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Impact of the 2012 pharmacovigilance legislation on the harmonisation of DHPCs in the EU

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Declaration of interest: This study was performed under the umbrella of 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

Direct healthcare professional communication (DHPC) is one of the most used measures to manage post-marketing drug risks in the EU. Previous research showed that there are substantial differences between countries for DHPCs published before 2013.

Objectives

The aim of the study was to analyse the content and timing of DHPCs sent out in Denmark and United Kingdom during January 2007-December 2016 in order to see if and how the implementation of the new EU pharmacovigilance legislation in 2012 have had an impact on the publication practice between the countries.

Methods

Data collection

All DHPCs from January 2007 to December 2016 were retrieved from national competent authorities, either from their websites (DKMA 2013-2017 and MHRA 2007-2016), or through a request for information (DKMA 2007-2012).
Letters were categorized as safety-related or not, and date of publication, drugs (ATC), EMA involvement and authorisation type (central/national) were recorded. For safety letters, adverse events (AEs, MedDRA) involved and recommendations were recorded.

Pairs of DHPCs published in both countries were identified based on ATC and publication date (<2yr), see **Figure 1**.

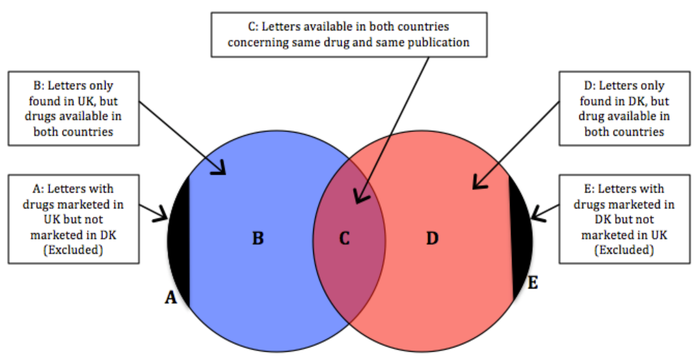


Figure 1. A schematic diagram of the classification made for safety DHCPs letters from Denmark and United Kingdom. The matching DHPCs are shown as 'C'. The DHPCs regarding drugs marketed in both countries but missing a matching DHPC in the other country is shown as 'B' for United Kingdom DHPCs and 'D' for Danish DHPCs. The DHPCs concerning drugs not marketed in the other country are shown as 'A' (drugs not marketed in Denmark) and 'E' (drugs not marketed in United Kingdom) were excluded and not dealt with in the analysis.

Within pairs timing of publication, AEs and recommendations were compared. DHPCs on drugs marketed in one country only were excluded.

Manual comparison of the DHPCs

All matching DHPCs from Denmark and United Kingdom ('C' in Figure 1 and 2) were additionally scrutinized and compared manually, and registered if the content of the letters was the same or not.

Statistical Analyses

Impact on harmonization of the DHPCs was assessed with regards to:

- The number of releases
- The content of the DHPCs
- Publication time of the DHPCs
- EMA involvement

T-tests were performed to determine differences before and after 2012 and between countries.

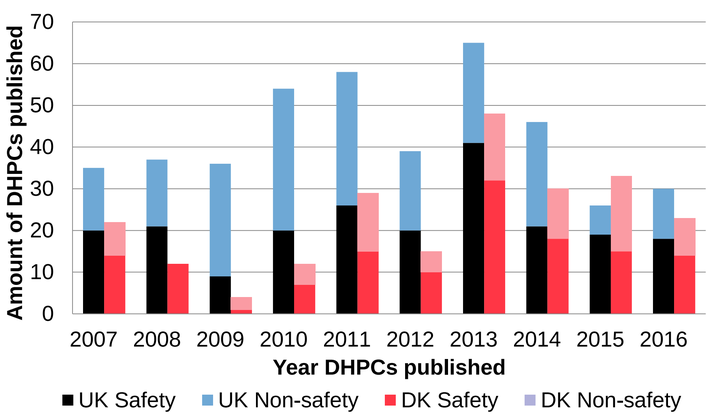
Results

Of the total of 228 Danish and 426 United Kingdom DHPCs letters 138 Danish (60.5%) and 215 United Kingdom (50.5%) were categorized as safety letters, see **Figure 2.** General characteristics of the letters are presented in **Table 1**.

