when AE occur in outpatients but is rarely done at the University Hospital in Kinshasa. More studies are needed to understand more and propose effective ways to implement patients' information on adverse drug reactions in Kinshasa.

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P126. Adverse Drug Reaction with Ivermectin in DRC, a Review of Committed ICSRs in 2010 and 2011

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Background: Onchocerciasis is one of the neglected diseases; it affects about 13 million individuals, most of whom live in the equatorial regions of Africa. The Democratic Republic of Congo is one of the most affected countries. The treatment includes administration of Ivermectin, usually during mass campaign. So, a large number of patients are exposed to the drug during a short period. Ivermectin is known to be also effective against Loa-loa, another filariasis for which the treatment should be gradual to avoid mass destruction of microfilaria which can cause encephalopathy. As a result, treatment of Onchocerciasis in patients co-infected with Loa-loa can lead to serious neurologic disorders. Monitoring, assessment and prevention of ADR is therefore crucial.

But data are scarce for DRC and Central Africa where are located most of the patients.

Objective: To determine the profile of ADRs occurring after ivermectin administration and the impact of Loa-loa co-infection, in the Pharmacovigilance System in DR Congo.

Methods: Through collaboration between The National Program for Onchocerciasis Control (NPOC) and the National Pharmacovigilance Center (CNPV) ICSRs on adverse event following administration of Ivermectin have been collected, analyzed and committed in the WHO database through Vigiflow. All committed ICSR in 2010 and 2011 were extracted from vigiflow as excel files and analyzed. ADRs were classified according to WHO-ART.

Results: Fifty-one ICSRs were committed and analyzed. Fifty patients had serious ADR, among which 48 with Loa loa co-infection. Twenty patients experienced neurologic reactions. Among them, 18 with Loa loa co-infection 14 of which had manifestations that may qualify as ***Loa loa encephalopathy associated to Ivermectin*** according to the Mectizan® Experts Committee criteria. Two of them died upon initiation of ivermectin treatment. Fifteen patients had conjonctival hemorrhages and 2 had Mazzotti reaction. The mean microfilaremia was 1 759/ml (0–17 540) and in 2 patients, Loa-loa microfilaria were found in Cerebrospinal Fluid.

Conclusion: As there is lack of new, safer medicines, the treatment of onchocerciasis with Ivermectin should be carefully monitored and Loa-loa co-infection thoroughly searched and managed before initiating treatment of onchocerciasis with ivermectin. Loa-loa infection must be actively searched each time there is serious adverse reaction with ivermectin.

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P127. A Cluster Randomized Controlled Trial to Assess an Educational Intervention to Increase Adverse Drug Reaction Reporting in Galicia (Northwest-Spain)

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Background: The continuous assessment of the benefit to harm balance of a marketed drug is based on the observation and succeeding reporting of the suspected adverse drug reactions (ADR) in clinical settings.[1] Underreporting delays alert signals, and therefore has a negative influence in public health. Educational interventions in pharmacovigilance have a positive impact in the reporting of ADRs.[2,3]

Objectives: To evaluate the participation of physicians, the effect and duration of the effect of an educational intervention in pharmacovigilance designed to improve the reporting of ADRs.

Methods: A spatial cluster randomized controlled study was designed: the intervention an control groups consisted of three spatial clusters (6 hospitals and 138 primary care centres) and four spatial clusters (7 hospitals and 267 primary care centres) respectively. The total period of study was eight months. The study was targeted to physicians with clinical activity.

The educational intervention consisted of two complementary approaches: an active one (group sessions) and a passive one (handing of educational written material and a reporting form). This strategy had successfully been applied in previous studies.[4,5] Interventions occurred from November 2007 to December 2008.

Results: Intervention participation was 53.7% in hospital and 60.5% in primary care settings. The reporting of ADRs in the intervention group increased 80% (95% CI 76-85%) after the educational intervention.

Reporting increased more markedly in the first four months following the intervention. In the first quarter, RR was 2.3 (95% CI 2.2-2.4). The effect decreased during the second quarter although it continued to be statistical significant. In the second quarter following the intervention, in the treated group, reporting rate was 25.2% (95% CI 21.2-29.3) greater compared to the control group, adjusted to basal values.

Conclusions: ADR reporting rate per 1000 physicians-month increased in the treated group from 1.73 to 2.89 following the intervention. The effect remained observed in the period of study after the educational intervention.

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P128. Study of Anti-TB Drugs Side Effects Monitoring Situation in the Republic of Armenia

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Introduction: Development of Multi Drug Resistant (MDR) tuberculosis (TB) is a major problem in the World, in Armenia as well. Weaknesses of drug regulation, particularly, these of drugs side and adverse effects monitoring system in hospitals can contribute to such problems. Most patients on treatment for drug-resistant TB experience at least one side-effect, and a recent study has shown that two thirds of such patients have had at least one medicine stopped temporarily or permanently as a result of ADRs.[1] Patients who stop taking anti-TB medicines pose a risk to themselves and to others.[2]

Aim: To identify the weaknesses of anti-tuberculosis drugs side effects monitoring system in the hospitals of the Republic of Armenia.

Methods: We performed a retrospective observational study of TB patients' medical histories in hospitals and ADRs reports of anti-TB

medicines for the period from 2008 to 2011. All results entered into database. Statistic analysis was undertaken using SPSS 16.0. The seriousness was considered according to the ICH E2A guidelines.

Results: The results showed that from all ADRs reports 20.6% (n = 122) referred to anti-TB drugs. The majority of ADRs (58.2%) were reported among the MDR TB patients. The most described ARDs are: gastrointestinal disorders (51.4%), allergic reactions (15.6%), and hepatic disorders (5.4%). The ADRs majority occurred in 21-60 age group patients, predominately in men. Medical histories' observation showed that patients stopped taking a medicine permanently (20.2%) or temporarily (35.6%), and 27.9% took ancillary medication.

The imperfections of anti-TB drugs ADRs monitoring system in hospitals was the absence of information about event outcome (recovered, not recovered cet.) and seriousness (hospitalization, death, cet.), which makes the assessment of seriousness impossible.

Conclusion: This study has identified the weaknesses of anti-Tb drugs side effects monitoring system in hospitals, defined the most frequently described ADRs in Armenia, and the medicines, which cause a higher risk of treatment suspension or prolongation. These data will be used for development of risk management plan.

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P129. Cases of Liver Failure in Association With Flupirtine in The German Spontaneous Reporting Database

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Introduction: Flupirtine is a centrally acting, non-opioid analgesic. In Germany, flupirtine prescription increased over the years. In 2010, more than 30 Mio DDD were prescribed.[1] The Drug Commission of the German Medical Association notified healthcare professionals about reports on hepatitis in association with flupirtine in 2007.[2] Further case reports and study results were published. However, frequency and causality of drug-induced liver injury in association with flupirtine remains under discussion.[3-5]

Aim: To assess causality and to identify risk factors of severe liver injury associated with flupirtine treatment.

Methods: We collected data on acute liver failure associated with flupirtine treatment from original reporting documents and database records in the German spontaneous reporting system. Causality was assessed by using the CIOMS/RUCAM score. Severity was classified according to the scale by the Drug-Induced Liver Injury Network, DILIN.[6]

Results: Between 2003 and 2011, 37 reports of acute liver failure in association with flupirtine were identified. Median age of patients was 49 years (range 28–72), 30 patients (81%) were female (two-thirds of flupirtine prescriptions are for women). In most cases, the indication was musculoskeletal pain. Median time was 61 days (range 14–365) from initiation of treatment until the reaction. 5 patients died, in 2 cases liver transplantation was performed, in the remaining cases patients recovered or outcome is unknown. Ten cases were insufficiently reported for performing causality assessment. From the remaining 27 cases, the causality was assessed as highly probable in 1 case, probable in 9 cases, possible in 15 cases and unlikely in 2 cases. Alternative causes for liver injury were concomitant drugs known as hepatotoxic in 18 cases (NSAIDs 11, antipsycotics 5, Esomeprazol 1, Ranitidin 1).

Conclusions: This analysis supports the signal of a serious hepatotoxicity of flupirtine. Possible risk factors are longer duration of therapy and concomitant therapy with other hepatotoxic drugs. We strongly suggest that the frequency of drug-induced liver injury associated with flupirtine is investigated to allow proper risk-benefit assessment for this drug.

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P130. Design And Development of an Integral System of Pharmacovigilance

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Introduction: The Mexican Official Policy 220, establishes the guidelines for installation and operation of the Pharmacovigilance (PV) in Mexico, indicates the activities of PV should be reported to the National Pharmacovigilance Center. The Institutional Center of PV as part of the Integral Center of Pharmaceutical Services at PALIA Institute of Jalisco Secretary of Health receives reports of suspected Adverse Drug Reactions (ADRs) in the mexican official format, besides analyzing, reviewing and evaluating all information contained in these reports. Due to the amount of information is increasing every year it is essential to design and development of a database to provide store, organize and analyze information contained therein.

Objective: Design and develop an integral system of PV, using a database to facilitate capture the notifications of suspected ADR's, and further analysis and evaluation.

Methodology: For design and development of the database is formed by a multidisciplinary team of students in Computer Engineering, Computer Systems Engineering and Chemical Pharmaceutical Biologist, advised by the pharmacist chief at Palia Institute. The engine was programmed in MySQL 5.5.17 and the management system database DK7 JAVA platform. Was added the Naranjo's algorithm in the analysis of the parameters contained in ADR's report of suspected in order to semi-automatically evaluate the causality of the reports. Once linked these elements, we performed test phase in which the results

shown by the system were compared with those obtained manually by applying the Naranjo's algorithm.
Results: Was designed and developed a trial version of an analytical database called *Sistema Integral de Farmacovigilancia* (SIFaV 1.0) which has the ability to store, organize, sort, search and evaluate the parameters contained in the ADR's report format. The SIFaV 1.0 has a graphical interface in separate tabs for easy viewing and fill in the fields. It also allows semi-automatic assessment of causality of suspected ADR's using Naranjo's algorithm. Currently SIFaV stage is identification of possible failures of the software, using fictitious information, in order to identify potential programming errors. In later phases the aim is to capture information from reports of actual ADRs.
Conclusions: Databases are an increasingly important technology. After beating the test phase, it is feasible to implement more advanced versions SIFaV in hospitals, state centers of PV, colleges, pharmaceutical Industry, in order to improve drug safety through applications in investigation, detection and signaling farmacoepidemiológicas and evaluation reports.

P131. Improvements in Drug Policy of Indian State of J&K Through Persistent Advocacy and Logical Interventions by Civil Society Forum

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Background: The draft drug policy of the Indian state of Jammu and Kashmir was made available on its official website in the year 2009 by the Ministry of Health and Family Welfare. On studying the draft it was found to be deficient in many important aspects. Hence a sustained campaign was launched by Civil Society Forum, a group of activists drawn from diverse sectors like health, education, media, trade, industry, politics etc in order to incorporate necessary changes in the draft policy.
Objective/Aim: To emphasize upon the importance of civil society interventions and involvement in policy making process and decisions, with a view to bring changes in government drug policies, necessary to ensure quality, safety, efficacy, availability and affordability of medicines.
Methods: Through sustained lobbying, persistent advocacy, persuasive pressure, wide consultations and logical interventions, Civil Society Forum Kashmir got some significant changes incorporated in the draft drug policy of J&K state, introducing some fresh policy initiatives and novel approaches to tackle common problems of drug use in the society like spurious drugs, drug abuse, misuse of drugs belonging to Indian Systems of Medicines, over-the-counter sale of prescription drugs, recall and disposal of unwanted drugs etc.
Results: Draft drug policy formulated by the J&K govt. in 2009 was mainly focussed on selection, procurement, storage and rational use of drugs particularly in govt health facilities. However it was totally deficient in vital policy provisions related to spurious drugs control, AYUSH drugs control, control of prescription drug abuse, recall and disposal of uwanted drugs, drug licensing regulation, control of unethical promotion of drugs, drug prosecution, hospital and clinical pharmacy services, pharmacy education regulation, drug price control, medical financing/health insurance, blood banking and transfusion, etc. Through civil society interventions some of these provisions were accepted by the J&Kgovernment for incorporation in the modified draft whereas few others were rejected. Net outcome of interventions was that qualitatively a better draft could be evolved.
Conclusion/Discussion: Taking cue from the Indian state of Jammu and Kashmir, this paper demonstrates the need and importance of inclusion of civil society in policy making process and decisions for achieving the overall goal of making drugs of standard quality, good efficacy and reasonable safety available to common masses, particularly at govt. health centres. Experiences gained from J&K emphasize upon the need to replicate such activism in other Indian states too.

Table I. Fresh policy initiatives suggested in maiden drug policy of J&K state through civil society interventions

Rational Medicine Promotion Policy	Control of AYUSH Medicines
Drug Licensing Policy	Disposal of Unwanted Medicines
Rational Blood Banking/Transfusion Policy	Hospital Drug Management Policy
Drug Prosecution Policy	Cosmetics Control Policy
Drug Recall Policy	Drug Safety Monitoring Policy
Spurious Medicines Control Policy	Clinical Pharmacy Services Policy
Drug Abuse Control Policy	Pharmacy Education Policy
Drug Price Control Policy	Pharmacy Regulation Policy

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P132. Pharmacovigilance Training Customized to Hospital Setting Needs

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Pharmaceutical Industry

A training program was specifically designed to cover the needs of 3 Oncology Hospitals and 1 Psychiatric Hospital in Mexico City. The needs of these hospitals were focused on: new Patients Safety Programs, Hospital Quality Certification, and implementation of a Pharmacovigilance Department.
The program designed for the Oncology Hospitals is the following:
- 6 to 8 weekly sessions of 2 hours each one
- Topics covered on each session:
  - Session #1:
    - Pharmacology and manufacture of biotechnological drugs
    - National and International Regulation on Biotechnological and Biosimilar drugs
    - General recommendations to implement a Pharmacovigilance Unit in hospitals
- Session #2:
  - Epidemiology of adverse drug reactions and medication errors
  - Economic aspects of adverse drug reactions and medication errors
  - History of Pharmacovigilance (spontaneous notification of ADRs)

- National and International Regulation on Pharmacovigilance
- Definition of adverse drug reaction and adverse event
- Classification of adverse drug reactions

• Session #3:
- Variability in the response to drugs
- Mechanisms of drug-drug interaction
- Interactions among cancer drugs

• Session #4:
- Interactions between cancer drugs and alternative medicine (i.e. Saint John's wort – *Hypericum perfolatum*)
- Adverse drug reactions with cancer drugs: Cardiotoxicity
- Adverse drug reactions with cancer drugs: Cutaneous toxicity
- Adverse drug reactions with cancer drugs: Various toxicities (respiratory, neurologic, hepatic, etc.)

• Session #5:
- Notification of adverse events to Mexican Health Authority
- Pharmacoepidemiology and Active Pharmacovigilance (Drug utilization studies, cohort and case-control studies)

• Session #6:
- Pharmacovigilance databases
- Signal detection
- Causality assessment in Pharmacovigilance (Bradford-Hill; OMS-UMC; Naranjo; Karlz-Lasagna; RUCAM; etc.)

• Session #7:
- Differences in adverse events reporting among physicians, nurses, and patients in Oncology
- The pharmacist's rol in Pharmacovigilance in the hospital setting
- Activity: proposal and design of an internal form for adverse event reporting

• Session #8:

1. Therapeutic Drug Monitoring (TDM) and it's benefits in Cancer treatment
2. Planning methods in Pharmacovigilance (passive monitoring; stimulated reporting; active pharmacovigilance)
3. Publication of adverse events – guidelines

Hands-on exercises included the report of true adverse events; a final group proposal of an internal form; completion of the local authority form; examples of signal detection using the PRR methodology

In total, the mean number of people trained and certified on PV was 65 persons from the 3 Oncology Hospitals.

- Physicians and nurses from the Medical Oncology Department (Oncologists, Internists, Anesthesiologists)
- Nurses from the Chemotherapy Unit
- Epidemiologists
- Medical Director of the Oncology Hospital / Oncology Departmen
- Pharmacists
- Heads of Quality Department
- Administrative staff: Head of drug purchase

• **Results:** One out of the three Oncology hospitals trained on Pharmacovigilance has already implemented a Pharmacovigilance Department.

P133. Adverse Drug Reactions Detected During Anesthesia Time by Anesthetics and Other Drugs in Mexican Patients at Regional Public Hospital

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Introduction: Many anesthetics and other kind of drugs are used during the surgeries.[1] Several adverse drug reactions (ADRs) are presented during trans-anesthesia period.[2,3] Nevertheless, these are not reported and they are sub estimated. In Mexico, we have not the culture to report these reactions. There are not reports to reveal these data, so we do not know the most frequent drug and kind of reactions developed by ADRs. In Mexico, to classify and evaluate ADRs we have to use the NOM-220 which represents the Mexican norms of Pharmacovigilance.[4]

Aim: To collect all ADRs by spontaneous notification in operating room during trans-anesthesia period, during 2008 to 2011 period, to evaluate and to classified this, according to NOM-220.

Methods: We performed a prospective observational study of ADRs reported by spontaneous notification at operating room at O.P.D Hospital Civil ''Dr. Juan I. Menchaca'' during anesthetic time. The study was realized during October 2008 to December 2010. All data were collected by SSA-03-021 formatand each one was evaluated by Naranjo's Algorithm to classify them. Sex and age were registered too. These reports were sent to Secretaría de Salud (SSA) to be evaluated and registered it at National data base for ADRs.

