University of Copenhagen

FACULTY OF HEALTH AND MEDICAL SCIENCES

Copenhagen Centre for Regulatory Science

THE IMPACT OF THE NEW PHARMACOVIGILANCE LEGISLATION ON THE HARMONISATION OF DIRECT HEALTHCARE PROFESSIONAL COMMUNICATIONS ACROSS EUROPE

Authors: Iris Joosse, BSc[1,2], Marie Louise de Bruin PharmD, PhD[1,2], Christine E Hallgreen, PhD[2]

[1]Utrecht Institute for Pharmaceutical Sciences (UIPS), Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, the Netherlands.
[2]Copenhagen Centre for Regulatory Science (CORS), University of Copenhagen, Denmark.

Declaration of interest: This study was performed under the umbrella of the Copenhagen Centre for Regulatory Science (CORS). CORS is a cross-faculty university anchored institution involving various public (Danish Medicines Agency, Copenhagen University) and private stakeholders (Novo Nordisk, Lundbeck, Ferring pharmaceuticals, LEO pharma) as well as patient organisations (Rare Diseases Denmark). The centre is purely devoted to the scientific aspects of the regulatory field and with a patient-oriented focus and the research is not company-specific product or directly company related.

Introduction

Background

Until today, significant inequalities in healthcare persist around the world and within Europe. In order to realise more equality in quality of healthcare, safety information should be equally harmonised across the EU. This is one of the objectives of the new pharmacovigilance (PV) legislation effective from 2012, giving particular consideration to the harmonisation of Direct Healthcare Professional Communications (DHPCs) across Europe. DHPCs (or 'Dear Doctor-letters') are communications by which valuable safety information is sent directly to individual healthcare professionals, to inform them of newly surfaced safety information.

Aims

To determine if the pharmacovigilance legislation had an impact on the harmonisation of DHPCs issued among countries under the jurisdiction of the EMA. A priori, a higher rate of harmonisation in the availability of DHPCs in the EU was expected to be seen in the years after the new pharmacovigilance legislation had come into effect compared to the period before that.

Methods

Data collection

The impact of the PV legislation was studied using a pre-post study design including DHPCs from 6 EU countries; Austria, Czech Republic, France, Germany, Ireland, and Spain. DHPCs disseminated between 2007 and 2011 and between 2013 and 2017 by the national competent authorities (NCA) of the 6 countries were identified through their respective webpages in April '18.

DHPCs which did not fulfil the GVP module XV list of situations for which a DHPC should be disseminated were excluded.

For all letters, information about the dissemination date, the medicine concerned (recorded by ATC code), a statement on NCA or EMA involvement and the general topic was collected. The authorisation procedure, either centralised or a national procedure (mutual-recognition and decentralised), was collected for each medicine.

Identifying the total number of unique messages, was done in a tiered process. All DHPCs with an ATC code unique to one DHPC were considered unique messages. For all DHPCs with min. one additional letter concerning the same ATC code, data on adverse drug reactions (ADRs) of concern were recorded. DHPCs with an ATC-ADR combination unique to one DHPC were considered unique messages. DHPC with min. one additional letter with the same ATC-ADR combination were manually compared to determine if they conveyed a unique message.

Statistical Analyses

DHPCs were regarded as harmonised when the specific message had been issued in ≥80% of the countries the drug had effectively been marketed in. The proportion of harmonised DHPCs within each period of time were statistically compared with a χ^2 test. A sensitivity analysis using other definitions of harmonisation (e.g. ≥60% and 100%) was run. The distribution of the degree of harmonisation of messages issued before and after the PV legislation was plotted.

Results

A total of 1939 DHPCs were identified from the 6 NCAs. Of these, 1325 were included in the primary search, in an additional search 10 more letters were identified and included (**figure 1**).

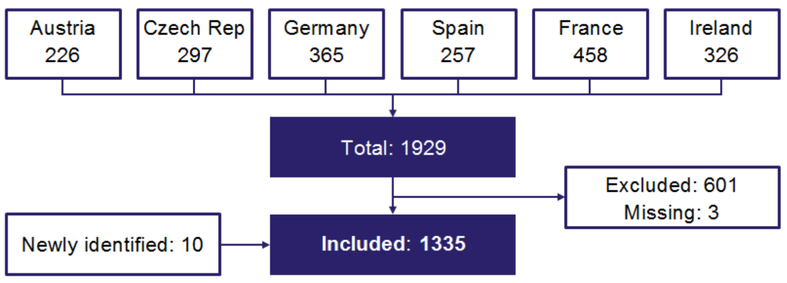

Figure 1. Flow diagram of inclusion process

The number of DHPCs per year fluctuated over time, with a peak in total volume in 2013 and a relatively low volume in 2009 (**figure 2**). Overall, more letters were send out between 2013 and 2017 (441) than the period before the implementation of the PV legislation (709).