Figure 2. Flow diagram of the included and excluded Danish and United Kingdom DHPCs and the grouping to safety and non-safety DHPCs.

The number of DHPCs per year as well as the proportion of safety-letters fluctuated over time, with a peak in total number in 2013 in both countries, see **Figure 3**.

Figure 3. The number of the safety and non-safety DHPCs published in Denmark and United Kingdom in the time period 2007 to 2016.



Among the safety letters, a significant increase was observed with respect to the number of releases available in both countries before (38/103, 37%) and after (73/101, 72%) 2012 (p<0.0001), see **Figure 4**.

With respect to content, 118/119 DHPC pairs in group C (99%) concerned the same letters. As a result, no changes over time were observed in the proportion of same letters.

Figure 4. Distribution of ratio of the releases of matching DHPCs publications in 2007-2016. The mean value for the proportion of 'C' was 0.37 ± 0.48 before 2012 and 0.72±0.45 after 2012.

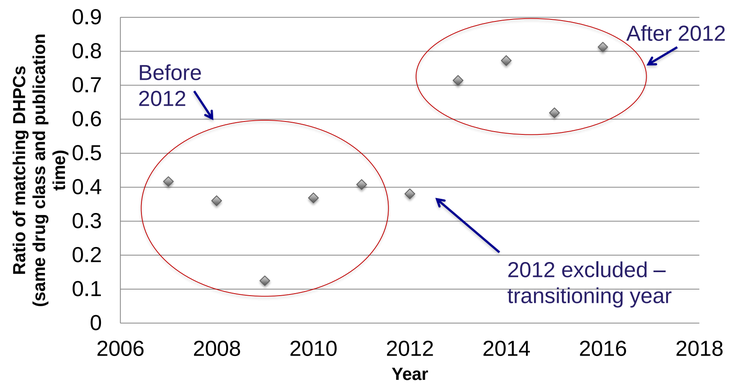


Table 1. Summary of the characteristics of the safety DHPCs from Denmark and United Kingdom for drugs, which have marketing authorization in both countries.

	DHPCs in United Kingdom only (Group B)		DHPCs pairs (Same ATC and time published) (Group C)		DHPCs in Denmark only (Group D)	
Year published	Total (n=88)	%	Total (n=119)	%	Total (n=18)	%
2007	10	11.4	10	8.4	4	22.2
2008	13	14.8	9	7.6	3	16.7
2009	7	8.0	1	0.8	0	0.0
2010	12	13.6	7	5.9	0	0.0
2011	12	13.6	11	9.2	4	22.2
2012	12	13.6	8	6.7	1	5.6
2013	10	11.4	30	25.2	2	11.1
2014	4	4.5	17	14.3	1	5.6
2015	6	6.8	13	10.9	2	11.1
2016	2	2.3	13	10.9	1	5.6
Drug class (ATC code 1 level)						
A (Alimentary tract and metabolism)			12	10.1		
B (Blood and blood forming organs)					6	33.3
J (Anti-infectives for systemic use)	10	11.4	11	9.2		
L (Antineopl./immunomodul. agents)	32	36.4	44	37.0		
M (Musculo-skeletal system)	15	17.0				
N (Nervous system)					4	22.2
Authorization type						
Centralized	59	67.0	91	76.5	8	44.4
Nationalized	29	33.0	28	23.5	10	55.6
Age classes (time between approval and publication of DHPC)						
0-3 years	24	27.3	40	33.6	1	5.6
3-10 years	33	37.5	41	34.5	3	16.7
10+ years	31	35.2	38	31.9	14	77.8

Timing of these letters with a recorded exact publication date (n=91) did not differ significantly (p=0.38) before 2012 (DK letters published 9 days earlier than UK letters) and after 2012 (UK letters published 6 days earlier than DK letters).
EMA involvement increased by 4% (being 92.1% before 2012 and 95.9% after 2012). However, a t-test showed no statistically significant difference (p-value > 0.05) in EMA involvement before and after the year 2012.

Conclusion

The pharmacovigilance legislation impacted on number of identical releases available in both countries and has thereby led to more harmonization between these two European countries with respect to DHPC publications.