Results: Doses employed to each drug were according to literature. 62 ADRs were collected. These ADRs were produced by atracurium 31%, propofol 17%, fentanyl 6%, midazolam 6% and the rest by others. ADR most frequent was RASH (generalized or cutaneous). The rest of them were classified as probable ADR. According to literature of ADRs of anesthetic and similar drugs found, our percentages are highest to those.[5]

Conclusions: Even that this study not shows the incidence or ADRs during operating time, this is the first study in Mexico to reveal the principal drugs involved in ADRs in this area and its main signs. The use of several drugs at the same time could be involved as a risk factor to develop ADRs as well as the way they are administrated so, it could be an opportunity to evaluated it and may be to normalizing speed infusion of drugs as well to improved research in this area within Mexican population.

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P134. Results of a Pregnancy Registry with Interferon Beta 1a and Challenges Faced for the Comparator

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Biogen Idec

Background: The onset of multiple sclerosis (MS) typically occurs between the ages of 20 and 40 years, often affecting women during their reproductive years. The high prevalence of MS in women during their

reproductive years means that use of disease-modifying therapies (DMTs) is likely to be widespread among women of childbearing potential. A formal pregnancy registry was established in the United States to prospectively evaluate the effects of intramuscular interferon beta-1a (IM IFN beta-1a) on pregnancy outcomes. This registry has been completed.
In addition to the results of this registry, the questions and challenges faced for a comparator will be reviewed.
Objective: Analyze prospective pregnancy outcomes in women with MS who were exposed to IM IFN beta-1a within approximately 1 week of conception or during the first trimester of pregnancy.
Methods: The AVONEX Pregnancy Exposure Registry was a prospective observational pregnancy registry conducted in the United States. Information on IM IFN beta-1a exposure, potential confounding factors (eg, medical and gestational history, other medications, smoking, and/or alcohol use), and pregnancy outcomes was collected at registration (baseline), 4-5 months of pregnancy, and 8-12 weeks post partum (paediatric follow-up) in order to detect any evidence of teratogenic effects or increased risk of spontaneous loss in pregnancies exposed to IM IFN beta-1a.
Results: At registry completion, there were 302 evaluable pregnant women and 306 evaluable outcomes. Of the 306 outcomes, which included 4 sets of twins counted separately, there were 272 live births, 28 spontaneous abortions, 5 induced abortions, and 1 stillbirth. The rate of spontaneous abortions in women who enrolled prior to 22 weeks of gestation was 10.5% (28 of 266 evaluable pregnancies; 95% confidence interval, 7.2%-15.0%). Birth defects (cases with at least 1 major defect) were reported in 17 of 306 known outcomes.
Conclusions: The AVONEX Pregnancy Exposure Registry is the largest prospective registry for IM IFN beta-1a to date. The spontaneous abortion rate observed in the registry is consistent with the 15% spontaneous abortion rate in the US general population. No patterns suggesting an unusual distribution of defects were observed and no specific signals of concern were found. The long-term impact of MS therapy on birth outcomes is important to understand and should be taken into consideration when making risk/benefit assessments and treatment decisions.

References

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P135. Video of Puppet Theatre as an Educational Training into the Hospital to Improve ADR Reports and to Promote Patient's Security

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Introduction: The most common way to teach pharmacovigilance to the health team at hospitals is through conferences or intensive courses, but in underdeveloped countries as México, the assistance for this is too poor. In our Hospital, as Hospitalary Pharmacists at our working day (on weekends), we presented 4 conferences and we had only 14 assistances so, we detected to necessity to change the way to teach it. Therefore, we created a puppet theatre on this topic and then we saw the necessity to spread this important information many times so it was important to create this video.
Aim: To develop a video with Puppet Theatre as a way to teach pharmacovigilance into health team as well as to spread several skills to improved the security during patient's attention.
Methods: To recruit all necessary to created personages, scenography, etc. was the first step; most of the materials were recycled. Each figure was created, as well as the libretto, scenography and audio was developed. Personages were: a patient, a nurse, a doctor, a pharmacist and others. The libretto included pharmacovigilance history, how nurses or doctors could report adverse drug reactions and different tools to improve the security during patient's attention. Pictures were included as part of this one to present each personage at the last time.
Results: Our first goal was to develop a puppet theatre and start with some representations, later, was to practice these representations to improve the quality. Then, video was film with and it was the main result. Duration time to video is 10 minutes. It includes some comedian phases but much important information too.
Conclusions: Our next step will be to spread this video into the different areas at our Hospital including all journals work and to establish the guidelines to measure the impact of this video. Then, will be to project it by Secretaría de Salud (the most important health organism in México) and SICalidad (Federal Mexican program to increase the quality in health's services). This video will be used to training most of the health team in different cities and it could be a basic tool to promote pharmacovigilance culture and its importance.

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P136. Implementation of a Pharmaceutical Care for Pediatric Patients with Congenital Heart Disease and Hospital Acquired American Children Cardiological

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Introduction: The method Dáder was designed by the University of Granada in Spain, the first consensus emerging in the year 1998, which defined the problems related to drugs in 2002, makes a second consensus and in 2007 performed an update which redefines and expands the concept of Drug Related Problems (DRP) in the third consensus of Granada Negative Outcomes of Medication (MRI).[1,2]
Aim: The main objective of this study was to implement a pharmaceutical care program targeting pediatric patients with congenital and acquired heart disease in Latin American Children's Cardiological Hospital ''Dr. Gilberto Rodríguez Ochoa''
Methods: Was used Dáder methodology based on the detection, prevention and resolution of MRI.
Results: We proceeded to perform Pharmacotherapy follow (SFT) to 303 pediatric patients who participated in the study of whom 130 patients (42.90%) were female and 173 male (51.09%) comprising ages zero days to 18 years. Receiving drug therapy was mostly greater than or equal to five drugs of which are necessary MRI identified 14 (17.5%), 13 MRI of effectiveness (16.25%) and 53 of Security (with 27

of quantitative safety (33.75%) for a total of 80 MR. All cases were mild except for one serious transcended in death. The main drugs involved were those of the cardiovascular group (C) with 57.89% of total drug and NMR were in all cases interventions were accepted by 100%.
Conclusions: Interventions were made after the SFT which allowed greater control over the pharmacotherapy of patients appreciating the pharmaceutical profession to join the health team actively.

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P137. Study of Adverse Drug Dermatological Associates in Two Hospitals of Capital Region

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Introduction: Studies worldwide show that adverse drug reactions (ADRs) are one of the frequent causes of admission in hospitals, with skin reactions which have a higher incidence of occurrence, which in turn is associated with a high percentage mortality (30%).[1-3]
Aim: To study of adverse drug dermatological associates in two hospitals of capital region.
Methods: We performed a prospective study of 3 months for determine the incidence and direct costs associated with treating dermatological ADRs at the University Hospital of Caracas and the Carlos Arvelo Military Hospital. In the first phase of the study was the literature review which was drawn up information material on dermatological ADRs delivered in the talks held in the second phase, finally in the third stage the results were tabulated and made the conclusions and recommendations.
Results: The total of 26 reports was found, only the Military Hospital, as at the University Hospital there was no report. We obtained the same number of reports for female and male patients (13 reports), being the age group between 18 and 55 years presented the highest number of RAMs (16 reports).The anti-infective produced the highest number of RAMs with 6 reports (23.1%), then anti-inflammatory 5 reports (19.2%), followed by corticosteroids with 4 reports (15.4%). The most reported ADRs were erythema (7 reports), followed by reaction acneiform (4 reports) and erythroderma (3 reports). Direct costs associated with the resolution of the ADRs were variable, the least expensive was the acneiform eruption that cost $68.06 and the most expensive, erythema multiforme which reached $2615.44.
Conclusions: The reporting of ADRs is not common practice in health professionals, creating a sub-registration. It is necessary to have constant promotional strategies that promote voluntary reporting and decision making in the health sector in Venezuela.

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P138. Identification and Resolution of Drug-Related Problems (DRPs) in Respiratory Medicine Patients at a Tertiary Care Hospital

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Background: Present study addresses the drug related problems and needs of the study patients. There are no studies or data available on drug related problems and needs among Kashmiri population and the concept of rational use of medicines is yet to take off in any of our healthcare facilities. None of the hospitals in the entire state of J&K has any Drugs and Therapeutics Committee, Drug Information Centre, Hospital Drug Management Policy, Standard Treatment Guidelines, Standard Hospital Formulary, Management Information Systems for drug store management and inventory control, scientific drug distribution mechanism or Pharmaceutical Care Clinics.
Objectives: Identification, resolution and prevention of drug related problems and optimization of therapy outcomes.
Study Design: Prospective, interventional, cohort study.
Setting: Medication review in all respiratory medicine patients.
Study Population: A total of 182 patients of all age groups, of which 121 (66.48%) were males and 61 (33.51%) were females, with respiratory disorders admitted to the Internal and Pulmonary Medicine ward of a tertiary care hospital over a period of six months.
Methods: Medication use data was collected and reviewed by the pharmacy practitioner. Drug-related needs and problems of patients were assessed. Pharmaceutical care plans were formulated and medication interventions proposed.
Outcome Measures: Drug-related problems/needs, interventions, therapy outcomes.
Results: A total of 388 Drug Therapy Related Problems/Pharmaceutical Care issues with an average of 2.29 DRPs per patient were identified and a total of 233 interventions were made, besides imparting patient education and counselling to 177 patients. Pharmaceutical Care Services offered to the study patients proved beneficial in terms of better patient compliance, their improved health-related quality of life, optimized therapeutic outcomes.
Conclusions: Identification and resolution of drug-related problems (DRPs) in respiratory medicine patients has proved to be fruitful in all respects among the study patients. There is need to replicate this study to all other wards of the tertiary care hospital for the benefit of patients.

P139. Tools Development for Vigilance Process in Community Pharmacy

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Introduction: The FDA has expanded vigilance network to pharmacies for the reason of risks early detection in community. However, almost pharmacies have limited knowledge on vigilance system, and also the basic tools for them. If the pharmacies have been supported on effective vigilance tools, they will be one of risks detection sectors which be network of Health Product Vigilance Center inThailand.
Aim: To develop vigilance tools for pharmacy.
Methods: We developed the tools by combining concept of hospital's ADRs monitoring and Good Pharmacy Practice sharing experiences

among experts from Thai FDA, The Community Pharmacy Association, Faculty of Pharmaceutical Sciences, Chulalongkorn University, and pharmacists, and feasibility issues were identified in collaboration with a large work setting.

Results: Vigilance tools were identified to 4 parts; 1) guideline), 2) training), 3) committee, and 4) reporting.There are 5 topics in the guideline; introduction to an important of pharmacovigilance, risks in focus, risk management, irrational drug use, How to submit reports. Training course was organizes for pharmacists, 50% of targeted group had participated with fruitful recommendations. For sustainable development of pharmacy vigilance, the committee will set up the annual plan and regular meetings. A month after reporting-guideline was implemented in pharmacies, 6 reports from 2 pharmacies were received by Health Products Vigilance Center (HPVC). Of these, were classified to 3 drug groups; genito urinary system and sex hormone, central nervous system, and general antiifectives, which ADRs were atrial flutter, abdominal pain, and rash.

Conclusions: These finding suggest that the system's tools; guideline should be used widely, and regular reviewed. Training courses are expected to organize by FDA for better quality and quantity reports. Furthermore, any modern communication tools and social networks will be used to promote and higher reach new targeted pharmacies. The monthly committee meeting should be held. Finally, the vigilance tools should be continuing evaluated and developed for widely use in community pharmacy.

P140. Patient Reporting of Adverse Drug Reactions; Experience of Toulouse Regional Pharmacovigilance Center

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Introduction: In 2011, patients could report adverse drug reactions (ADRs) in almost fifty countries worldwide.[1] In France, patient reporting of ADRs was legalized in June 2011. The main objective of the study was to quantify and to describe the characteristics of ADRs reports transmitted by patients to Toulouse Regional PharmacoVigilance Center (RPVC) in 2011. The secondary objective was to compare the characteristics of patients' ADRs reports to those from health professionals.

Methods: We analyzed patients' ADRs reports received at Toulouse RPVC during 2011 and we compared their characteristics to those from general practitioners (GP) and pharmacists received at the RPVC during the same period. We excluded notifications corresponding to benfluorex since specific procedures were implemented by Regulatory Authorities for this drug.

Results: During 2011, Toulouse RPVC received a total of 23 ADR reports from patients, 153 from GP and 122 from pharmacists. There was a significant increase of patients' ADR reports after June 2011 (3.6 versus 0.4 ADR reports per month; $p = 0.02$). Most of the patients' ADR reports were sent by patient himself (76%) and were medically confirmed (78%). Whatever the group of reporters, the average age of the person who experimented the ADR was about fifty years and there was a slight prevalence of females. Patients' ADR reports were more serious than those from GP and pharmacists (78% of serious ADRs for patients' reports versus respectively 38% and 28% for GP and pharmacists; $p = 3.4.10^{-7}$). Evolution of the ADR in patients' reports was more often represented by a ''patient not yet recovered'' compared to those from health professionals, associated mainly with a ''recovery without sequelae''. Whatever the type of reporter, about thirty percent of ADRs were ''unexpected''. Patients' reports seemed to be more often associated with ''musculo-skeletal'', ''nervous system'' and ''psychiatric'' affections than health professionals ones, whereas there was no difference for suspected drugs. Lastly, in 52% of patients' ADR reports, suspected drugs had been the subject of warnings by medias because of their ADRs.

Conclusion: Most of the ADRs reported by patients were ''serious'' and medically confirmed, ''unexpected'' for 30% of them. This study suggests that patients' ADR reports could contribute to a better evaluation of drugs safety profile.

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P141. Adverse Drug Reactions Reported for Children: What are the Differences Between the FDA AERS and the WHO-UMC VigiBase?

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Introduction: Information on the safety of drugs used in children is crucial but so far existing and readily available datasources from spontaneous reporting databases as AERS (FDA), VAERS (FDA/CDC) and VigiBase (WHO-UMC) are under-used. Recently, WHO-UMC published a seminal paper on the characteristics of reports within VigiBase.[1] Little is known on the content with respect to paediatric reports in AERS and whether there are any similarities and differences between the different ADR-databases. Knowledge on these characteristics is important to choose the most optimal source for specific research questions.

Within the GRiP network (Global Research in Paediatrics-Network of Excellence) we aim to implement an infrastructure to stimulate and facilitate the development and safe use of medicine in children.

Aim: To study the characteristics of paediatric ICSRs (individual case safety reports) within AERS in comparison with paediatric reports within VigiBase.

Methods: Characteristics of paediatric ICSRs within VigiBase were derived from the recently published paper by Star et al. [period 1968-Feb 2010].

AERS-data was downloaded from the FDA-website for the period Jan 2004-Dec 2011. From the ICSRs, the non-vaccine related reports on children (0–18 yrs) were selected. To control for duplicate reporting, each unique ICSR was only included once.

Characteristics of the reports, including the reported drugs and events, were described and stratified by age-groups.

Table I. Top 3 reported drugs and ADRs within AERS by age groups (relates to abstract no. P141).

Age 0–27 days	Age 28 days–23 months	Age 2–11 years	Age 12–17 years
Reported drugs			
Zidovudine (2.9%)	Palivizumab (3.3%)	Atomoxetine (4.9%)	Isotretinoin (3.4%)
Vitamines (2.1%)	Paracetamol, combinations (3.0%)	Methylphenidate (2.1%)	Atomoxetine (2.4%)
Ampicillin (1.6%)	Ibuprofen (1.6%)	Paracetamol (1.7%)	Methylphenidate (2.1%)
Reported ADRs			
Drug exposure during pregnancy (6.3%)	Pyrexia (1.8%)	Vomiting (1.6%)	Vomiting (1.3%)
Premature baby (2.6%)	Vomiting (1.8%)	Pyrexia (1.4%)	Headache (1.2%)
Maternal drugs affecting foetus (2.3%)	Convulsion (1.5%)	Drug ineffective (1.4%)	Nausea (1.1%)

Results: From AERS we included a total of 106 122 paediatric ICSRs (55% boys) (58% from the US) with a median of 1 drug [range 0–157] and 3 events [1–94] per ICSR. Mean age was 9.1 years. 90% was submitted through expedited (15 days) (65%) or periodic reporting (25%) and 10% by non-manufacturers. In comparison with VigiBase, which included 3 472 183 reports (53% boys) (39% from US), reporters in AERS were more often consumers (25 vs 4%) and less often physicians (32 vs 55%). Most commonly reported drug classes in AERS were 'Neurological' (58%), 'Antineoplastic' (32%) and 'Anti-infectives' (25%) versus 'Anti-infectives' (33%), 'Neurological' (29%) and 'Dermatological' (12%) in VigiBase. Most commonly reported SOCs were 'General' (13%), 'Nervous system' (12%) and 'Psychiatric' (11%) for AERS and 'Skin' (35%), 'General' (20%) and 'Nervous system' (19%) for VigiBase. Most frequent reported drugs and ADRs by age-groups are presented in table I.

Conclusions: In comparison with VigiBase, in AERS there are more ICSRs reported for neurological and antineoplastic drugs. This might be explained by the large proportion of study-reports in AERS or be biased due to different study-periods.

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P142. The Use of Complementary and Alternative Drugs by Cancer Patients

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Background: The use of complementary and alternative medicines (CAMs) has been enlarging worldwide and has been increasing between healthcare consumers, patients, and health professionals that are becoming an important segment of adepts of these techniques.[1-5] These therapies involve different approaches such as acupuncture, herbal and dietary medicines and mind and body techniques as meditation and yoga.[1] It is estimated that in the United Kingdom a quarter of total population uses CAMs, while in Germany, France or Australia, this value increases up to half of the population.[6] Portuguese patients follow European and American tendencies and the number of patients searching for alternatives to conventional medicines is growing, especially among cancer patients. CAMs are used to control disease or to manage symptoms associated to cancer or cancer treatments.[2-6] It is important for health professionals to be alert on the use of CAMs by patients due to its possible interactions with anticancer drugs.[2,5]

Objective: Study aimed to review information available in order to identify the medicinal plants most used by cancer patients and to collect information about their risk of adverse events when taken concomitantly with the different types of medication on cancer treatments.