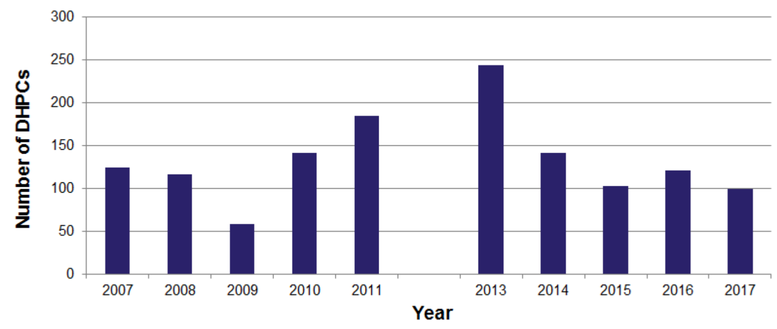

Figure 2. Yearly total volume of DHPCs.

The majority of DHPCs related to medicines authorised through the centralised procedure, and most included a statement on EMAs and/or NCA involvement. Austrian letters included a statement on involvement of the NCA only (**table 1**). The general topic of most letters related to new risks or changes in recommendation for use of the medication.

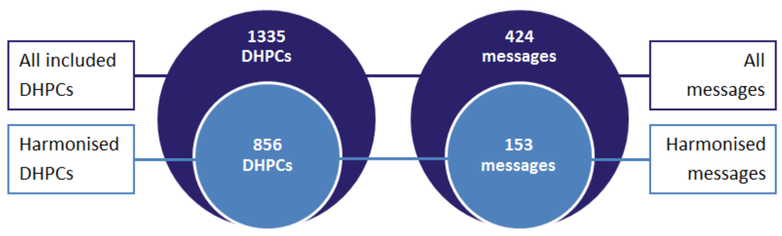

Figure 3. DHPC collection and corresponding messages

Table 1. General characteristics of included DHPCs.

	Austria	Czech R.	Germany	Spain	France	Ireland	Total
N	188	190	241	224	264	228	1335
Authorisation procedure							
Centralised	138	132	163	153	155	168	909
Nationalised	50	58	78	71	109	60	426
Competent authority statement							
None	0	29	35	28	5	23	120
EMA (+NCA)	0	141	176	162	169	178	826
NCA only	188	20	30	34	90	27	389
General topic							
Suspension	13	11	14	13	27	6	84
Change in use	60	68	81	80	98	81	468
Availability issue	1	11	22	1	4	7	46
(New) risks	113	99	122	129	128	131	722
Ongoing assessment	1	1	2	1	7	3	15

The 1335 letters comprised 424 unique messages (**figure 3**). The proportion of harmonised DHPCs was significantly higher after the enactment of the new PV legislation than before (67.3% versus 60.5%, p <0.01). Within the sensitivity analysis, an increase in harmonisation was observed from 29.6% to 52.3% (p <0.001) in DHPCs issued in all six countries (**figure 4**).

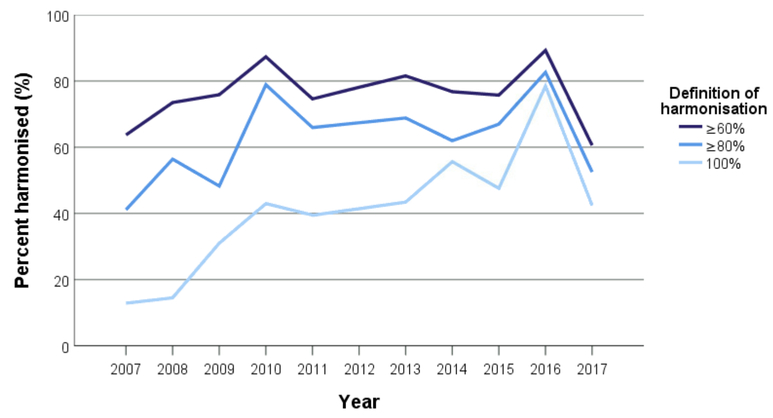

Figure 4. Percent harmonisation in DHPCs issued in the six countries

After 2012, a drop is seen in messages issued in ≥80 but <100% of the countries, whilst fully harmonised messages increase (**figure 5**).

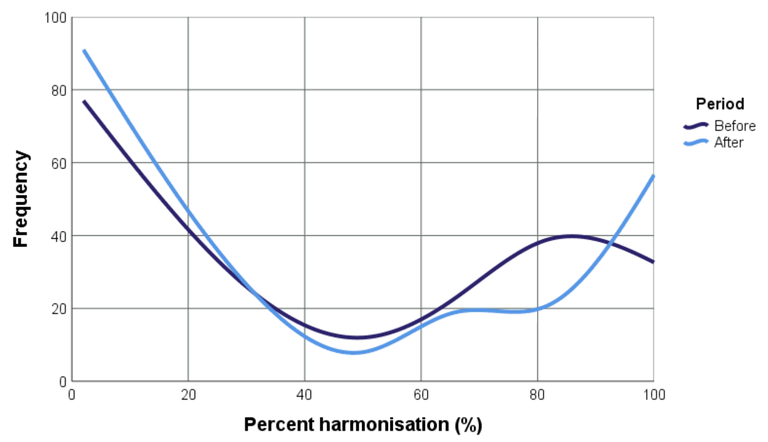

Figure 5. The distribution of messages of all compositions.

Conclusion

A moderate improvement in harmonisation of DHPCs disseminated between 2013-2017 and 2007-2011 in six EU Member States was found, largely due to a shift to more fully harmonised messages. It remains unclear whether the harmonisation can be attributed to the impact of the new PV legislation or to national changes instead.

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