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### Drug Safety Scientometrics Overview Highlights Public Health Issues

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# Drug Safety scientometrics overview highlights public health issues.

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## Introduction

### *Drug safety*

Although clinical trials are required for all new drugs before market approval, firms and drug regulatory agencies regularly face adverse drug reactions (ADR) in postmarketing phase which conduct to drug warning or withdrawal with deleterious impact on public health. Therefore, Drug Safety (DS) also known as Pharmacovigilance, is the science of monitoring ADR (Cobert, 2012). Despite that DS has a social welfare function, it has not been the study of any scientometrics analysis

### *Objectives*

Our goal is to fill this gap by mapping the DS literature. This analysis might highlight some trends, the role of drug regulatory and firms in diffusing information, understand better some DS controversial events, help scholars in mastering pharmacovigilance literature, and it contribute to further development on literature-based discovery of ADR with the help of natural language processing.

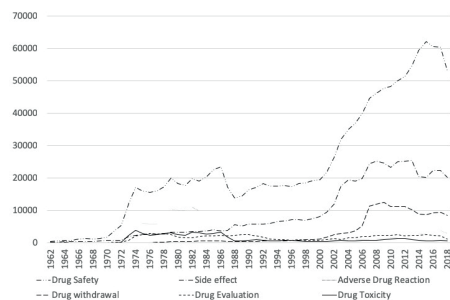
## Materials & Methods

Literature search on DS was run in Scopus<sup>®</sup> database until 31/12/2018, with a query across the title, abstract or keywords in all types of records using a string of 21 different keywords identified as Mesh terms after mindmapping the MesH hierarchy. A corpus of 1,3350,138 documents was analyzed. In addition, a specific query on DS journals was run and 8,854 documents were isolated. Bibliometric analysis was done using Scopus embedded statistic functions and descriptive statistics analyses were run using Excel<sup>®</sup> and Xlstat<sup>®</sup> add-in package. Visualization of bibliometric network was performed with VOSviewer<sup>®</sup>, a network analysis software. “Reference Publication Year Spectroscopy” (RPYS) analysis (Marx, 2014). toward the identification of the historical roots of DS research field was done using CRexplorer<sup>®</sup>, a software for cited references analysis. delayed recognition (DR) publications were identified with the calculation of the Beauty coefficient (B), a parameter-free (Ke, 2015).

## Results

### *Drug Safety research trends*

A corpus of more than 1.3 M DS documents were gathered (72% articles, 14% reviews, 4% letters and 12% others). If publications on DS were published early during the 20<sup>th</sup> century with the founding of the FDA (1938), we focused our analysis after the Kefauver-Harris Amendment (1962) which revolutionize drug assessment after the thalidomide birth defect tragedy. Publications on DS started to rise with some delay in the early 70’ and then, the number of publications stayed stable around 18.000 publications/year until 2001 (Figure 1).



**Figure 1. Trends of Drug Safety publications.**

Then DS publications increased steady reaching 60.000 publications/year in 2015. Publications in DS journals represent only 1.57%. In the last 20 years, only 0,15% of the DS publications were sponsored by pharma firms. An analysis of press releases in Factiva<sup>®</sup> database identified a peak of media news covering DS between 2005-2009 at the time of anti-cox2 drugs withdrawal. The analysis of co-occurrence of words in the corpus of DS journals’ papers visualize distinct keywords’ groups centred around “Pharmacoepidemiology”, “Safety”, and “Pharmacovigilance”, which changes along the last 20 years (data not shown). We undertake a detailed trends analysis of the main keywords. Figure 1 show the trends of the top 5 keywords by total publications numbers (side effects: 510,101; Adverse Drug

Reaction (ADR): 166,297; Drug withdrawn: 154,233; Drug evaluation: 82,913; Drug toxicity: 61,953). Some keywords in use at the beginning are no longer cited and *vice versa*. Since the anti-cox2 controversy, the main keywords associated with DS publications is “Side Effect” and not anymore ADR.