Methods: We conducted a search in PubMed database with the terms "cancer" AND "herbal medicines" and articles found were chosen based on relevance of title for the importance of herb-drug interactions in cancer patients.

Results: Review revealed a high prevalence of use of CAMs between cancer patients and their difficult to admit it to their physicians. Several studies showed an elevated number of herb-drug interaction. This alerts to the fact that the use of herbal medicines along with anticancer drugs should be avoided, or at least divulged to health professionals in order to find what possible interactions can be establish. In Portugal herbal medicines are sold freely under the range of dietary supplements. Some studies developed in Portugal demonstrated that due to lack of specific regulation for this type of products, the adverse effects associated to each product and possible interactions with other medicines, as long as poor information by suppliers to consumers, could be considered a public health problem, namely to cancer patients.

Conclusion: Results are an evidence for the importance of the knowledge about complementary and alternative medicines used by cancer patients and to assess healthcare professionals' familiarity and attitudes towards its use by patients.

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P143. Quality of Adverse Drug Reaction Reports: An Algorithm (QADRA) to Reappraise the Efficiency of Spontaneous Reporting Systems in Pharmacovigilance

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Background: The quality of an ADR report is usually based on its seriousness.[2] Variables other than seriousness, such as the notoriety and the plausibility, should be considered for the quality of an ADR report.[2]

Aim: To create and validate an algorithm for the evaluation of the quality of ADR case reports.

Methods: The present algorithm has been developed on the basis of the following quality criteria: causality, notoriety, clinical relevance and completeness. A random sample has been selected from the overall number reports of ADR recorded in the Italian national database during 2009 (n = 15 906). Assuming that p of ''good quality'' reports in the source population was 30%, it was estimated a sample size of 153 reports which would have allowed a 0.05 type I error with a power of 80%, given an alternative proportion (p) of 0.2. Each report has been evaluated by two panels of experts blinded one another and towards the study question. The cases had to be classified as ''good quality'' or ''poor quality'' on the basis of clinical introspection. The final assessment constituted the ''gold standard'' to validate the algorithm. Afterwards, to inspect the predictive ability of our score, receiver operator characteristic (ROC) curves were constructed, and areas under the curve (AUC) were calculated along with sensitivity and specificity values. The most discriminative cut-offs were therefore identified to categorize the score into ''high'', ''intermediate'' and ''low'' quality.

Results: The two panels assessed 21.6% of reports as having ''high'' quality. For what concerns the QADRA score (score range 0–15), its median value was equal to 6 (4–7, 25 and 75 centile, respectively). The area under the ROC curve was 0.93 (95% CI: 0.88-0.97). Herein, the cut-off points <6, from 6 to 7 and >= 8 indicated the best balance between sensitivity and specificity, and they could be used to categorize reports as 'high', 'intermediate' and 'low' quality (AUC = 0.87; 95% CI: 0.80–0.92), respectively.

Conclusion: The present algorithm has shown to be a good predictive tool of the quality of a single ADR report. Several application of our algorithm should be investigated in the future, both for scientific purposes and healthcare system management. Although further validation analyses are required, our algorithm can be currently proposed as the most complete tool to assess the quality of a single ADR report in pharmacovigilance.

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P144. Acute Hepatitis Caused by Green Tea Infusion: A Case Report

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Background: The consumption of tea originated in Asia thousands of years ago and was introduced progressively all around the world. Tea is obtained from the leaves of *Camellia sinensis*. The green tea is obtained by an unfermented process and the main chemical components are polyphenols, particularly epigallocatechin gallate (EGCG) and epicatechin gallate.[1] In the literature there are some reports of adverse hepatic reaction associated to green tea.[1,2]

Aim: To describe and discuss a case of acute hepatitis caused by the use of green tea infusion.

Methods: During a case-control study on hepatic failure we selected the present case and collected patient additional data. The presence of heavy metals in the used tea infusions was performed using an inductively coupled-plasma mass spectrometry.

Results: A woman went to the Emergency Room for abdominal pain and nausea; the blood check showed ALT level 780 U/L and total bilirubin level 1.15 mg/dL. The abdominal echography and other blood parameters were normal. Every day over the previous 9 months the patient drank two or three cups of several brands of green tea infusions and she stopped this behavior when abdominal pain was persistent. Her medical history did not report the use of drugs or toxic products. Markers for HBV and HCV were negative. She was hospitalized because of the persistent high levels of liver function tests; ANA, ENA, ASMA, AMA, LKM were negative. Liver biopsy described a ''drug toxic damage''. After four months of stopping the use of green tea infusions, the liver function tests were normalized. The presence of heavy metals in tea infusion cannot justify the observed liver toxicity in our patient.

Conclusions: In the literature there are some cases similar to this one.[1,2] The hypothesis is that may be a correlation between the catechins contained in green tea and hepatotoxic effects even if actually there isn't no particular evidence of this because these products are sometimes misused and they also may be contaminated. The mechanism of hepatotoxicity of green tea is unknown. In some animal studies it was found that high concentrations of green tea extract induce acute toxicity in the liver cells of rats and in particular high doses of EGCG can be associated with hepatic necrosis in rats. However, considering that the concentration achieved in humans by these metabolites is probably low, it is conceivable that the mechanism of damage is idiosyncratic-metabolic or allergic.[1,2]

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P145. Adverse Reactions of Statin Drugs: Reported from Thailand Surveillance System

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Introduction: Statin is a class of prescription drugs for reducing blood levels of low-density lipoprotein. It is known that this drugs group has

Table I.

System Organ Class	Total (%)
Skin and appendages disorders	3075 (42.19)
Body as a whole – general disorders	1321 (18.12)
Musculo-skeletal system disorders	855 (1.16)
Cardiovascular disorders, general	620 (8.50)
Central & peripheral nervous system disorders	509 (6.90)

had the serious risks in many system organ classes. Recently, the US FDA has recommended for new additional information, including adverse reactions in serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment. New warnings are also stated to drug interactions of statin and protease inhibitors drugs group with hyperglycemic effects and serious events to patients. The central nervous system disorders are also known to be aware of using these drugs. The review of those adverse events followed by system organ class will reveal the adverse events of statin in Thai patients. The monitoring in specific drugs group or doing risk management for surveillance system in country would be developed.

Objective: This study aims to ascertain adverse reactions in statin drugs, by system organ class. The adverse event from statin drugs were reviewed until year 2011.

Methods: Descriptive study was done for studying the characteristic of adverse reactions. The source of information is from Thai Vigibase (the national adverse reactions database) at the specific time of the study. The characteristic of adverse events were analyzed.

Results: A total number of 7288 reports with statin drugs-adverse events were analyzed. Simvastatin was the most drugs reported in statin group. The adverse events were mostly from skin and appendage disorders (42.19%). 103 reports of liver and biliary system disorders were reported. 3.68% of these were serious. Hepatitis was the most serious adverse reactions from liver and biliary system disorders (6.26%). In metabolic and nutritional disorders, oedema adverse events were most reported. The three most adverse events from central nervous system were dizziness, headache and vertigo. As from the quality of reports as World Health Organization criteria, 67.46% were grade 2. The provision information of those adverse events have been proposed for amendment in Thailand for risk management of statin drugs group.

Conclusions: Skin and appendages disorders were the most serious adverse events reported in Thai patients. Hepatitis was the most serious adverse reactions from liver disorders, some of these led to hospitalization and fatal outcome.

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P146. Can the EU-ADR Database Network Detect Drug Safety Signals Faster than Spontaneous Reporting System?

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Background: Several ongoing initiatives are exploring if mining electronic health records (EHRs) may fasten the process of drug safety signal detection. We investigated if the signal concerning rofecoxib and acute myocardial infarction could have been identified in EU-ADR database network faster than spontaneous reporting system (SRS), and earlier than rofecoxib withdrawal (30th September 2004).

Methods: EU-ADR distributed network comprises of seven EHR databases covering approximately a population of almost 30 million persons from four European Countries during the years 1996–2010. Harmonized data extraction and analysis has been conducted in all databases through custom-built software Jerboa, which allows for data aggregation and elaboration while databases remained locally. A signal was defined as statistically significant (p-value <0.05) and at least two-fold increase in the risk for AMI with rofecoxib, as compared to all the other drugs, using Longitudinal Gamma Poission Shrinkage. Concerning spontaneous reporting system, FDA AERS database and as EB05 = 2 as threshold for signal detection have been considered. Stratifying by consecutive quadrimestre till rofecoxib withdrawal, we measured the first point in time in which signal concerning rofecoxib and AMI would have been identified in EU-ADR network and FDA-AERS. On average, one year time gap should be also considered for data transferring in EU-ADR network.

Results: A total of 685 cases exposed to rofecoxib were captured in EU-ADR network during the years 2000–2004. Since the third quadrimestre of 2000, EU-ADR network would have been able to identify a strong signal concerning rofecoxib and AMI as 847 609 person-days of exposure to this drug was available. In the same quadrimestre a Relative Risk = 4.46 (95% Confidence Interval: 2.84-6.72) was found. With respect to FDA database a strong signal could not be identified. The number of reports of AMI due to rofecoxib increased substantially after the drug withdrawal as a results of lawyers reporting.

Discussion: The use of a system such as EU-ADR could have led to a faster rofecoxib removal from the market. In general, these systems may be helpful in the strengthening of signals identified using other sources.

Conclusions: EU-ADR database network would have been able to detect a strong signal concerning rofecoxib and acute myocardial infarction around three years earlier than rofecoxib withdrawal and faster than SRS. System such as EU-ADR may be a valid tool for signal strengthening concerning events such as acute myocardial infarction.

P147. What is the Additional Contribution of Mining Electronic Medical Records for Signal Detection? The Experience of EU-ADR Project

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Background: In the last ten years, data mining methodologies have been developed using spontaneous reporting system (SRS) databases for drug safety signal detection. Due to challenges associated with

SRS, more recently, the possible contribution of mining electronic health records (EHR) for signal detection has been explored.
Objective: To compare retrospectively sensitivity and specificity as well as agreement rate of signal detection concerning 10 events in the EU-ADR database network vs FDA-AERS database.
Methods: EU-ADR network comprises of seven databases from four European Countries covering a population of almost 30 million persons. A set of 10 events (e.g. acute myocardial infarction and acute liver injury) warranting priority for monitoring in pharmacovigilance were inspected for their association with drugs captured in EU-ADR and FDA-AERS. In EU-ADR, drugs with statistically significantly ($p < 0.05$) increased RR (≥2, and ≥1.5 in a sensitivity analysis) were identified as potential signals. In SRS, threshold of EB05>2 was used. To evaluate sensitivity/specificity of the systems, a reference standard was created by selecting for each event 5 drugs being positively and 5 being negatively associated. Moreover, agreement rate between the two system concerning signal detection related to 541 drugs was evaluated.
Results: The detection of known drug-event associations in the EU-ADR system varied based on the nature of the events (e.g. 20% for AMI and 80% for UGIB) and increased substantially if the analyses was restricted to the period preceding first regulatory action (from 20% to 80% for AMI). Across all ten events, EU-ADR and SRS reported respectively a sensitivity = 45% and 77% and a specificity = 96.0% and 97.1%.
Sensitivity and specificity of EU-ADR were respectively 72.1% and 82.0% when considering RR≥1.5 as threshold. Looking at the list of 541 drugs, the agreement rate was 66.6% but changed across the events. EU-ADR detected more signals concerning events with high frequency in general population (e.g. AMI, UGIB).
Discussion: Mining of electronic medical records is an alternative option for drug safety signal detection and may contribute to complement/strengthen traditional pharmacovigilance methods, especially concerning events with high frequency in general population and not commonly reported as drug-induced.
Conclusions: Detection of signals in EHR may change across different types of adverse events and is influenced by the effect of regulatory actions aimed at risk minimization, once the signal is discovered.

P148. Safety of L-Asparaginase in a Child Cohort with Acute Lymphoblastic Leukaemia

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Introduction: L-Asparaginase is an universal component of therapy for childhood acute lymphoblastic leukaemia (ALL) since the 1970s. Three formulations of L-Asparaginase, derived from different bacterial sources, are available. Most of the commonly used asparaginase preparations are derived from *Escherichia coli* (Kidrolase®). *Erwinia chrysanthemi* asparaginase (Erwinase®) derived from *Erwinia chrysanthemi*. Erwinase® is an alternative preparation antigenically distinct from *Escherichia coli* asparaginase. Furthermore, polyethyleneglycosylated (PEG) asparaginase (Oncaspar®) is formed by convalently attaching polyethylene glycol to the native *Escherichia coli* asparaginase.
Aim: To evaluate the safety of L-asparaginase in a children cohort with ALL.
Methods: From 1st January 2008 to 31st December 2011, all children (aged 1–18 years) with newly diagnosed ALL, treated by *Escherichia coli* asparaginase were included in this study. All side effects were systematically collected from medical patient file.
In first line, therapy was started with *Escherichia coli* asparaginase preparation. If an adverse drug reaction (ADR) occurred with *Escherichia coli* asparaginase, *Erwinia chrysanthemi* asparaginase was substituted. Patients who experienced an allergic event while receiving *Erwinia chrysanthemi* asparaginase were then switched to PEG asparaginase.
Results: Forty-seven patients included in this study were treated by *Escherichia coli* asparaginase. Twenty-six of these patients (55%), six years old on average, presented at least one ADR to *Escherichia coli* asparaginase. Thirty ADR were reported. Twenty-three patients developed an allergic reaction, one an allergic reaction and hepatic cytolysis, one antithrombin-3 deficiency, one laryngeal oedema and lip swelling, one abdominal pain and one cerebral venous thrombisis. Twenty-four ADR were serious.
Twenty-one patients were switched to *Erwinia chrysanthemi* asparaginase. One patient, aged four years, experienced allergic reaction to *Erwinia chrysanthemi* asparaginase. This ADR was serious.
Three patients were switched to PEG asparaginase. One after allergic reaction to *Erwinia chrysanthemi* asparaginase, two after allergic reaction to *Escherichia coli* asparaginase. One patient, aged 15 years developed an allergic reaction and other patient, aged 10 years developed an acute pancreatitis. The two ADR were serious.
Conclusion: During therapy with intravenous form of *Escherichia coli* asparaginase, fifty-five per cent of children have presented an ADR. *Escherichia coli* asparaginase appears not well tolerated. A reassessment of the therapeutic regimen would be desirable.

P149. Congenital Toxoplasmosis and Pyrimethamine/Sulfadoxine Overdose: Still No Pediatric Formulation

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Introduction: Since the end of the fifties, the combination pyrimethamine (PYR)/sulfadoxine (SDX), FANSIDAR®, is used for the treatment of congenital Toxoplasma gondii infection to avoid serious complications like chorioretinitis. Currently pediatric forms are prepared from adult tablets.
Aim: To describe adverse effects occurred in a newborn due to misuse with overdose of PYR/SDX.
Case Report: A girl of 5 days old received a dose of 3.75 mg PYR and 75 mg SDX daily instead of once every 10 days. Her mother had reached term, the newborn was normal at birth. After a month of daily treatment combined with folinic acid, the drug delivery mistake was discovered, the treatment was stopped. The PYR/SDX plasmatic concentrations were 973 mcg/l and 290 mg/l, respectively. No clinical signs were observed. Blood test revealed anemia (9.5 g/dl), leukopenia (6.6 g/dl) and thrombocytemia (598 G/l). One week later, anemia increased (8.8 g/dl) associated with persistence of a leukopenia (8.3 G/l) and thrombocytemia (780 G/l). PYR and SDX blood level were 497 mcg/l and 114 mg/l respectively. After 3 weeks, plasmatic concentrations of PYR and SDX decreased to 241 mcg/l and 34 mg/l respectively, hematological disorders persisted. The treatment was reintroduced to adequate dosage.
Discussion: Congenital toxoplasmosis treatment commonly used to treat infected children is PYR 1.25 milligrams/kilogram plus SDX 25 mg/kg every 15 days combined with folinic acid 5 mg/week for 2 years. We report the case of an asymptomatic newborn who received

a dose equal to 15 times the recommended dose. There is no reference therapeutic range for PYR/SDX. The plasmatic concentrations above are the highest reported to date for a newborn.[1]

According to the WHO, in countries where the incidence of congenital toxoplasmosis is high, up to six newborn in 1000 can be infected at birth. However, pediatric galenic formulation is still lacking. Accidental overdoses have been already described with serious adverse effects including frequently seizures. Moreover, as in our case, they may be asymptomatic, which is falsely reassuring and can lead to underestimate the toxicity.

Conclusion: Pediatric formulation is needed for the treatment of congenital toxoplasmosis. Monitoring of blood counts should be done systematically in children under PYR/SDX. Pharmacological clarification on congenital toxoplasmosis treatment is necessary. Preparation of pediatric forms should be referred to hospital pharmacies.

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P150. Insulin Glargine and Risk of Death or Cancer: A Cohort Study in the French National Healthcare Insurance Database

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Background: A higher risk of cancer in insulin glargine (IG) than in human insulin (HI) users was suspected, and a study was performed to investigate this using the *Echantillon Généraliste de Bénéficiaires* (EGB) database. This suspected increased risk of cancer was not confirmed, however since increased mortality might hide an increased risk of cancer, the combined outcome of death or cancer was also studied.

