Objectives: Within the context of methods development and evaluation in the EU-ADR project, we propose a reference standard of drug-adverse event pairs acknowledged to be associated (i.e., 'true positive') and drug-event pairs where there is currently no 'known proof' of such association (i.e., 'true negative').

Methods: The reference standard was constructed for ten top-ranked events judged as important in pharmacovigilance based on the following criteria: (1) 'trigger for drug withdrawal'; (2) 'trigger for black box warning'; (3) 'leading to emergency department visit or hospitalization'; (4) 'probability of event to be drug-related'; and (5) 'likelihood of death'. A stepwise approach was employed to identify which, among a list of drug-event associations, are previously well-known (true positive associations) or highly unlikely (true negative associations) based on published scientific literature, drug product labels, spontaneous reports made to pharmacovigilance database systems, and expert opinion. Only drugs with adequate exposure in EU-ADR to allow detection of an association were considered. Manual verification of 'true positive' and 'true negative' associations was independently performed by two researchers with expertise in clinical medicine, pharmacoepidemiology, and pharmacovigilance. A third expert arbitrated in case of disagreement between evaluators.

Results: 95 drug-event combinations comprised the reference standard, which included 45 'true positive' associations and 50 'true negative' associations for 10 events of interest: bullous eruptions; acute renal failure; anaphylactic shock; acute myocardial infarction; rhabdomyolysis; aplastic anemia; neutropenia; cardiac valve fibrosis; acute liver injury; and upper gastrointestinal bleeding. For cardiac valve fibrosis, there was no drug with adequate exposure in the database network to permit detection of a 'true positive' association.

Conclusions: Proper evaluation of new signal detection methodologies calls for the creation of a reference standard, the purpose of which is to better define the predictive value of such methodologies and their added value to the current pharmacovigilance armamentarium. The reference standard is by no means definitive, however, and should be seen as dynamic. As knowledge on drug safety evolves and new issues in drug safety arise, this reference standard will need to be re-evaluated.

Reference

1. Hauben M, Aronson JK. Defining 'Signal' and its Subtypes in Pharmacovigilance Based on a Systematic Review of Previous Definitions. Drug Saf 2009; 32 (2): 99-110

Periodic Safety Update Reports

OP06. The Outcome of PSUR Assessments of Biopharmaceuticals

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Background: Recent changes introduced to European legislation amend the requirements for the submission of periodic safety update reports (PSURs). However, information on the outcome of PSUR assessment is lacking.

Aim: To describe the outcomes of PSUR assessments.

Table I. Proportion of PSUR assessments leading to SPC changes in various subgroups

	SPC change [n (%)]	p-Value[a]
Period covered by PSUR		
≤6 months	19/50 (38)	1.00
>6 months	8/20 (40)	
Time between report and IBD		
≤5 years	8/23 (35)	0.80
>5 years	19/46 (41)	
Mechanistic class		
Monoclonal antibodies	10/18 (56)	0.10
All other	17/52 (33)	
ATC group		
Immunomodulators and antineoplastics	15/26 (58)	0.02
All other	12/44 (27)	
a 2-sided Fisher's Exact test.		

Methods: A cross sectional analysis was performed of all PSURs and PSUR assessment reports (AR) issued between July 1st 2008 and June 30th 2010 for all biopharmaceuticals centrally approved in the European Union. PSURs and PSUR ARs were obtained from the repository of the Dutch Medicines Evaluation Board, CBG-MEB.

Results: PSURs and PSUR ARs were collected for 70 products. Most products in the sample belonged to the ATC group of antineoplastic and immunomodulating agents (n = 26, 37.1%). Of the 70 PSURs included in the sample 26 (37%) covered a period of 6 months, 24 (34%) a period of 1 year and 20 (29%) a period of more than 1 year.

The most common outcome of PSUR assessment was monitoring a possible safety issue, which was requested in 55 (79%) of all ARs. Of these, 23 (42%) included new safety concerns not identified before. New safety concerns were identified in 35% of the PSURs that were issued within 5 years of the international birth date (IBD) of the product, and in 40% of the PSURs submitted after 5 years of the IBD (p = 0.795). Cumulative reviews of data relating to a possible safety issue were requested in 31 (44%) of the PSUR assessments and 27 (39%) of the assessments resulted in proposals and/or requests to change the Summary of Product Characteristics (SPC). The proportion of assessments resulting in SPC changes in various subgroups is presented in table I.

Conclusions: PSUR assessments are an important tool in the dialogue between regulators and marketing authorization holders. PSUR assessments are involved in the safety management of both new and well established products. New safety concerns occur throughout the lifecycle of biopharmaceuticals and may occur more often for products in different therapeutic and mechanistic classes.

Vaccine Pharmacovigilance

OP07. The Italian Surveillance of HPV Vaccination

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Objectives: To carry out an active surveillance of common events on 9- to 26-year-old women receiving human papillomavirus vaccine (HPV) in Italy. The surveillance of HPV vaccination is included in the