### Drug Safety publishing actors

The top 5 countries publishing on DS are in the order: USA (31%) United Kingdom (9%) Germany (7%), Japan (6%) and Italy (6%). However, the EU countries account as much publications than US underlying the importance of the EMA. Moreover, all BRICS countries ranked in the top 30 countries (data not shown). The DS research intensity was further explored at country level by looking at any correlation between DS publications, population size, health expenses by GDP and pharmaceutical expenses per capita (source: OECD) (Table 1).

**Table 1. Correlation matrix (Pearson)**

	DS pub.	Pop. size	Health % GDP	Pharma exp.
DS pub.	1	<b>0.911</b>	<b>0.762</b>	-0.194
Pop. size	<b>0.911</b>	1	<b>0.597</b>	-0.026
Health % GDP	<b>0.762</b>	<b>0.597</b>	1	<b>-0.490</b>
Pharma exp.	-0.194	-0.026	<b>-0.490</b>	1

NB: Values in bold are different from 0 with  $\alpha=0,05$

The top 3 publishing institutions are Harvard Medical School (US), INSERM (FR) and Veterans affairs (US) with more than 10.000 total publications each. NIH (US) is ranked only 10<sup>th</sup> and FDA (US) is lagging behind after 50<sup>th</sup> with 3763 publications. To be notice, the 1<sup>st</sup> pharma firm, Pfizer, ranked 12<sup>rd</sup> with 6891 publications (data not shown).

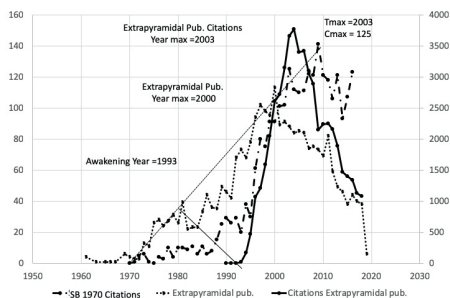
### Drug safety historical roots

To gain historical insight on important past DS publications, we run a RPYS analysis. The deviation of the number of Cited References (CRs) from the median pinpointed years 1959, 1977, 2005 and 2012 as more significant than the others (data not shown). To identify the CRs responsible for these peaks, we sorted the list of unique CRs published by their citations' frequency. The top publication was a paper on “A method for estimating the probability of adverse drug reactions” (Naranjo, 1981).

### Delayed Recognition of Drug Safety publications

To identify DR papers in DS, we calculate the “Beauty coefficient” for the top 400 most cited (between 10127 and 556 citations) papers on DS. We identified 8 candidate DR papers among which the publication of Naranjo (1981) (data not shown). We further explored an interesting case with B=393, an article describing “A rating scale for extrapyramidal

side effects”. This publication has been delayed for 23 years and its citations awakening with the rise of interest in extrapyramidal side effects (EPSE), a drug-induced movement disorder by antipsychotics.



**Figure 3. Delayed Recognition of EPSE.**

### Discussion

While DS is a major issue, we reported for the first time a landscape analysis of the literature. It reveals some characteristics: (1) research increase recently (2000') while major drug regulation backed to 1960' (2) it is a heterogenous research field which concepts evolved a lot in half century (3) most of publications are published outside core journals, probably by clinicians (4) the contribution of the industry is marginal, even if some firms are publishing a lot, raising questions about the industry responsibilities (5) US and EU countries are leading as expected because of the size of their drug market, but there is no correlation with pharmaceutical expenses (6) US federal institutions are lagging behind the universities in reporting DS (7) anti-cox2 ADR controversy has awakened DS research field (8) identification of DR papers raise questions about resistance to the discovery of ADR and therefore its public health impact. Further studies are in need to measure if DR papers are linked to delayed drug withdrawn. Finally, our analysis supports the prospective for literature-based discovery in DS.

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