Objective: To estimate the risk of death or cancer in IG than in HI type 2 diabetes users using the EGB database.

Methods: The EGB is a representative 1/97th permanent random sample of the national healthcare insurance system database that covers approximately 80% of the French population. It includes claims reimbursed since 2003 for approximately 600 000 beneficiaries.

The study population was all adults (≥18 years) with at least 2 dispensations of insulin between 1 January 2003 and 30 June 2010, without diagnosis of cancer at the time of first insulin dispensation, or death in the following month, and with no more than 1 year without claims. Four cohorts were defined according to incident or prevalent use and whether one insulin was used exclusively or predominantly (≥80% use time). Cox proportional hazards time-dependent models stratified on the propensity score quartiles for use of IG vs HI, and adjusted on insulin, biguanide and sulfonylurea possession ratios, were used to assess the risk of death or cancer.

Results: Exposures varied from 2273 to 614 patient-years for incident exclusive IG or HI users respectively, and from 3125 to 2341 patient-years for all predominant IG or HI users. Adjusted HR for death or cancer associated with IG compared to HI was: 0.58 (95% CI: 0.32-1.06) for incident exclusive users, 0.63 (95% CI: 0.36-1.07) for incident predominant users, 0.56 (95% CI: 0.33-0.95) for prevalent exclusive users, and 0.56 (95% CI: 0.36-0.87) for prevalent predominant users.

Conclusions: There was no increased risk of death or cancer in type 2 diabetic users of IG compared to users of HI. However, the risk was statistically decreased by about half in prevalent IG users, a finding that warrants further exploration.

P151. Adverse Drug Reactions to Antibiotics in the DRC Pharmacovigilance System

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Background: Antibiotics need to be uses only in bacterial infections. They are cited among the most widely used drugs of all in developing countries where high are found rates of infections like in DRC. Antibiotics are supposed to act on the bacteria, leaving the patient's organism safe. But they induce some effects on the patients some of which are ADRs and can be serious. Monitoring their adverse drug reactions is therefore of paramount importance.

Objective: To determine the frequency, types, severity of adverse reactions to antibiotics reported to the DRC National Pharmacovigilance Center.

Méthods: All individual Case Safety reports (ICR) related to antibiotics committed in Vigibase by the DRC National PV Centre in 2010 and 2011 were extracted as excel files and analyzed. ADRs were classified according to the WHO-ART.

Résults: A part from the ACSR of Polio vaccine and of NECT collected during special occasions, 344 ICSR were collected on regular reporting from health care providers. Of these ICSR, 55 (16%) were related to antibiotics. Of the 55 patients, 32 were female, 23 male. This may be reflecting the fact that female sex is considered as a risk factor for ADRs.

The most incriminated group was beta lactams (penicillins and cephalosporin) (34%) followed by sulfonamides (29%) and quinolones (13%). But the most incriminated antibiotic was cotrimoxazole, an association of a sulfonamide (sulfamethoxazole) and trimethoprim. Seventy five ADRs were observed (1.3 ADRs per antibiotic), 21 of them (28%) were serious. The reasons for seriousness were hospitalization (9 patients), life threatening, 4 patients and death (2 patients). For 6 patients the reason was "other". According to WHO-ART, Skin and Appendage disorders were the most frequent (47% of all ADRs), followed by general disorders and gastrointestinal system disorders (13%) each. Skin and appendages disorders were mainly represented by rash (34%), pruritus (17%), bullous eruption (11%), Epidermal Necrolysis represented 6% (2 cases) but were all fatal.

Conclusion: Antibiotics induce a wide range of ADRs, some of which may be serious and even fatal. Women seem to be more affected. Heathcare professionals should take this into account by avoiding unnecessary prescription of antibiotics, monitoring ADRs in all patients taking these drugs. Special attention needs to be paid for female patients. Most of these ADRs were immunoallergic and they can be avoided if the patient allergy is known.

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P152. Development of Minimum Criteria and Assessment of Sibutramine's Risk Minimization Plans

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Background: In October 2011, Resolution n. 52 was published withdrawing three anorexigens from Brazilian drug market: anphepramone, fenproporex, and mazindol. Based on benefit-risk assessment, sibutramine was not withdrawn but healthcare professionals were obligated to report AE associated to sibutramine as well as MAH should present risk management plans specific for the drug, among other actions.

Objective: To describe the development of criteria required for sibutramine's risk minimization plan and the assessment of these plans, performed by Pharmacovigilance Office (GFARM) at Anvisa.

Methods: First we performed a pre-assessment of all plans in order to create a baseline for the actions proposed by MAH. Criteria were discussed by GFARM's team, focused on sibutramine's risks, specially cardiovascular ones, and based on current Brazilian pharmacovigilance legislation (Resolution n. 4/09), guideline for risk minimization plan, and international references (FDA, EMA). Considering the criteria developed, we then assessed all 18 plans received and classified them according to number of criteria fulfilled.

Results: Six minimum criteria were developed, such as implantation of mechanisms for risk communication to physicians and patients and creation of an internal consulting board to discuss clinical aspects related to sibutramine use and to continuously evaluate changes in sibutramine's risk/benefit profile, among other actions. Checklist distribution for sibutramine prescribers was considered recommendable criterion. The categories according to the number of criteria fulfilled were: A – 5 to 6; B – 3 to 4; and C – 0 to 2. A From 18 plans received, none were classified in category A, 17 in B and 1 in C. Although the plan classified in category C has fulfilled less than 50% of minimum criteria, it was approved because it presented other risk minimization actions that were considered valuable, despite these were not listed as a criterion.

Conclusion: Risk minimization plan is an effective tool to control and monitor specific concerns related to drug adverse events. That is why national regulatory agencies (NRA) should be capable to perform suitable assessment of these documents. The method described here, based on all-data (and not on case-by-case) assessment proved to be fast and satisfactory for NRA which are starting to evaluate risk minimization plans. Although Anvisa has only started to assess risk minimization plans since 2010, the documents received for sibutramine containing drugs had a reasonable quality.

P153. Safety Profile of Aclasta Infusion: Experience of Adverse Events Reporting in Mexican Postmenopausal Women: Results of Year 2011

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Introduction: Aclasta® (Zoledronic acid), an inhibitor of osteoclast-mediated bone resorption, indicated as treatment for osteoporosis, is applied annually through an intravenous infusion to reduce the incidence of hip, vertebral and non-vertebral fractures and to increase bone mineral density. The Core Data Sheet (CDS) include as the adverse reactions more frequent: myalgia, arthralgia, fatigue, pain (*very common*), lethargy, dyspnea, dyspepsia, abdominal pain. musculoskeletal and joint stiffness, joint swelling, thirst, acute phase reaction (*common*) *and* uveitis (*uncommon*).

Table I. Distribution of AEs reported with Aclasta®

Musculoskeletal Disorders	87
General Disorders and Administration Site Conditions	14
Nervous System Disorders Disorders	6
Eye Disorders	5
Gastrointestinal Disorders	3
Metabolism and Nutrition	2
Skin and Subcutaneous Tissue Disorders	2
Infections and Infestations	2
Renal and Urinary Disorders	1
Respiratory, Thoracic and Mediastinal Disorders	1
Blood and Lymphatic System Disorders, Psychiatric Disorders, Ear and Labyrinth Disorders	0

Aim: To describe the safety profile of Aclasta® in Mexican postmenopausal women during 2011 from adverse events (AEs) reports received in Novartis Mexico.

Method: The Pharmacovigilance department of Novartis received reports of spontaneous adverse events reports of different sources (physicians, patients, marketing programs, clinical trials, literature reports). The search was done of the period of 01-Jan-2011 to 31-Dec-2011 with the following conditions: postmenopausal female, age over 50 years old, all reported events from all the sources. After this, the reports were grouped in to therapeutic areas (i.e. musculoskeletal, events of post infusion syndrome, etc). A frequency analysis was performed and finally we made a comparison with the information on the Aclasta CDS.

Results: During the mentioned period a total of 123 adverse events reports were received for the pharmacovigilance department, of this 28 (22.7%) were considered serious and 95 (77.2%) as non-serious. The 70.7% of the patients experienced some musculoskeletal disorders (myalgia, arthralgia, bone pain, pain in extremity), 16 were considered serious and 71 non-serious, the most of this symptoms were related to post-infusion syndrome which resolved quickly (4 or 5 days) after the infusion. The 11.4% (14 cases) of the patients experienced general disorders (very common: fever; common: flu-like symptoms, chills, fatigue, asthenia, pain, malaise) and administration site conditions. We received 2 cases of uveitis, (1.63%) were evaluated as related to treatment with Aclasta® by the treating physician (table I). In 2011, in México 18 474 units of Aclasta® were sold infusion and we received 123 adverse events with this data the reporting rate of AEs was: 0.0035 reports/10 000 sold units.

Conclusion: The reported events have been described as the expected in the CDS and during the study period no new adverse reactions were reported in Mexico. About the most frequently reported AE's (musculoskeletal), the 81.6% were mild or moderate and all this reactions are potentially preventable using NSAIDs and properly hydration, as stated in the CDS.

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P154. Hepatic Safety of Antibiotics in Paediatric Primary Care: A Case-Control Study Using Electronic Healthcare Databases

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Background: Antibiotics have been associated with hepatotoxicity[1,2] but the risk has not been quantified in the pediatric population.

Aim: To quantify the association between antibiotic use and hepatotoxicity in children and adolescents.

Methods: We performed a population-based case-control study combining three European electronic primary care databases over the years 2000–2008: The Integrated Primary Care Information database in the Netherlands, plus the PEDIANET and Health Search/CSD Longitudinal Patient Database in Italy. Cases of hepatotoxicity in the paediatric population.

Results: 1035 paediatric cases of hepatotoxicity were matched to 103 306 controls. Current use of antibiotics was associated with a 4-fold increased risk for hepatotoxicity compared to non-use [OR adj. 4.1 (95% CI, 3.2 to 5.3)]. Significant associations were found for current use of the following single agents: co-trimoxazole [OR adj 5.9 (2.3 to 15.1)]; rokitamycin (4.5, 1.4 to 15.0) and clarithromycin (3.2, 2.0 to 5.2) among macrolides; amoxicillin/clavulanic (2.6, 1.8 to 3.9) and amoxicillin (2.0, 1.3 to 3.1), among penicillins; and ceftriaxone (5.0, 2.0 to 12.7), cefuroxime (4.7, 1.4 to 15.2), ceftibuten (4.1, 1.8 to 9.4), cefpodoxime (3.6, 1.3 to 10.0), cefixime (3.5, 1.9 to 6.4) and cefaclor (2.7, 1.3 to 5.6), among cephalosporins. Except for rokitamycin, the associations remained significant when studying cases confirmed by specialist only.

Conclusion: This study provides risk estimates of hepatotoxicity in children and adolescents using antibiotics. Current use of co-trimoxazole, some cephalosporins and macrolides and amoxicillin with or without clavulanic acid in paediatrics is associated with an increased risk for hepatotoxicity.

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P155. Population-Based Healthcare Databases for Paediatric Studies: Early Results from the GRiP Network Global Survey

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Background: The available healthcare databases on infants, children, and adolescents are not adequately utilized to conduct post-authorization drug utilization and safety studies. The lack of a federation of healthcare databases restricted the capacity for meaningful investigations in these vulnerable populations.[1] Moreover, the lack of shared methodologies to specifically retrieve paediatric information hinders access to valuable information.

Objectives: One of the aims of the Global Research in Paediatric (GRiP) network (http://www.grip-network.org) is to identify and describe automated population-based healthcare databases that can provide medication and clinical information for paediatric pharmacoepidemiological researches on a global scale.

Methods: We performed a web-based survey among all databases that were identified through manual revision of the pharmacoepidemiology/pharmacovigilance conference abstracts, the Bridge.to.Data database or by direct knowledge of the members of the GRiP network. The survey included questions concerning: (i) contact information for database and responsible person; (ii) nature of database (possible linkage of drugs prescriptions and/or clinical data with population); (iii) demographic, clinical and drug/vaccine related data provided, and (iv) accessibility of the database for future collaboration in paediatric studies.

Results: Ninety-nine databases (in Europe, North and South America, in the Asian-Pacific area, and Africa) were invited to participate to a survey. So far, 15 answers were received, corresponding to a response rate of 15%. In total, 73% of the respondents (N = 11) accepted to collaborate with the GRiP network for future pharmacoepidemiology studies. The collaborating databases are located in 5 different European countries: Germany, United Kingdom, Denmark, Netherlands, and Italy, except for the MediGuard database that is available in more than 1 country. The data sources were set up between 1986 and 2007 providing around 16 million of total cumulative number of paediatric population (0–18 years). Eight databases capture outpatient records and 3 both, outpatient and inpatient data from primary care physicians and/or insurance claims. Both medication and clinical information are described in 10 databases. Patient-level linkage between drug prescription and clinical data is feasible for all databases.

Conclusions: The databases agreed to participate provide an enormous potential for paediatric pharmacoepidemiological studies. Those databases that failed to reply will be contacted in the coming months which hopefully results in participation from automated population-based healthcare databases in North and South America, in the Asian-Pacific area, and Africa. This initiative is important as large databases are needed for paediatric pharmacoepidemiology research in terms of power and long-term follow-up.

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P156. Paediatric Pharmacovigilance in Cuba

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In Cuba works an excellent National Pharmacovigilance System since 1996, which is one of the best within the Americas. The foundation of the system is based on spontaneous reporting of adverse drug reactions. Two have been the pillars of the effectiveness of this system in children at the community: the existence of family physicians with the presence of small centers of primary health care, located within the community, called consultorios, and at the hospital level: Pharmacotherapeutic committees focused on the management of drug safety. Previously in one province, Camagüey, where its work is oriented to know the performance of the system in relation to pharmacovigilance in children, it found a reporting rate of 634 reports per million children in 2008, much higher than previously reported in other countries, which was increased significantly to 2031 reports per million children in 2010, after implementing an education strategy on drug toxicity and pharmacovigilance to health professionals attending directly to children. The current work's areas of the pharmacovigilance system in children are focused on improving reporting rates, because it recognizes that it is still below that the real figures, and improve the clinical utility of the system.

P157. Update Analysis of the Adverse Events of Desvenlafaxine (PRISTIQ®) From 28 Jan 2009 to 31 May 2012 Received by the Drug Safety Unit Pfizer, Mexico

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Pfizer

Introduction: Desvenlafaxine succinate is registered and approved for treating major depressive disorders and vasomotor symptoms associated with menopause (VSM). This product is classified as a dual inhibitor of the reuptake of serotonin and norepinephrine.

PRISTIQ® (desvenlafaxine) was first registered on 29 February 2008 worldwide, while in Mexico it was on 28 January 2009. It is the only non-hormonal therapy that clinically shows efficacy and sometimes it's the only alternative for patients who have contraindications under hormonal therapy.

Mexico has reported 55 spontaneous adverse events (AE) for both indications. All the cases reported has had a proper follow-up according to internal procedure and on local regulations based on NOM-220-SSA1-2004 (Installation and Operation of Pharmacovigilance).

Aim: Analyze the different types, frequency, source of reports and actions taken of the adverse events reports with PRISTIQ from the birth date to 31 May 2012.

Methods: The analysis of the reports will be based on the data base of Pharmacovigilance of Pfizer, which includes all of Mexican Republic from 28 January 2009 to 31 May 2012.

The AEs will be correlated to the data base upon number of cases depending on the seriousness. Differentiate the AE according the indication prescribed as well as the source of notification or reporter (physician or consumer) and the action taken depending on the severity of the AE. And finally ''a pool'' of all of the AEs received according to the indication.

Results: The results showed that there are more non-serious AE reported. Regarding the indication prescribed, vasomotor symptoms associated with menopause have more related AE. In Mexico, it is more frequent that consumers report than physicians do. It is more common that patients withdraw the product as an action taken in response to the AE. And finally, for VSM the most frequent AE is constipation (16.7%) and fatigue (11.7%) and for depression is headache (17.6%) and anxiety (17.6%).

Conclusions: The results reported during this period confirm that the number of cases notified for Mexico does not represent a significant quantity in relation to the commercialized products. Although it is of vital importance to intensify the programs of Pharmacovigilance in the health centers, private practices, drug stores in order to increase the safety profile of PRISTIQ®. On the other hand, local Health Authority should assume a more intensive role of Pharmacovigilance to improve the security of the products commercialized in Mexico.

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P158. Analysis of Adverse Events Reported of Atorvastatine (LIPITOR®) Received by the Drug Safety Unit (DSU) Mexico from 01 August 2002 to 31 May 2012

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Pfizer

Introduction: High cholesterol is a risk factor for heart attack or stroke. Therefore, the importance of LIPITOR® because this Atorvastatine not only reduces the risk of heart attacks, certain types of cardiovascular surgery, but also stabilizes plaque and prevents strokes though anti-inflammatory and other mechanisms. Lipitor works inhibiting 3-hidroxy-3-metilglutanicoenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevelonate, one of the primary steps in the biosynthesis of cholesterol which limits the cholesterol rate. Lipitor was commercialized on 01 AUG 2002 in Mexico. Lipitor was considered the best sale drug in the whole pharmaceutical history. On the other hand, it's important to mention that with medication always comes some adverse events that's why it's necessary to advise to DSU, so these adverse events reports could be submitted to Local and Global Health Authorities and safety's patient always be safeguarded.

Aim: Analysis of the cases for Atorvastatine (LIPITOR®) received in Drug Safety Unit Mexico from 31 May 2006 to 31 May 2012.

Methods: A retrospective analysis of adverse event reports received in DSU Mexico according to Data File in Safety Mexico, considering factors such as gender, age and event type.

