Results: Our method detected signals of severe hepatotoxicity for troglitazone and propylthiouracil 2–5 years earlier than the time of initiation of regulatory action. No signal of severe hepatotoxicity was detected for bosentan which was launched with a hepatic boxed warning and nefazodone which was labeled with a hepatic boxed warning in 2002. Nevertheless, signals indicating non-severe and/or non-specific hepatotoxicity were detected for bosentan since launch and for nefazodone since 2005. For all nine drugs without known hepatotoxicity, no severe hepatotoxicity signal was detected.

Conclusions: The results indicate that a method based on severity classification is useful in early detection of severe hepatotoxicity and can add value to routine pharmacovigilance. Nevertheless, further studies are needed to evaluate its effectiveness.

666. Prevalence and Characterization of Potential PPI-Clopidogrel Interaction in a Prescription Database in 2006–2009

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Background: Recent studies discovered a potential risk for adverse cardiovascular events associated with the dual use of clopidogrel and omeprazole/esomeprazole. FDA and EMA have recently discouraged the combined use of these agents unless strongly indicated.

Objectives: The aim of this study was to assess the annual prevalence of these potential drug-drug interactions (pDDIs) in Campania, an Italian Region of almost 5.5 million inhabitants, from January 2006 to December 2009.

Methods: We conducted a retrospective cohort study on the 2006–2009 Campania outpatient pharmacy databases of residents, aged 6–95 years. Based on the ATC classification system, prescriptions of the two proton pump inhibitors and clopidogrel were retrieved for the analysis.

Results: Omeprazole users were 185,883 (3.4% of all residents) in 2006, to 422,811 (7.8%) in 2009; esomeprazole users were 181,620 (3.3%) in 2006, to 69,858 (1.3%) in 2009; clopidogrel users were 8,750 (0.2%) in 2006, to 11,893 (0.2%) in 2009. 37.9/100,000 residents were exposed to at least one concomitant prescription of omeprazole-clopidogrel in 2006; this rate showed a trend towards an increase, up to 57.7/100,000 residents in 2009. 25.4/100,000 residents were exposed to at least one concomitant prescription of esomeprazole-clopidogrel in 2006; this rate showed a decreasing trend, with 8.8/100,000 residents in 2009. Marketing of generic omeprazole probably accounted for these different temporal patterns. As about one out four patients with clopidogrel received also a prescription of omeprazole/esomeprazole, anagraphical characteristics of concomitant cohorts are quite similar to those of clopidogrel cohorts (70% men, mean age 66 years). 70–80% of patients with concomitant events of both pDDIs received prescription of interacting drugs in the same day (co-prescriptions).

Conclusions: In 2009, out of almost 12,000 Campanian patients treated with clopidogrel, 3,600 were exposed to over 16,000 concomitant prescriptions of omeprazole/esomeprazole, with a potential increased risk of cardiovascular outcomes.

667. The EU-ADR Alliance: A Federated Collaborative Framework for Drug Safety Studies

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Background: EU-ADR is a European research project resulting in a computerized system exploiting data from electronic healthcare records (EHR) for early detection of adverse drug reactions. The system identifies drug-event associations from epidemiological data and uses computational and text mining techniques to substantiate them in the light of current biomedical knowledge. EHRs of +30 million patients from several European countries are available. The EU-ADR system has been initially built for addressing relevant events for drug safety surveillance such as upper gastrointestinal bleeding, anaphylactic

shock, acute renal failure, rhabdomyolysis, myocardial infarction, etc.

Objectives: Based on the resulting system, the EU-ADR Alliance is devised as a collaboration framework for running studies and answering drug safety questions in a federated manner, using extracted data from multiple European private and public EHR databases.

Methods: The EU-ADR Alliance will be composed by members bringing in relevant expertise (EHR databases, information technologies). It is based on the concept of federated databases, non-competition with its members, independence and scientific interest. It will undertake commissioned or members individual studies and the annual Alliance Research Plan. The advantage of running studies through the Alliance is that more powerful studies can be set up and run faster, given that a governance structure and working methods are in place.

Results: EU-ADR Alliance candidate member organisations include eight European EHR database with access to +45 million patients from Italy, Netherlands, UK, Germany and Denmark. A proof of concept phase is ongoing. Studies contracted by the European Medicines Agency will utilise the EU-ADR Alliance concept and operations. These studies concern the patterns of use of oral contraceptives; exploring an association between cardiac valve disorders and the use of biphosphonates and the monitoring of the effectiveness of risk minimisation in patients treated with pioglitazone-containing products.

Conclusions: The EU-ADR Alliance will provide an unprecedented framework to run drug safety studies across EHR databases with important power and speed benefits.

668. Fragile Skin? From Sensation to Evaluation

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Background: "Fragile skin" is a subjective (experienced) and objective (clinically evaluated) perception of the skin's condition. "Fragile" skin is based on constitutional factors concerning the structure and function of the epidermal "barrier" (although any disturbance of this structural barrier inevitably leads to elicitation of inflammatory reaction). It can thus be defined as a constitutional lower resistance threshold to minor environmental aggressions. Just like a baby's skin, "fragile" skin is delicate and requires special skin care which would allow strengthening of skin's natural protective qualities.

Objectives: The aim of this work was to evaluate the subjective perception of "fragile skin", i.e., to see whether the notion of "fragile skin" has a precise connotation with adult subjects from four different countries with diverging cultural, ethnical and geographical background: France, Spain, Sweden and Japan

Methods: In each of the four countries, a sample representative of the overall adult population was prepared by the CSA Santé. A series of questions were asked, including: "Do you think that you have fragile skin?" A total of 4,500 subjects were questioned.

Results: At the Question: "Do you have fragile skin": 29% of French, 34% of Spanish, 25% of Swedish and 52% of Japanese respondents answered "yes". It was therefore observed that approximately one-third of the European population considered their skin to be fragile, while for Japan it was one in two persons. Trends according to gender were identical in all countries, with women consistently higher in number to express the sentiment of having fragile skin: 39% in France, 33% in Spain, 28% in Sweden and 59% in Japan

Conclusions: This evaluation of representative populations provides a series of unprecedented responses in terms of subjective perception of fragile skin. These results now need to be confirmed by objective evaluation on the basis of relevant and specific tests. The nature of the correlation between the dermatosis and the propensity to claim to have fragile skin also needs to be specified. The notion of fragile skin is evidently a part of the personal experience of a non negligible portion of any given country's population addressed in this study.

669. Drug Screening Tests Improve Treatment Retention in a Cohort of Outpatients Starting Opioid Substitution Therapy

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Background: According to French guidelines concerning opioid substitution treatment (OST), drug screening tests are recommended for the follow-up of opioid-dependent patients. However, their value in ambulatory practice has not been studied.

Objectives: To assess the value of drug tests in the therapeutic management of opioid-addicted patients in an outpatient setting.

Methods: A retrospective cohort was built from the January 2009 to June 2011 data of the French health insurance system database for the Midi-Pyrenees region. Patients starting opioid substitution treatment, defined as patients with no reimbursement for an opioid substitute during the previous 6 months, were included from July 2009 and followed for 12–24 months. Two groups of patients were

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