Results: To analyse the serious adverse events (SAE) was taken a sample of 30 cases, which shown 50% of the SAE's was dead and unknown cause of dead. For this event the majority was experienced by females (26.66%) and 23.33% males from 50 to 70 years old, central nervous system diseases 16.66% presented in females the majority were 80 years old, 3.33% was a myocardial infarction, 3.33% Leucopenia, 10% were musculoskeletal problems associated with other event and also was more common in females, 3.33% sensorineural disorders, 3.33% gastrointestinal problems, 6.66% experienced skin and tissue problems and 3.33% other disorders.

Conclusions: It's necessary to create new strategies to increase the number of adverse event reports with Lipitor for DSU Mexico. It's really important to received this information because once the case is processed by DSU is analysed to consider if the event was related or not related to Lipitor and that will be the way to watch safety of patients and to establish confidence in our product. In addition it's relevant to comment that although death has represented the 50% of

the sample it's necessary to consider other factors that could lead to this event such as suspend the medication abruptly or the existence of concomitant medication.

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P159. Adverse Events Reported for Heptavalent Pneumoccocal Conjugate Vaccine (Prevenar®) and Pneumoccocal Conjugate Vaccine 13-Valent (Prevenar 13®) in Mexico and Worldwide

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Pfizer

Introduction: Streptococcus pneumoniae (pneumococcus) is the leading cause of bacteremia, bacterial meningitis, bacterial pneumonia and acute otitis media in children under 2 years old. Heptavalent pneumococcal conjugate vaccine Prevenar® helps protect against seven strains of S. pneumoniae (4, 6B, 9V, 14, 18C, 19F and 23F). In 2007, given the high burden of pneumococcal disease and the proven efficacy of heptavalent conjugate vaccine (PCV7), the World Health Organization recommended the priority inclusion of PCV7 in childhood immunization programs worldwide.

The other vaccine is 13-Valent (Prevenar 13®) this vaccine helps protect against strains of S. Pneumoniae 4, 6B, 9V, 14, 18C, 19F, 23F) but also strains of S. Pneumoniae 1, 3, 5, 6A, 7F and 19A, it was designed to provide broader pneumococcal disease coverage. The use of this vaccine has the potential to further decrease the incidence of IPD and its complications.

Aim: To determine the frequency and source of reports events temporally associated with vaccination of heptavalent pneumococcal conjugate vaccine PREVENAR 7V® and PCV 13-valent (PREVENAR 13®) reported to the Safety unit at global and national levels to compared the number of doses distributed to the number of EA reported following administration of PCV7 and PCV13

Methodology: Analysis from events reports temporally associated with vaccination (ETAV) of PCV7 and PCV 13 in Mexico from 2000 to 2012.

Results: Revision of one hundred and eight reports ETAV reported nationally with PCV from 2000 to 2010. Most of the reports in Mexico and worldwide are considered non serious and ETAV. The most frequently reported type of ETAV both nationwide and globally, were classified as: general problems at application site. The following ETAVs most commonly in Mexico were general problems and from application site (38%), respiratory problems (29%) and gastrointestinal problems (16%). Worldwide general problems and from application site (35.5%), nervous system problems (17.4%) and problems in the skin and subcutaneous tissues (10.9%). For 2011 in Mexico according to Drug Safety Unit (DSU) were two spontaneous with PCV7 and for 2012 there were not cases reported. For PCV13 from 2011 to 2012 according to DSU the cases were serious.

Conclusions: Develop strategies to increase the number of reported events temporally associated with vaccination in the country, which would allow greater accuracy of data, since the number of recorded adverse events does not represent a significant amount in relation to marketed doses.

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P160. Intensive Pharmacovigilance to Rituximab in University Hospital Fundación Santa Fe de Bogota (HUFSFB): Preliminary Results

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Background: The Food and Drug Administration (FDA), Health Canada and the INVIMA (Agency in Colombia) have issued alerts about cases of patients deaths treated with Rituximab in systemic lupus erythematosus.

According to reports received in the INVIMA, the rituximab can cause adverse drug reactions (ADR) reported in patients with rheumatoid arthritis, with immune responses that cause allergic symptoms such as hypersensitivity and anaphylaxis. The rituximab have massive use in the HUFSFB, we considered do an active monitoring of ADRs experienced by patients in whom rituximab was used independent of the pathology for which it was used.

Aim: To identify the ADR that can be associated with use of Rituximab, establish causality, the indication for which is prescribed and the usefulness of premedication in patients in the HUFSFB.

Methodology: A drug utilization study, descriptive, observational, retrospective, with active search based on review of medical records. Patients studied in their therapy: from 1 January 2011 until 22 August 2011.

Results: We followed a total of 37 patients during the study period, most common diagnoses were Hodgkin lymphoma (44%) and non-Hodgkin lymphoma (32%); 5 patients had a RAM (14%), chills were experienced in 2 cases (probable), itching/rash (probable), tachycardia and bronchospasm (probable) and thrombocytopenia (possible) in one case each.

In 97% of cases was at least one drug premedication to patients with the following distribution: 73% hydrocortisone, 43% loratadine, 32% acetaminophen, 27% dexamethasone, 24% clemastine, 3% diphenhydramine, 3% methylprednisolone.

The percentage of patients who received drugs premedication and however ADRs presented was 12%.

Conclusion: The percentage of patients who experienced ADR has been relatively low, it is important to monitor in prospective form, to know if we have not all events registered in the medical record. However, we know that the ADR were mild in severity, and without relation with the international alerts. Should be continued under observation all the patients about the warnings issued recently. The Hospital decided to generate a document to to standardize of premedication and drug administration.

The authors declare no conflict of interest.

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P161. Implementing a Risk Management Plan for Fingolimod: Descriptive Analysis of Spontaneous Adverse Events and its Potential Use on Pharmacoeconomic Evaluations

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Introduction: Risk Management Plans (RMPs) are an essential tool to assess the risk-benefit balance of drugs.[1] Although they are not required currently in Mexico, the Pharmaceutical Industry and Health Authorities have taken action to include them in local laws. Physicians are not involved enough in these activities, especially on adverse events (AEs) reporting[2] in which the data generated could provide insights on economic impact of drugs.[3] In this way, Novartis Mexico developed a specific program to communicate, monitor and minimize risk, based on the global RMP of fingolimodfirst oral medication in a new class of modified therapies for Multiple Sclerosis (MS).[4]

Aim: To present a descriptive and direct cost analysis of fingolimod AEs notified to Novartis Pharmacovigilance unit after implementation of a RMP.

Methods: The program of communication, monitoring and risk minimization includes three stages: 1 – Medical training, prior to prescribing fingolimod, 2 – First dose evaluation and 3 – Follow-up monitoring. Special focus was directed on face-to-face training to MS-Neurologists regarding Pharmacovigilance, RMPs, AEs reporting importance and Fingolimod safety monitoring plan. AEs were analyzed regarding origin, physician causality and severity. A descriptive cost analysis was estimated from the identification of AEs and their associated medical treatment. The resources used to treat AEs were evaluated using the unitary cost list of a State Health Care System IMSS.[5]

Results: A total of 71 AEs were detected from 25 reports up to May 2012: 70% were reported by physicians; among all AEs, 38% were considered serious and only 2.8% discontinued the drug due to adverse events. The most prevalent event was the decrease in lymphocyte count (10%) without infections. An estimated average cost by each event was $1828 MX (130.66 USD), the average of cost per patient was of $5191 MX (371.06 USD).

Discussion/Conclusion: As far as we have reviewed in the literature, there is not currently a similar model to communicate risks in Mexico. The program increased the fingolimod adverse events reports by physicians consistent with the expected safety profile. Although no complete economic analysis was carried out, this exercise gave us the opportunity of consider the impact that pharmacovigilance activities have on the generation of data that should be added to local pharmacoeconomic studies among all pharmaceutical industries. By strengthening the risk management system, we would prevent high costs and avoid preventable AEs.

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P162. Experiences from Consumer Reports in Brazil

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Background: Spontaneous reporting is the basic method of information in pharmacovigilance. A set of reports allows the detection of rare adverse drug reactions (ADRs), which can be quite severe, from the strengthening of a causal relationship and the generation of a hypothesis. However, this method has some limitations, such as the lack of the real number of patients exposed and the high rates of underreporting.[1,2] It is estimated that less than 10% of all serious ADRs and 2–4% of all non-serious ADRs are reported.[3] The underreporting may delay signal detection and cause underestimation of a problem size. One strategy to reduce underreporting is to search for data in different sources of information, such as the consumer report.[4]

Objective: To describe major experiences of drug adverse events (AE) reported by consumers.

Methods: Since 2001, Brazilian Health Surveillance Agency (Anvisa) has a specific reporting system for consumers named Sisfarmaco. In addition, Anvisa also offers other communication channels for consumers such as e-mail, ombudsman and telephonic service. These may be used to report ADRs as well. Experiences resulting from consumer reports were searched and two important ones were chosen for this paper. All information related to the cases were collected and evaluated.

Results: In 2004 Anvisa received consumer reports of fulminant hepatitis by off-label use of flutamide. Five young women had the same AE associated to treatment of alopecia, hirsutism and acne with the drug. These indications were not authorized by the Agency. In two women there was attempt of liver transplant, but it was not succeed; four patients deceased. A safety alert was published and widely spread, especially among dermatologists.[5] In 2011, many cases of pain associated to use of a brand-specific somathropine use were reported by patients, generating a possible safety signal related the product. Anvisa then consulted the Sentinel Hospital Net, composed by almost 200 institutions, about this specific somathropine. According to the answers obtained, the signal was considered strengthened and laboratorial analyses were requested. Investigation is still in course.

Conclusion: The examples described of safety signals highlight the importance of ADR reports sent directly by consumers. The information provided can contribute to monitoring the ADRs and to clarifying important issues related to drugs. Considering this, Anvisa has included as an administrative indicator the responsiveness to consumers that use the communication channels mentioned above.

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P163. Hearing Loss in Mexican Children with Cancer Who Receive Cisplatin

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Introduction: Cisplatin has been widely used as a chemotherapeutic agent for a variety of paediatric malignancies. One of the most severe and debilitating adverse drug reactions experienced by patients who receive cisplatin therapy is ototoxicity, specifically permanent bilateral hearing loss (BHL). Although this problem has been extensively documented in the literature, information regarding Latin-American patients is scarce.

Objective: To describe the frequency and severity of ototoxicity in children treated with cisplatin in a tertiary care paediatric hospital in Mexico City.

Methods: Detailed medical and drug histories, including use of cisplatin as well as other drugs known to cause hearing loss, were collected from patient medical records. Audiology test were collected in paediatric patients (<18 years) with solid tumour cancers, at baseline, during treatment and at the end of the cisplatin chemotherapy management. Hearing loss was classified according to the Common Terminology Criteria for Adverse Events.

Results: Fifty-nine patients, 3 to 17 years of age, were included in this study. 52% were male; osteosarcoma (64.4%) was the most common cancer type. BHL, mainly in frequencies over 4000 hz, was observed in 22% of patients during treatment and in 59% of patients at the end of chemotherapy (OR = 1.65 [95% CI 1.253-2.172], p = 0.0001). In a multivariate analysis we found that BHL was independent associated with cumulative dose, age, treatment scheme and tumour type.

Conclusion: Hearing loss in Mexican children who receive cisplatin therapy is similar to that reported previously in other populations. Although ototoxicity was related to chemotherapy cycle number, it cannot be positively correlated only with cumulative dose of cisplatin, tumour type or age. Further research is required to fully characterize the inter-individual variation in ototoxicity in Mexican patients.

P164. Perception of Medication Errors in Healthcare Professionals in Kinshasa

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Background: Medication errors (ME) are common in clinical work and consists of failure during the treatment process (prescribing, dispensing and administering medicines). They can lead to severe morbidity, prolonged hospital stay, unnecessary diagnostic tests, unnecessary treatments, and death.[1] Adverse drug events (ADE) resulting from ME are preventable. In one study, 45% of the ADE were due to ME.[2] A clear understanding of healthcare professionals (HCP)'s perceived risk of ME is needed in order to protect patients from avoidable harm. This can also improve ME reporting.

Objectives: To describe the perception and knowledge of medication errors in HCP.

Methods: This prospective study included one tertiary and three secondary hospitals of Kinshasa with a focus in paediatrics and emergency departments, intensive care units, using a questionnaire describing HCP background, occurrence of ME and their management, contributing factors, types of ME, common drugs involved, medical issues, availability and utilization of therapeutic protocols, reporting of ME.[3]

Results: Of five hundred questionnaires distributed, only two hundred one questionnaires were returned by nurses and physicians (general practionners and specialists) and analysed. One third of HCP underestimate or are not aware of ME incidence. Seventy three percent of them reported some ME experiences in their practices, 49% estimated that ME can often occur in unconfident, not strict or inexperienced HCP. Fatigue (14%), understaff (35%), night duty (25%), emergency (11%), lack of training (52%) were thought by HCP to be the main contributing factors of ME occurrence. Therapeutic protocols are not available in some cases (34%). Common ME experienced concerned administration (36%, mainly administration schedule error) and prescription (33%, wrong rate of intravenous administration particularly). Anti-infectious drugs (42%, antibiotics, antiviral, antimalarials), analgesics (22%), NSAIDs (34%), drugs commonly used in emergency departements (18%) are largely thought to be more susceptible to lead to ME. Some of HCP don't report ME because of fear of prosecution, of blame or to see their incompetence exposed. Twenty percents of HCP has reported death consecutively to ME experience.

Discussions and Conclusions: ME is recognized as major safety issue during medication use process by HCP but the necessity of monitoring and reporting remains a huge challenge. A National PV Centre can deal with it. There is need to develop effective programs or communication strategies for stimulated ME reporting, secondary to determine incidence and causes of ME in order to prevent or minimise certains errors.

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P165. Adverse Drug Reaction Surveillance and Pharmacogenomic Assessment: Using the Canadian Pharmacogenomic Network for Drug Safety (CPNDS) Methodology to Improve the Health of Mexican Children

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Background: The debilitating and lethal consequences of severe adverse drug reactions (ADRs) cause 5–7% of all hospital admissions, an

estimated 2 000 000 severe reactions, and over 100 000 deaths each year in the USA. Drug safety and pharmacovigilance are emerging disciplines in Mexico, for which spontaneous reporting of adverse drug reactions (ADRs) and active surveillance for ADRs are rare. In an effort to develop these important disciplines, The Centro de Investigacion y de Estudios Avanzados del IPN (CINVESTAV-IPN) and the Hospital Infantil de Mexico Federico Gomez in Mexico have partnered with CPNDS to undertake ADR surveillance and pharmacogenomic studies to determine patient risk of ADRs. CPNDS has successfully identified and published novel genetic associations with ADRs, and is recognized worldwide as a leader in this area. As a large-scale knowledge translation project, CPNDS is training Mexican surveillance personnel and collaborating to conduct research in Mexico to determine if results from studies in mainly Caucasian populations are applicable to populations with different ethnic backgrounds and conduct additional priority studies for Mexico.

Methods: Building upon CPNDS methodology, the project will study specific genetic biomarkers of toxicity for a given drug. The success in establishing genetic associations with ADR risk depends on very detailed clinical characterization of ADRs, including the temporal relationship between the drug and reaction, concomitant drug therapy, comorbidities, and subsequent treatments. We will conduct high-throughput genomic analyses with samples from patients with ADRs as well as matched controls. The first surveillance focus in Mexico is cisplatin-induced ototoxicity in children.

Results: Training of Mexican research scientists is ongoing at the Child and Family Research Institute and the British Columbia Children's Hospital, Vancouver, British Columbia, Canada. Regulatory requirements have been met and surveillance for hearing loss induced by cisplatin in Mexican patients has begun. Results of this trial will determine if genetic markers previously identified by CPNDS are also applicable to Mexicans. Following steps will include the identification and study of ADRs of special interest to Mexican health system. This pragmatic approach aims for the Identification of predictive biomarkers of ADR risk that can be used as part of an ADR risk-mitigation strategy.

P166. Monitoring of Spontaneous Adverse Events with Enbrel® (Etanercept) Received by the Drug Safety Unit Pfizer, Mexico from 2000 to 2012

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Introduction: The report of spontaneous adverse events by the Marketing Authorization Holder is mandatory according to Mexican Law (NOM-220-SSA1-2002). Biological drugs (also called ''biotechnologic drugs'') represent a very effective therapeutic option, with tolerable adverse effects. Adverse effects reported with Enbrel® to Mexican Health Authority by Drug Safety Unit Pfizer, Mexico have shown until this time a good safety profile although is important reinforce the channels of communication with the Ministry of Health, academy and pharmaceutical industry to care the safety of patient and provide more tools in the medical prescription with these drugs.

Aim: To analyse adverse events from spontaneous reports with Enbrel® reported to National Pharmacovigilance Center by part of Drug Safety Unit Pfizer, Mexico from 31 May 2000 until 31 May 2012.

Methods: We performed a retrospective analysis with data obtained of local reports of Enbrel® (etanercept) reported to the National Pharmacovigilance Center in Mexico for the period from May 31st, 2000 to May 31st, 2012. All adverse events were described as were reported by the primary reporter and related for therapeutic indication, source of report, age of patient, gender of patient and the outcome only for the serious adverse events.

Results: The results obtained of cases (n = 100), 30% of cases were considered serious (n = 30). All adverse events reported were 92 (38 serious, and 54 non-serious). The source of these reports was: 42% from patients or relatives and 58% from Health Care Professionals. Female patients with over 18 years old, were the population with more frequency in reports (51%). The therapeutic indication which has more adverse events reported was rheumatoid arthritis. The outcomes of serious adverse event were: recovered (30%); not recovered (13%); in recovering (3%); unknown (54%).

Conclusions: This analysis showed that Enbrel® has good safety profile in the Mexican population, although is considered a low rate of reporting from patients and Health Care Professionals due to lack of interest or ignorance in the Pharmacovigilance Program in Mexico. The safety in biological drugs has taken great importance with the introduction of biosimilars (called in Spanish ''biocomparables'') in the Mexican market. For this reason is very important increase the diffusion of reporting and reinforce the channels of communication with the Ministry of Health, academy and pharmaceutical industry to care the safety of patient and provide more tools in the medical prescription with these drugs.

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P167. Evaluation of the First-Year Therapy with AZT/3TC/NVP: An Analysis of 500 Patient's Records

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Background: Highly Active Antiretroviral Therapy (HAART) decreases morbidity and mortality among HIV-infected persons.[1,2] For many patients, the life prolongation coexisted with the decrease of life quality because of adverse drug reactions.[3] In 2009, after benefit/risk assessment of stavudine (d4T), the World Health Organization (WHO) recommended the use of zidovudine (AZT) in developing countries. Democratic Republic of Congo is one of the countries which adopted the use of Lamivudine (3TC)/Nevirapine (NVP/Zidovudine (AZT) as the first-line regimen. There is need to evaluate this new therapeutic protocol.

Objective: To determine the safety of this regimen during the first year of treatment.

Method: This retrospective cohort study was realized in ACS AMO-Congo, which is a facility for the treatment of HIV positive patients in Kinshasa. Records of 500 patients aged more than 14 and who started HAART with AZT/3TC/NVP during 2009 were collected for a one-year period. Safety data (both clinical and biological parameters) for this period were analysed.

Results: The average weight increased progressively and the average increase reached 6.7% of the initial weight after twelve months of

treatment. The average CD4 rate increased from 263/mm^3 to 354/mm^3 (35% of the initial rate). The average hemoglobin rate decreased from 10.8 g/dl to 9.2 g/dl and the percentage of grade 4 anemia increased from 3% to 20%. There was necessity of first-line regimen substitution in 40 patients (8%). For 22 of them, adverse drug reactions, mainly anemia (16 patients), rash (3 patients), neuropathy (2 patients) and unspecified NVP toxicity (1 patient) required the treatment substitution. There was substitution of NVP in 25 patients and AZT in 13. In 16 patients, there was substitution of NVP because of tuberculosis treatment. Treatment failure was reported in 5 patients (1%). Twelve patients died (2.4%), anemia was the main cause of death in 5 of 12 patients.

Conclusions: The effectiveness of AZT/3TC/NVP regimen in this study can be illustrated by increasing of body weight and CD4 lymphocyte rate. Unfortunately, the adverse drug events occurrence is not uncommon. The main problem remains the occurrence of anemia, which can lead commonly to first-line regimen substitution or to death if it's serious. Monitoring of anemia is needed in countries that use AZT/3TC/NVP as the first-line regimen.

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P168. Emergency Contraception, Effectivenes, Safety and the Role of Pharmacists

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Emergency contraceptive pills (ECPs) are the most frequently used form of post-coital contraception. They are available by prescription (ulipristal) and over the counter (OTC). ECPs have higher doses of estrogens, progestins, or both hormones then regular oral contraceptive pills (combined-COCPs or progestin only-POCPs). The mechanism of action of ECPs depends on the time of ovulation, sexual intecourse and ECP use. ECPs can delay or prevent ovulation, impair formation of the corpus luteum, and prevent implantation, but do not affect an implanted fetus. ECPs are contraindicated only in pregnancy. Breastfeeding women may safely use progestin-only ECPs, but the use of ulipristal is not recommended.

However, due to the short duration of exposure and low total content of hormones, ECPs can be safely used even when COCPs are contraindicated (risk of stroke, heart disease, blood clots, or other cardiovascular problems). EC do not cause serious or long-term side effects, although women might experience some minor adverse effects (nausea and vomiting, abdominal cramping, menstrual disturbances, breast tenderness, dizziness, headache). Additionally, benefits of preventing pregnancy outweigh the risk associated with the EC use. Thus, in many countries all over the world, ECPs are approved as OTC medicines or they have a''dual label''. Although ECPs can be used up to four times during a month, they are not a regular method of contraception. Data are not available on the safety of current regimens of ECPs if used frequently over a long period of time. Emergency contraception is most effective if it is taken within 72 hours after sexual intercourse and up to 120 hours after unprotected sexual intercourse.

Unintented pregnancy is more frequent if the use of ECP was delayed. Also, no specific data are available about the interactions of ECPs with other drugs. However, it seems reasonable that drug interactions would be similar to those with regular oral contraceptive pills and can potentially lead to reduced effectiveness of ECPs. Thus, pharmacists can play a critical role in preventing unintended pregnancy by dispensing ECPs in a timely manner and providing advice on the use of ECPs. This paper gives most recent overview on emergency contraception and compares the safety of ECPs and COCPs based on VigiBase™, WHO individual case safety reports database. In addition the results of a survey conducted in Serbia regarding pharmacists' knowledge of EC and dispensing practice are summarized.

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P169. An Exercise on Pharmacovigilance for Sophomores

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We developed a practical exercise in which second-year medical students have to apply the main principles and procedures of pharmocovigilance in a specific clinical case context. The exercise was designed by means of Flash© (animation and multimedia software), it consists in a sequence of specific problems that arise during the development of the exercise. Students have to solve them by means information searching in the web with teachers' advice. The clinical case was taken from a case report of a woman with heart failure and chronic obstructive pulmonary disease (COPD) who develops syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH) as an adverse drug reaction (ADR) after the administration of moxifloxacin to treat an exacerbation of COPD. The exercise has seven different stages from which students get information to base suspicion of adverse drug reaction (ADR):

1. *Case presentation*: patient information, symptoms and physical examination. In this stage the student should ask for information related with ADR appearance.
2. *Medical records:* patient's previous diseases, allergies, use of drugs or herbal products.
3. *Test and evolution:* results of laboratory, imaging tests and treatment are presented. Student should explain and discuss the possible origin of the abnormalities observed in the clinical tests.
4. *Diagnosis and evolution:* in this moment the SIADH is diagnosed, the group discusses the vasopressin physiology, SIADH physiopathology and the etiologies for this syndrome.
5. *Case resolution:* patient discharge and ambulatory management. Students should discuss about drugs that could produce SIADH and methods to assess causality of ADR.
6. *Causality assessment:* students should use Naranjo's algorithm and classify the causality between moxiflocacin and SIADH development.
7. *Report*: student should complete the ADR report issued by COFEPRIS.

As conclusion of the exercise, teachers and students discuss about the importance and implications of pharmacovigilance in their professional practice.

We carried out the pilot probe in May 2012

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P170. Acute Naphthalene Poisoning in a Newborn. A Case Report

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Background: Acute naphthalene poisoning by inhalation, although less common than oral, is also observed. In domestic use, naphthalene is often presented as white balls and used as insecticide to protect clothes. The effects on human exposure had been less studied. Naphthalene is readily absorbed into the systemic circulation following inhalation, ingestion or dermal exposure. In most cases, there are symptomatic and supportive measures.

We report a case of poisoning with naphthalene in neonate in contact with sheet treated with naphthalene; stopping of the exposure and good ventilation have been sufficient for resolution.

Case Presentation: A newborn was treated for a bacterial infection and kept in an incubator. At the second day of hospitalization, newborn presented agitation and dyspnoea. There was a strong smell of naphthalene at opening of the incubator. The mother revealed that she had been using naphthalene mothballs as conservative for the clothes of her baby. The management consisted of a good ventilation and change of the clothes. After a few hours, all symptoms resolved. Causality assessment was ''probable'' according to the WHO method.

Discussion: Naphthalene mothballs of naphthalene are still of courant use in Kinshasa especially because of its low cost. No attention is paid because they are considered to be safe. However, acute exposure to naphthalene can cause adverse effects such as nausea, vomiting, abdominal pain, diarrhea, headache, confusion, profuse sweating, fever, tachycardia, tachypnoea and agitation which may lead to convulsions and coma. Haphthlene can lead to haemolysis especially in case of G-6-PD deficiency. Newborn are more at risk of naphthalene-induced haemolysis than adults. The imputability of this case is probable. In this casedosage of the stable metabolites of naphthalene in the urines and the enzymatic activity of G-6-PD should have been done.

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P171. Starting to Walk: Training Programs for Health Professionals on Pharmacovigilance

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Educational institutions and National Pharmacovigilance Centre play a central role in encouraging inclusion of the principles and methods of pharmacovigilance and the study of iatrogenic diseases at undergraduate and postgraduate levels in schools of medicine.

It is well documented that there is a need to provide health professionals with the skills required to evaluate drug information critically and to decide how the safety profile of a drug might be applied to a particular patient. Pharmacovigilance system should be oriented to promote availability of reliable drug information to improve standards of use and to reduce the frequency of adverse reactions.

There is lack of training and updating opportunities in Mexico to develop the knowledge, attitudes and skills to deal with safety drugs monitoring and information systems management. National and international current health policy and social needs demand to Schools of Medicine to offer training programs to professionals involved in pharmacovigilance practice and theory. For this reason, the Pharmacology Department at the Faculty of Medicine UNAM offered a 42-hour course to staff of different health professions that are working in regulatory issues, hospitals, academic institutions and pharmaceutical industry. The pharmacovigilance course took place on the first 2012 semester derived from this a diploma course has been organized to start in October 2012. Results: a description of personal data and expectations. Data analysis of knowledge assessment showed differences with respect to participants' profession.

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P172. Electronic Prescription as a Tool for Preventing Medication Errors, and Potential Use in Continued Education in a Teaching Hospital

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Background: Teaching hospitals' mission is not only to give the best medical care but also to provide the most appropriate medical training. Pharmacological therapeutics is one of the basis of current medical treatments, but it's increasingly complex due to the number of pharmacological or biological substances marketed, their many interactions and the huge amount of knowledge needed to prescribe one or more drugs. Manual and handwritten prescriptions cause a number of operational delays and are more likely to cause medication errors. Computerized Physician Order Entry (CPOE) Systems can reduce both the number of adverse drug reactions (ADRs) and medication errors (ME). Besides, one can take advantage of a process that demands prescription's attention for introducing warnings and their explanation, as educational elements for continued physicians' training.
Aim: To design and set a system of electronic prescription linked with other hospital entries, such as laboratory, hematology service, and Health Insurance Systems funding patients' medicines and diagnostic tests (due to Health System's characteristics) for a teaching 170 beds hospital, with secondary, tertiary and highly specialized attention.
Design: The CPOE system should be able to be used in all hospital prescriptions (internal and external), the discharge and daily hospital indications. It should be able to stop the prescription process in the medication usually taken by the patient isn't consigned, to demand allergy history data, laboratory data (especially blood cells counts, hepatic enzymes, creatinine, CPK). The system should be able to send warnings in case of errors in doses, frequency of doses, administration route, pharmacokinetics interactions, and possible pharmacogenetic variations (affecting both pharmacokinetics and pharmacodynamics). Drugs will be identified with Anatomical Therapeutic Chemical (ATC) code; fixed marketed combinations will have an additional code.
Discussion: Different studies have shown that users, especially senior physicians, tend to override warnings because they consider alerts are not adapted to clinical context and patient's characteristics. This Computerized Physician Order Entry (CPOE) System is intended to fit in a complex setting with a number of behavioral disadvantages (pyramidal decision-making structure, huge physician's working load, mistrust to innovative approaches, hostility to control procedures). The success of a CPOE system in reducing ME and ADRs rely not only on system's design (adaptation to needs and realities, not time consuming) but on physicians' attitudes.
Conclusion: This CPOE system has to be tested in practice both in its ability to reduce ME and ADRs as well as in its utility as a continued medical education tool.

P173. Neglected Populations, Neglected Diseases, Neglected Pharmacovigilance: A Review of Publications on Chagas Pharmacovigilance

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Background: Chagas is an endemic infectious protozoan disease in South America affecting around 8 million people in 18 endemic countries, most in South America. It's a leading cause of cardiomyopathy and death due to cardiovascular disease. Mainly transmitted through the vector's feaces (*Triatoma infestans*), Chagas disease can be also transmitted through infected bloods tranfusion, congenital infection and more rarely, oral contamination, organ transplant from an infected donor and laboratory accident. Being a poverty disease, in endemic countries efforts have been mainly focused in control vectorial transmission. Due to migrations, dissemination of Chagas disease in Europe and the USA, blood screening tests improved in order to prevent transfusional transmission.[1,2] However, effective and safe therapies are still lacking. Treatment is currently based on nifurtimox and benznidazole, both poorly tolerated, especially in adults. While pharmacological therapy's proved efficacy in childhood and in acute disease, its benefits in preventing cardiomiopathy in chronic stage are still controversial for adult patients who need prolonged treatment and are at risk of important adverse effects.
Aim: To evaluate the number of publications reporting pharmacovigilance studies in Chagas disease.
Method: Systematic searchs performed in PubMed with the terms "Chagas AND pharmacovigilance", "nifurtimox OR beznidazole AND pharmacovigilance", "Chagas AND adverse effects", "Chagas AND adverse effects AND nifurtimox OR benznidazole", limits: "Humans".
Results: The searches containing "pharmacovigilance" retrieved only one result, a pharmacovigilance study performed by the sponsor (Switzerland). The search with terms "Chagas AND adverse effects AND nifurtimox OR benznidazole" yielded 328 results. Articles reporting adverse effects in cohorts of patient were conducted in Brazil (5), Spain (4), Argentina (2), Switzerland (1), and one reporting the experience of 10 years in Honduras, Guatemala and Bolivia, from Médecins sans Frontières (1). Case reports from Spain (2), France (1) and a case serie in newborns from Bolivia (1) reported treatment's adverse effects, while case reports from endemic countries focused on clinical presentation and complications of Chagas's disease cases. One systematic review from Spain was performed with the aim of assessing the benefits and harms of benznidazole's therapy in adults with chronic stage.
Conclusion: Few publications report formal pharmacovigilance studies. Pharmacological therapies have to improve in order to treat effectively and safely this neglected disease both in acute and chronic stage and more efforts have to be made in developing pharmacovigilance of Chagas disease in endemic countries.

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P175. Tamsulosin and Gynecomastia: Data from the Italian Spontaneous Reporting System

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Background: Gynecomastia is caused by drugs in 10–25% of all cases.[1] It is defined histologically as a benign proliferation of the glandular tissue of the male breast and clinically by the presence of a rubbery or firm mass extending concentrically from the nipple(s). There are evidences of gynecomastia due to 5α-Reductase inhibitors as finasteride and dutasteride but there aren't available studies about gynecomastia associated with tamsulosin use in literature. To date, gynecomastia is not reported in the Summary Product Information (SPC) of the drug. Aim of this study is to evaluate the cases of gynecomastia tamsulosin-induced in the Italian spontaneous reporting database (Rete Nazionale di FarmacoVigilanza - RNF).

Methods: Adverse reaction are coded in the RNF using both MedDRA and WHO-ART. Cases of gynecomastia has been defined as reports associated to WHO-ART Preferred terms Gynaecomastia, Breast enlargement, Breast pain male, Breast pain and Breast discomfort.
Results: Up to December 2011 about 132 800 reports are present in the RNF, excluding vaccines and reports from the literature. In the whole database 247 reports have been associated to tamsulosin, whereas in 699 reports tamsulosin has been reported as concomitant drug. Eight cases of gynecomastia associated to tamsulosin have been reported: two of these have also dutasteride as concomitant drug. Other 10 reports with gynecomastia have tamsulosin as concomitant drug. Eight of these have been associated to another 5α-reductase inhibitor (dutasteride or finasteride). Time of onset showed a great variability from 1 day to 4 years since the start of therapy. Among cases with tamsulosin as the only suspected drug, no information on laboratory analyses was available. A positive dechallenge has been reported in two cases.
In the WHO database (Vigibase) 78 reports of gynecomastia in which tamsulosin is indicated as suspected/concomitant drug are present. These reports have been submitted by eleven different countries and tamsulosin is the only drug suspected in fifty of them.
Conclusion: A high number of cases of gynecomastia in reports with tamsulosin are present in the RNF. Most of these reports have tamsulosin as concomitant drug or have also other 5α-reductase inhibitor leading to a difficult causality assessment. However, in six cases tamsulosin is the only reported drug suggesting an association to gynecomastia also for this drug. The combination tamsulosin-gynecomastia should probably be highlighted in product information.

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P176. Liver Injury as the First Clinical Feature of DRESS: A Proof of Concept Study

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Background: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome) is characterized by the association of fever, severe skin eruption, lymphadenopathy, hypereosinophilia, atypical lymphocytes and organ involvement such as hepatitis, carditis, interstitial nephritis, or interstial pneumonitis.[1] Much active research based on the skin injury as the first symptom of this drug-related disease has been investigated. It is well known that liver disorder occurs in over 80% of DRESS cases[2] and some authors suggested that liver injury could be the first symptom occurring before skin involvement.[3] It would be interesting to further investigate this topic.
Objective: The aim of the study was to investigate, among the DRESS syndrome spontaneous reports recorded in the French Pharmacovigilance Database (FPD), the possible occurrence of liver injury as the first clinical feature.
Method: A retrospective study was carried out. A query was performed on 12th January 2012 on all spontaneous reports with the term "dress" on narrative. Among these spontaneous reports, we selected and described DRESS reports with a liver injury occurring before other any symptoms. A liver injury was defined as alanine aminotransferase above twice the normal. Diagnosis of DRESS syndrome was not performed with using diagnosis criteria of regiscar.

Table I. Description of DRESS cases with initial liver injury (n = 21)

Gender [n (%)]	
Male	10 (48)
Female	11 (52)
Age [y]	
Mean	55
Median	54
Range	18-90
Skin disorder [n (%)]	
Yes	16 (76)
No	5 (24)
Delay from drug intake to liver injury [days; mean (SD)]	27 (20.7)
Delay from drug intake to skin disorder [days; mean (SD)]	32 (12.44)

Results: A total of 1121 spontaneous reports were retrieved from the FPD with 577 cases showing a liver injury. Among these reports, an initial skin injury occurred in 438 cases and simultaneous liver and skin injuries occurred in 118 cases. The 21 remaining reports showed an initial liver injury while 5 of them did not point out any skin injury. In average, the onset of drug liver injury occurred approximately 5 days before the skin injury.
Discussion/Conclusion: This study has shown that skin manifestations in DRESS syndrome were frequent but not systematic and occurred in some reports after a liver injury. Indeed, in 21 reports, liver injury occurs before skin injury. Among 118 reports with simultaneous liver and skin injuries, some cases displayed high transaminases rate suggesting that the exact onset of liver failure was not really known and probably earlier. These results are probably underestimated because index date is still based on skin injury and not on liver injury, leading to an under-reporting of cases without skin disorders. It will be necessary to carry out an additional prospective study with a larger scale for a better therapeutic approach and the possibility to design causality assessment criteria of DRESS syndrome.

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P177. Different Clinical Manifestation of Hypersensitivity to Acetylsalicilic Acid and Non-Steroidal Antiinflammatory Drugs (NSAIDs): Four Case Reports as Examples of Different Subpopulations

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Background: Hypersensitivity to acetylsalicilic acid (ASA) and NSAIDs can be non-immunological; Ig-E-mediated allergic reactions,

and non-immediate reactions after several days of drug's administration.[1,2] Patients with asthma and urticaria are at high risk of aspirin and NSAIDs hypersensitivity and can present serious and life-threatening adverse drug reactions (ADRs).[1,2] Clinical finding can vary and can be related with different hypersensitivity mechanisms. We present four cases with different clinical presentation:

Case 1: a 51-year-old man, with a history of asthma and bronchospasm and facial angioedema with aspirin since childhood. He presents nasal, etmoidal, frontal and maxilar polyposis, peripheral eosinophilia and eosinophilic rhinoconjuntivitis (aspirin-induced Asthma – AIA – or aspirin-exacerbated respiratory disease)

Case 2: A 43-year-old woman, with a history of asthma, brochospasm with NSAIDs, nasal polyposis and allergic rhinitis. (ASA triad to aspirin and other NSAIDs)

Case 3: A 60-year-old woman, with nasal polyposis, allergic rhinitis, with symptoms of intolerance to NSAIDs (rhinorrhea, severe dyspnea with emergency admission). The mechanism would be the ciclooxigenase-1 inhibition (COX-1), which precipitates a non-allergic hypersensitivity reaction.

Case 4: A 52-year-old woman, with a history of chronic urticaria, rhinitis, and urticaria, angioedema and broncospasm after NSAIDs (diclofenac, paracetamol) and aspirin. The mechanism would be the induction or exacerbation of skin lesions through inhibition of COX-1.

Conclusion: Different manifestations of hypersensitivity to ASA and NSAIDs could reflect different subpopulations and possibly, partially different mechanisms. These different manifestations should be identified throughout clinical diagnosis as subset of a same hypersensitivity condition. In these patients, the use of acetylsalicilic acid and NSAIDs must be avoided due to the high risk of serious adverse events and life-threatening effects. Physicians, pharmacists and patients should be aware of these ADRs in order not to treat hypersensitivity symptoms with ASA or NSAIDs.

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P178. Like DRESS Syndrome in a 65-Year-Old Woman Treated with Losartan, Esomeprazole and Levothyroxine: Case Report

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Background: DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) is a life-threatening syndrome characterized by the presence of at least three of the following findings: fever, exanthema, eosinophilia, atypical circulating lymphocytes, lymphadenopathy, and hepatitis. Mainly allopurinol, sulfonamides, and aromatic anticonvulsants such as phenytoin, phenobarbital, and carbamazepina, but also many other drugs, such as vancomycin, ramipril, penicillin V have been reported as the cause of DRESS. Treatment is based on the withdrawal of the culprit drug and corticosteroids; however, diagnosis is difficult because its clinical features mimic other serious systemic disorders, like sepsis and cutaneous lymphoma, so that the culprit drug risk to not be identified.

Case report: A 65-year-old woman with a history of 9-month eritrodescamative rash with progressive worsening, was hospitalized because hypertensive crisis; the rash was treated with dexametasone and clorfeniramine with temporal remission and recidive. She presented mild-moderate eosinophilia. Losartan was replaced by carvedilol, hidrochlorotiazide and amlodipine. Levothyroxine was discontinued because of hyperthyroidism crisis. Skin biopsia showed pharmacodermia features. Skin rash worsened, with hair loss, lymphadenopathy and seizures. Phenythoin was prescribed for seizures; hyperthyroidism evolves to hypothyroidism and levothyroxine was reintroduced. Fever, eosinophilia, exantema, enantema and bradipsychia are new clinical findings. A viral infection (varicela) presented after three months

Discussion: The patient did not present hepatitis. Seizures could reflect neurological involvement from hypertensive lesions. Auto-immune thyroiditis can be related with immune imbalance, which could be also cause of viral reactivation or infection.

Conclusion: The value of this case is that "common" drugs could be also the cause of subacute, confusing and complex syndromes, with systemic involvement and life-threatening. Drugs should be always considered as a potential trigger of immune imbalance, which can lead to immediate or delayed hypersensitivity, organ damage and autoimmune diseases. When hypersensitivity mechanism is triggered, clinical findings don't disappear immediately with drug discontinuation. However, drugs currently administered should be always withdrawn or replaced when the patient present at least one clinical finding of drug hypersensitivity.

P179. Tramadol Use in Pregnancy: A Prospective, Comparative Study of Exposed Infants

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Background: Tramadol is a centrally acting weak opioid analgesic used to treat moderate to severe pain. Although reproductive toxicity studies did not show any increase in abnormalities, no prospective, comparative studies examining the safety of tramadol during pregnancy are available.

Objectives: To determine whether the use of tramadol during pregnancy is associated with an increased risk for major malformations and to examine rates of spontaneous abortions (SA), therapeutic abortions (TA), stillbirths, and the main characteristics of the newborns.

Methods: Twenty French pharmacovigilance centers prospectively collected data from patients or their healthcare providers following information requests regarding risk evaluation after tramadol exposure during early pregnancy. Patients were included if they were exposed between week 4 to 12 after the last menstrual period (LMP) and if the first contact occurred before week 22 after LMP. The exposed group (group I) was compared with two comparison groups namely a group exposed to other step-2 analgesics (group II) and a group exposed to non-teratogens (group III) during the same period.

Results: The outcome of 1370 pregnancies was fully documented including 151 patients from group I, 246 from group II (codeine in 104 and dextropropoxyphene in 142), and 973 from group III. Patients from the tramadol group were significantly older than in the other 2 groups (31.4 ± 5.7 years vs 29.7 ± 6 and 30.2 ± 4.9 in group II and III,

respectively). Gestational age at inclusion was similar between both exposed groups, but significantly lower in group III (9.3 ± 4.2 weeks vs 11.1 ± 4.9 weeks). The rates of major malformations were similar across groups (2.6% in group I, 2.9% in group II, and 2.1% in group III). Significant differences were noted in the rates of SA (15.9% in group I, 7.2% in group II and 4.7% in group III, $p < 0.001$) and TA (13.2% in group I, 9.8% in group II and 3.3% in group III, $p < 0.001$). Characteristics of the neonates assessed by the prematurity rate, the mean gestational age at birth, the mean birth weight and the rate of hypotrophic newborns were similar across groups.

Conclusion: Despite limitations due to the sample size, this prospective study suggests that exposure to tramadol during the first trimester of pregnancy is not associated with an increased risk of malformations.

P180. Safety Profile of Etifoxine: A French Pharmacovigilance Survey

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Background: Etifoxine chlorhydrate (Stresam®, Biocodex Laboratories, France) is a benzoxazine derivative approved for the treatment of psychosomatic manifestations of anxiety. Although this drug has been marketed since 1979, very few adverse effects (AE) are mentioned in the Summary of the Product Characteristic (SPC). They include drowsiness, benign cutaneous reactions and acute hypersensitivity reactions, such as urticaria and angioedema.

Objectives: To examine recent data on etifoxine-related AE by reviewing Individual Case Safety Reports (ICSRs) recorded by the French network of pharmacovigilance centers with a particular focus on unexpected AE.

Methods: Etifoxine-related ICSRs were extracted from the French Pharmacovigilance database (FPD) from 1/1/2000 to 30/04/2012. Only cases with sufficient information and no other obvious drug-related or non-drug causes were included for analysis.

Results: Of 285 ICSRs, 259 were retained for analysis and 116 (45%) were considered serious. There were 214 females (83%) and the mean age of the patients was 45 ± 19 years (12–98 y). According to yearly sales data, the overall incidence of AE was very low ranging from 14 to 40 cases recorded per million treatments. One case of death by suicide in a patient also taking duloxetine for the last 2 days was noted. The most frequent AE were dermatological or acute hypersensitivity reactions (65%) including 24 cases of severe toxidermia (DRESS: 5, erythema multiforme: 9, and Stevens Johnson syndrome: 5) and 7 cases of vasculitis or serum sickness-like reaction. One case of pemphigus vulgaris was reported and was marked by recurring lesions after etifoxine readministration. Liver disorders were reported in 25 patients including 20 cases of acute hepatitis. These were mostly reversible cytolytic hepatitis (16/20), occurring within the first 2 months of treatment in 85% of cases, and clinically symptomatic in 11 patients. One case of fulminant hepatitis requiring liver transplantation was also recorded in 1996. Other unexpected AE included 9 reports of reversible metrorragia in young women among whom 8 also took oral contraceptives and 2 had a positive readministration, and 4 cases of colitis including 3 biopsy-proven microscopic colitis with a positive readministration in one.

Conclusions: A number of unexpected and serious AE have been identified in this recent survey, in particular severe toxidermia and acute cytolytic hepatitis. An updating of the etifoxine SPC is therefore strongly needed.

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P181. Allopurinol-Induced Severe Cutaneous Adverse Reaction: A Case-Control Study

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Background: Allopurinol, a widely used acid uric-lowering drug, is one of the most frequently drugs involved in severe cutaneous adverse reactions (SCAR), namely Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Toxic Epidermal Necrosis (TEN) or Stevens-Johnson Syndrome (SJS).

Objectives: To better define risk factors and the incidence rate of allopurinol-induced SCAR.

Methods: All cases of allopurinol-induced SCAR recorded by the French Pharmacovigilance Centers between January 2008 and December 2010 were extracted and confirmed by a dermatologist. Spontaneous reports for which allopurinol was considered as a concomitant drug and recorded between January 2006 and December 2010 served as controls. Prescription data were obtained from the EGB (échantillon généraliste des bénéficaires), a permanent representative sample of the French national health insurance.

Results: Of 216 reports retrieved, 86 (65 DRESS and 21 SJS/TEN) were retained for analysis. One hundred and one controls were selected. As compared to controls, patients with allopurinol-induced SCAR were more frequently female (56.2% vs 32.7%) and received significantly higher doses of allopurinol (230.6 ± 93 mg/d vs 167.17 ± 70 mg/d). There were no significant differences between groups for comorbidity rates (chronic kidney disease, diabetes mellitus, arterial hypertension) or comedication uses (diuretics, beta-blockers, low-dose aspirin). After adjustment for patient's age, baseline renal clearance did not differ between groups. Inappropriate prescriptions defined as treatment of asymptomatic hyperuricemia were found in 50% of patients. The overall mortality rate was 14.1%, but all patients with SJS recovered, whereas 7.7% of patients with DRESS and 48.3% with TEN died. According to the EGB data, 552 627 patients were considered as new users of allopurinol over the same period. The incidence rate of allopurinol-induced DRESS or SJS/TEN was estimated between 0.17 to 2.25/1000 new users.

Conclusion: Results of this comparative study confirm previously described characteristics of allopurinol-induced SCAR, namely a dose-related effect and avoidability due to inappropriate indications in most cases. It also highlights female gender as a possible risk factor and challenges the unproven role of underlying renal function as a risk

factor for allopurinol-induced hypersensitivity. The estimated incidence rate is considered minimalistic due to the usual importance of under-reporting in pharmacovigilance.

P182. Bisphosphonate-Associated Cardiac Adverse Reactions: Reports from the Italian Database of Spontaneous Reporting of Adverse Drug Reactions

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Background: Oral and intravenous bisphosphonates (alendronate, clodronate, risedronate, pamidronate, ibandronate, and zoledronic acid) are front-line agents in the management of osteoporosis, malignant skeletal disease, and Paget's disease. In the USA, in 2006, there were more than 30 million prescriptions for oral bisphosphonates alone and in Italy, in 2011, bisphosphonates have been the third class of drugs most prescribed by physicians. Different kinds of adverse drug reactions (ADRs), such as upper GI adverse events, renal toxicity, influenza-like illness, musculoskeletal pain, osteonecrosis of the jaw, and ocular events have been associated to bisphosphonates. The association with cardiac side effects are limited in the literature and particularly focalized on the atrial fibrillation.[1,2] The Italian Summary Products Characteristics of clodronate, zolendronate, ibandronate, pamidronate lists some cardiac ADRs, only the SPC of zoledronic acid reports atrial fibrillation.

Aim: To describe and discuss the spontaneous reports of cardiac disorders associated to bisphosphonates from the Italian ADR database.

Methods: The Italian database on spontaneous reporting (IDvigilance) holds reports of suspected ADRs submitted since 1988. Every 6 months the database is analysed to filter out potential signals. Signal detection is done by qualitative case-by-case analysis and by using as quantitative methodology the Proportional Reporting Rate.

Results: Up to December 31st 2011, IDvigilance held 161 474 reports: 84% of them coming from physicians, 6% from pharmacists, 2% from nurses, and only 1% from consumers. In 1799 reports, one or more adverse reactions associated with bisphosphonate therapy were referred. Among these, 36 (2%) reported cardiac disorders as the preferred term. The percentage of female was 86%, the percentage of serious reports was 22% and the median age was 67 years. The drug more frequently reported was clodronate alone or in association with lidocaine (12 out of 36) followed by alendronate (8 out of 36) and zoledronic acid (7 out of 36). The most frequently reported bisphosphonates-related cardiac ADRs included hypertension (10 cases), tachycardia (7) and atrial fibrillation (4), most of them related to clodronate + lidocaine.

Conclusions: Some reports, in the Italian database, indicate possible cardiac ADRs in association with bisphosphonates. Physicians and patients who use bisphosphonates should remain vigilant for cardiac side effects and in particular for atrial fibrillation.

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P183. Signal Detection in the Italian Spontaneous Reporting System

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Introduction: Signal detection is the main goal of the spontaneous reporting systems. Few information is, however, available on the procedures for signal detection followed by different countries. Aim of this paper is to describe the signal detection process in the Italian spontaneous reporting system.

Methods: The Italian spontaneous reporting system is decentralized. Reporters send their reports to the Local Health Authorities (LHA) (about 400 in the whole of Italy) where they are inserted in the Italian spontaneous reporting database (RNF). Regional Pharmacovigilance Centers (RPhCs) have been inserted to support the activities of LHAs and to collaborate with the Italian Medicines Agency (AIFA) in signal detection. Actually 14 RPhCs are present. Adverse reactions are coded according to MedDRA terminology but WHO-ART terminology is also available through a specific bridge.

Results: A web-based tools (VIGISEGN) for data mining of RNF has been developed by AIFA through a research project with the University of Verona. The tool, accessible to all the RPhCs give the following information for each drug-event pair, grouped at different level (for drugs ATC groups III and V, for adverse reactions Preferred Term or System Organ Class with both MedDRA or WHO-ART): seriousness of the reaction, labelling of the reaction (according to the SPC), static and dynamic (trend over time) Proportional Reporting Ratio (PRR) values and 95% confidence intervals, static and dynamic reporting rate (reports/DDDs/1000 inhab/die). A list of drugs according to its ATC code is assigned to each RPhCs for signal identification. Criteria evaluated for signal identification include: number of reported cases, seriousness/labelling of the reaction, PRR value, causality assessment evaluation, use of the drug in the population. In addition to disproportionate analyses, the RPhCs perform a case-by-case analysis on the most interesting drug/ADRs pairs in order to analyze the information included in each report. The list of potential signal identified is discussed and analyzed in periodic meetings by a Commission including physicians, pharmacists, clinical pharmacologists, epidemiologists working in the RPhCs and in AIFA. The Commission selects a final list among the proposed signals for a detailed comment that may be used for regulatory purposes and/or publication on the AIFA's website. In the period from 2009 to 2011, 44 signals have been published on the AIFA's website (www.agenziafarmaco.it).

Conclusion: Signal detection process within the Italian spontaneous reporting system is carried out together with RPhCs through a combination of both disproportionate analyses and case-by-case evaluation.

P184. Ocular Adverse Events Following Immunization (AEFI): Data From the Italian Spontaneous Reporting System

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Background: Ocular disorders have been previously associated with vaccination. They include non-serious reactions like conjunctivitis, associated with hypersensitivity responses but also visual disorders including serious events like visual loss where causality assessment is often difficult. The aim of this study is to analyze the reports with ocular AEFI associated with vaccines in the Italian Pharmacovigilance database.
Methods: Vaccines are coded including ATC code. Reactions are coded with MedDRA terminology. Causality assessment of reports is made by the pharmacovigilance personnel working in the Regional Centres with the WHO causality assessment method for AEFI. All AEFI related to the MedDRA System Organ Class "Eye Disorders" reported after the vaccine administration have been selected and analysed.
Results: Up to December 2011, the Italian database contains more than 160 000 reports, 24 578 associated with vaccines. Among these 511 reports have at least one AEFI related to the MedDRA SOC Eye Disorders, 21% of these were serious The most frequent reported ocular AEFI is eyelid oedema (78 reports) followed by conjunctivitis (73), periorbital oedema (48), oculogyric crisis (35), photophobia (29), visual impairment (25) and strabismus (23). Vaccines most frequently associated with ocular adverse events were measles mumps and rubella vaccine (MMR) (121 reports), the hexavalent vaccine (92 reports), the pneumococcal conjugated vaccine (47 reports) the influenza vaccine (45 reports) and the human papilloma virus (HPV) vaccine (42 reports). Fourteen cases of strabismus were reported associated with the hexavalent vaccine. Six further cases of oculomotor paralysis were also associated to this vaccine. Cases of strabismus after hexavalent vaccine were often bilateral and confirmed by an ophthalmologist. Most of the cases had a time of onset of one or two days up to 14 days in one case. Only five cases reported a full recovery.
Five cases of strabismus have been reported after the MMR vaccine and a recent case on a partial third nerve palsy after MMR vaccination has been recently published.
Conclusions: Eye disorders have been associated with different vaccines. Some of these are unlabelled but before they can be considered as potential signals a causuality assessment together with specialized evaluation for individual cases in order to exclude that these ocular symptoms are manifestations of a neurological disease and the analysis of epidemiological data have to be performed.

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P185. Development of a Network of Information in Pharmacovigilance in Three Different Areas of Venezuela

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Introduction: The reports of adverse drug reactions (ADRs) who receive the National Pharmacovigilance Center of Venezuela comes mainly from the Capital area, for that reason it is reasonable to argue that the rest of the country is not getting the right information about the importance of pharmacovigilance.
Aim: To determine the degree of knowledge of pharmacomacovigilance that has the professional personal who works in the health public institutions in three different areas of the country. To make a proposal of implementation of a network of information in pharmacovigilance between the Capital and the selected areas.
Methods: We performed a survey which contains various questions as an instrument of compilation of information about the knowledge of pharmacovigilance. The survey was applied to the professionals of the health, who are employed at the public institutions of health in three chosen areas: an area near the Capital (Miranda), an area in the south (Amazonas) and an area in the Cariabean (Nueva Esparta).
We implement the means of diffusion with the intention of establishing a network of information in pharmacovigilance**:** production of informative billboards, distribution of triptics, presentation of chats directed the personnel of health and to the community.
Results: The results showed that among the polled ones in the different areas, about 75% answer that they know what is pharmacovigilance, about 70% of them have a real knowledge of a RAMs, however almost 60% said that they have never been in presence of a RAM, and those who had the opportunity to observe an RAMs did not report it since they said to have any knowledge about the yellow page, a educational campaign had been develop in order to emphasize the importance of pharmacovigilance, it includes the elaboration of triptics, chats and in those places where they have access to internet, we have promoted the report of RAMs on line and keeping a constant flow of information.

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P186. Systemic-Based Adverse Events of Some Fixed Antiretroviral Combinations Reported to the DRC National Pharmacovigilance Centre in 2010 and 2011

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Introduction: Antiretroviral drugs considerably improve the HIV-positive patients' longevity. Nowadays, they include several molecules. The World Health Organization recommends fixed generic combinations consisting of two nucleosidic analogues and one non-nucleosidic reverse transcriptase inhibitor ad primam. Those combinations consist of Triomune®/Nevilast®

(Stavudine 30/40 mg, Lamivudine 150 mg, and Nevirapine 200 mg), Duovir-N®/Zidolam-N (Zidovudine 300 mg, Lamivudine 150 mg, Nevirapine 200 mg); Duovir®/Avocomb® (zidovudine 300 mg and lamivudine 200 mg) which is combined with Nevirapine® 200 mg, Efavirenz® 600 mg. All the aforementioned combinations are used because of their efficiency and availability in the DRC. Through their accessibility to tri-therapy, the adverse events (dermatological, neurological, haematological, gastrointestinal, musculoskeletal, physical and metabolic) are more and more reported.
Objective: Identify the frequency of the adverse events linked to various fixed generic antiretroviral combinations of the system.
Methods: A retrospective analysis of adverse events of antiretrovirals induced by the 2010–2011 pharmacovigilance National Center in Vigiflow from notifications of adverse events of HIV-positive patients treated in the various hospitals of the DRC.
Results: During the years 2010–2011, seventy-four notifications were collected by the DRC Pharmacovigilance Center. The main adverse events indicated during the ARVS intake consist of Skin and appendage disorders (40%) of which 42,3% of rash due to Nevirapine (40%), Duovir-N (33,3%), Triomune® (20%), Efavirenz® (6,7%); furthermore, pruritus (38,6%) of among which 60% due to Triomune®/Nevilast®, Avocomb® (20%), Duovir-N® (10%) and the association Avocomb®-Efaviranz® (10%). 15, 3% of Steven Jonhson's Syndrome of which 75% due to Nevirapine® and 25% due to Duovir-N®. 3.8% of the nettle rash was due to Nevirapine®.
24% of Central & Peripheral Nervous System disorders with 77.7% of peripheral neuropathy with 42.8% due to Triomune®, Avocomb® (21.5%), Avocomb® + Efavirenz® (21.5%), Zidolam-N® (7.1%), Efavirenz® (7.1%); 11.1% of headache among which 50% due to Avocomb®, Nevirapine® (50%); 5.6% of convulsions with 100% due to Triomune® and neuritis among which 100% due to Triomune-.
12% of RBC disorders among which anaemia (55.6%) due to Duovir-N®/Zidolam-N®, Triomune®/Nevilast® (22.2%), Lamivudine® (11.1%) and Nevirapine® (11.1%) and the whole body disorders (7%), musculoskeletal disorders (7%), gastrointestinal disorders (7%) and Metabolic and nutritional disorders (7%).
Conclusion: The frequency of cutaneous adverse events is higher with generics containing Nevirapine, whereas neurological effects are noted with Stavudine, and haematological ones with Zidovudine.

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P187. The Progress of Control of Thalidomide in Brazil

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In 2005, it was detected the first record of the syndrome of thalidomide - phocomelia in Brazil in the XXI century, i.e. the beginning of a possible third generation (Schuler-Faccini L et al., 2007). In 2011, the Health Authorities found one more case was investigated and confirmed that the cause of self-medication was the mother of the child because of lack of control of the drug by the Basic Health Unit of the municipality. The emergence of new cases of Thalidomide Syndrome is concerning, as expected for this syndrome should be zero. The fragility of Health Information Systems in Brazil, accompanied by self-medication as a normal behavior of the population can be inferred that there is possibly a greater number of victims of Thalidomide, not yet identified. Given this universe of Brazil health authorities have launched a new legislation for the control of thalidomide. The aim of this paper is to describe the new legislation published for the control of thalidomide in Brazil. The methodological approach is based on a study to review the legislative framework related to the theme thalidomide. In addition to analytical reading, an interpretive reading allowed to relate the main changes the new legislation compared with the previous. There was an improvement over previous legislation. The new legislation allows a simplification of standards related to thalidomide in relation to the above clarification as to prescribers and other health professionals, guidance to patients due to changes in packaging materials and terms of clarity, control and monitoring of the drug by the National Health Surveillance; definition of responsibilities of Sanitary Surveillance and assists Pharmaceutical and the possibility of campaigns and training by the Ministry of Health, however, these advances will be sufficient to minimize the risks of emergence of cases of children born with the syndrome of thalidomide?

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Table I (relates to abstract no. P187).

Subject	Previous laws	New law
Contraceptive methods	Laws do not mention	Inclusion of effective methods of contraception
International code of diseases	Laws do not mention	List of all diseases with their authorized CID - Leprosy, STD /AIDS (idiopathic aphthous ulcers), lupus erythematosus, graft versus host disease and multiple myeloma
Use off-label	Laws do not mention	Guidance on how to request the National Agency of Sanitary Surveillance exceptional authorization for use of thalidomide in diseases not described above
Packaging	Laws do not mention	Inclusion of the image of a child affected by thalidomide
Notification of adverse reactions	Laws do not mention	Mandatory
Registration of prescribers and users	Laws do not mention	Establishment of registration of prescribers and users
Accountability criminal	Laws do not mention	Criminal liability for improper use

P188. Towards a Model Hospital ADR Program in Mexico: 66 Quality Indicators to Measure Outcomes and Benchmarks of Hospital-Based Pharmacovigilance

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Background: Pharmacovigilance systems identify and manage incidents of adverse drug reactions and medicine product defects. The primary objectives of in-house hospital programs are primarily improved quality assurance and risk management so that optimal drug therapy is delivered to all patients. Implementation of a scientific, patient-centered and evidence-based quality management system is critically important for modern pharmacovigilance and drug safety in general.

Purpose: The aim of this study was to develop a set of indicators for assessing quality, outcomes and benchmarks of hospital-based pharmacovigilance units which could set the basis to formulate guidelines for a model hospital ADR program in Mexico.

Methods: Expert panel consensus was used to develop a set of evidence-based key performance indicators to assess hospital monitoring and reporting programs for ADRs. The 8-hospital network *ASEGUREMHOS* served to validate 66 quality indicators as usable and pertinent for performance assessment of their pharmacovigilance units. The institutional review board at each hospital approved this study.

Results: Here we present a set of 66 indicators that were considered relevant and measurable to become part of the performance and outcome metrics of hospital-based pharmacovigilance systems. Our set of indicators was constructed based on *Donabedian's* structure, process, and outcome model and broken down into 6 core elements: human resources, report processing and management of pharmacovigilance data; documentary system; databases; organization and infrastructure; key performance indicators. The 66 indicators were weighed up and classified as essential, necessary or advisable.

Conclusions: Quality management systems for pharmacovigilance practices at hospitals must be robust and flexible in order to be able to identify needs for improvement in a timely manner and to implement corrective actions without delay. Here we present the first set of indicators to manage and measure quality of hospital-based pharmacovigilance systems in Mexico. The relevance, ready availability, sensitivity and specificity of these indicators make them suitable to be validated and used in other countries. Our work encourages the use of good pharmacovigilance practices in hospital settings to improve patient safety.

P189. Leucocytoclastic Vasculitis after Citric Acid Intoxication

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Background: Citric acid is widely used in detergent industry. Information about citric acid intoxication is limited. Its ingestion is a life-threatening condition that requires a multidisciplinary approach.

Case report: A 44-year-old male patient arrived to the hospital after a suicide attempt by taking 150 ml of dishwasher polisher. Vomiting was induced by his relatives before coming to hospital 4 hours after. Arterial blood-gas and electrolytes evaluation revealed blood-pH and potassium to be 7.15 and 6.13 mg/dL, respectively, and an increased plasma anion gap. Two weeks later, bilateral vocal cord paralysis was diagnosed and tracheostomy was performed. Internal Medicine consultation revealed a initial diagnosis of vasculitis and he was admitted to Internal Medicine Department. There was a diffuse cutaneous petechial rash which was nonpalpable and the largest one was about 2 cm diameter. The pathological punch biopsy sample taken from the lower part of the left leg, where there was diffuse rash, revealed leucocytoclastic vasculitis. One mg/kg prednizolone was started after vasculitis was confirmed pathologically. Cutaneous lesions recovered dramatically.

Discussion: Many drugs are indicated to cause leucocytoclastic vasculitis. Antibiotic, especially those of penicilin group and clarithromycin are reported to cause leucocytoclastic vasculitis and henoch-schönlein purpura. Other agents that may cause leucocytoclastic vasculitis development are non-steroid anti-inflammatory drugs, proplytiouracil, paracetamol, simetidin, streptokinase, metformin and acenocumaral. There's no other case in literature as ours who took foreign substances such as citric acid for suicidal purposes rather than treatment purposes. The only case found in literature about citric acid had metabolic acidosis with high level of anion gap, which recovered after ionized calcium infusion; however, its follow up do not report a leucocytoclastic vasculitis similar to our case.

P190. Acute Colchicine Intoxication in an Adult

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Colchicine is widely used for the treatment of various disorders primarily for gout, Behcet's Disease and familial Mediterranean fever. Colchicine poisoning is a rare, but well-described clinical entity with three phases, namely gastrointestinal complaints, multiorgan failure and if the patient survives, rebound leucocytosis and alopecia. In the second phase overwhelming septicemia, secondary to leucopenia is anticipated.

A 26-year-old female patient was admitted to our emergency department following a suicide attempt. She had ingested 20 mg colchicine an hour before admission. Her major complaints were abdominal pain, nausea and vomitting. Her vital signs were normal on admission with blood pressure 120/80 mmHg, heart rate 85 bpm and fever 36.7°C. Physical examination was unremarkable other than abdominal tenderness. Pertinent laboratory data were Hb: 14.5 g/dL (12–14 g/dL), WBC: 6.3×10^3 ($4–10 \times 10^3/\mu L$), platelets: 155×10^3 ($150–400 \times 10^3/\mu L$), urea: 25 mg/dL (7–46 mg/dL), creatinine: 0.63 mg/dL (0.6–1.2 mg/dL), Na: 135 mmol/L (135–145 mmolL), K: 3.8 (3.5–5 mmol/dL), aspartate amino transferase (AST): 64 IU/L (2–45 IU/L), alanin amino transferase (ALT): 18 (35–45 U/L), γ-glutamil transferase: 11 (30–40 IU/L), lactate dehidrogenase: 891 (<250 U/L), creatine kinase (CK): 103 IU/L (<149 IU/L), PTZ: 17.3 second (10–14 second), INR: 1.15 (1.1–1.4). Urine analysis was normal at her admission. Gastric lavage was performed and activated charcoal was administered immediately. On the first admission day there were no significant changes about her laboratory findings. On the second day of her admission PTZ (93.5 second), INR (6.1), AST (357 IU/L), LDH (4810 IU/L) and CK (635 IU/L) values were increased. On the third day of her admission she developed non-cyclic vaginal bleeding. On the fourth day she developed pancytopenia (WBC: $3.94 \times 10^3/\mu L$, Hb: 10.3 g/dL, PLT: $16.2 \times 10^3/\mu L$). Because of low platelet count, bleeding symptoms and clinical findings of liver dysfunction vitamin K injections, erythrocyte suspension, fresh frozen plasma and platelet suspensions was given 4 repeated doses. On the ninth day of admission, laboratory values

returned to normal.On the twenty-first day, hair loss which led to transient total alopecia, developed.
In conclusion, patients with colchicine intoxication are susceptible to infections, gastrointestinal symptoms and bleeding, hemodynamic instability, DIC, pancytopenia caused by bone marrow depression, hypocalcemia, ataxia, leukocytosis, and alopecia.

P191. Study to Evaluate Awareness about Pharmacovigilance Amongst Health Care Personnel: An Observational Prospective Study

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Background: No drug is devoid of adverse drug reactions (ADRs). Though every drug is given market authorization after its clinical trial but after its marketing is started drug is used in diverse populations and conditions. So it becomes essential to keep vigil over the safety concerns of the drugs. Adverse drug reaction reporting system therefore is of paramount importance to ensure the safety of patients, which is the scope of pharmacovigilance. Developed countries have developed pharmacovigilance systems since long back in 1960s but developing countries are struggling to establish their robust pharmacovigilance set up. In India also, the Government of India has started pharmacovigilance program of India (PvPI). Under this program the health care professionals' are expected to report ADRs to the ADR monitoring centres identified under PvPI. Awareness amongst the healthcare professionals is one of the factors to make PvPI successful. Therefore, present study was designed to assess the awareness of the healthcare professionals/students of North Indian region about pharmacovigilance.
Materials & Methods: A questionnaire comprising questions of different aspects of pharmacovigilance was prepared and given to the health care professionals for their assessment.
Results: It has been found that 33.26%, 36.9%, 13.51%, 16.29% of respondents were having excellent, good, average, poor knowledge, respectively, regarding fundamentals of pharmacovigilance. Knowledge of the reporting of the pharmacovigilance was excellent in 39.48%, good 32.61% and poor in 27.89% of respondents. 75.53% of respondents were able to give constructive opinion about the betterment of the system for reporting pharmacovigilance. 89% respondents were found in favour of establishment for pharmacovigilance system in hospital.
Conclusion: Conclusively more campaigns/ awareness programs should be organized for the healthcare professionals in order to make a robust and productive pharmacovigilance set up in India.

Table I. Grading scale to define the awareness of respondents

Class	Total no. of questions	Grading scale			
		Excellent	Good	Average	Poor
A	6	6	5, 4	3	≤2
B	2	2	-	1	0
C	3	3	2	1	0
D	4	4	3	2	≤1

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Table II. Scores earned by respondents in different classes of questions

Score earned	No of respondents from Class A earning score (%)	No of respondents from Class B earning score (%)	No of respondents from Class C earning score (%)	No of respondents from Class D earning score (%)
6	155 (33.26)	–	–	–
5	89 (19.09)	–	–	–
4	83 (17.81)	–	–	352 (75.53)
3	63 (13.51)	–	316 (03.86)	62 (13.3)
2	25 (5.36)	184 (39.48)	83 (17.81)	29 (6.22)
1	23 (4.93)	152 (32.61)	37 (7.93)	05 (1.07)
0	28 (6.00%)	30 (27.89%)	30 (06.43%)	18 (3.86%)