

Impact of the Intensified Reporting Requirements on reporting of suspected side effects of new pharmacological products in Denmark

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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

The Law of Intensified Reporting Requirement (IRR) has been implemented in Denmark since 2003; the law requires all healthcare professional (HCP), with prescription rights, to report all suspected adverse drug reactions (ADRs) in the first two years after marked authorisation. After this period, the HCPs are required to report suspected serious and unexpected ADRs.

Aims

The aim of the study was to compare ADR reporting for products while they are under IRR to the period after, for products under intensified reporting between 2003 and 2010 as well as to evaluate Danish physicians' awareness of the IRR. The goal was to assess whether the IRR has an impact on HCPs ADR reporting patterns.

Methods

Data collection

Drug cohorts were derived from the List of approved drugs in Denmark (DK) as of April 2017, retrieved from the Danish Medicine Agency's (DKMA) website. To be included drugs had to be:

- A medicine for human use
- An originator product
- Approved in in DK between 2003 and 2010

Excluded were, generic medicines, vaccines and veterinary products. Drugs were also excluded if ADR reports excised for the product prior to it marketed date or if drug consumption did not exceed 100 units/1000 inhabitants during follow-up period.

For the drug cohort marketing date, ATC code were identified. Drugs were followed for a period of 6 years after marketing date. Year one was considered to be year marketed in DK if the date was within first half of a given year, and following year if marked date was in the second half. IRR periods were considered to be year 1 and 2 of follow-up period.

For the full follow-up period all Danish spontaneous ADR reports for medicines including information about reporting year, who made the report and seriousness of ADR report, were collected from the interactive Adverse Drug Reaction overviews, at the DKMA website. Drug utilisation for the follow-up period was collected from MedStat.dk, data on drug utilization is aggregate per calendar year.

Survey study

In addition a survey among physicians taking the course 'Sundhedsvæsnets Organisation og Ledelse' organized by the Danish Health Authorities, an obligatory course on the Danish the medical specialist education, was conducted. The survey was distributed to all physicians taking the course between May 2017 and June 2017.

The questionnaire consisted of three questions, one to collect information about years of experience as a physician, and two multiple-choice questions assessing the physicians knowledge about IRR. With one correct statement out of five statements about IRR for each of the two questions.

Statistical Analyses

Impact of IRR were assessed with regards to

- Distribution between number of serious and non-serious ADR reports
- Distribution of number of HCP reported ADR reports
- Number of ADR reports per consumed unit drug

Chi2 test were to determine difference in distribution of number of serious ADR reports and distribution in number of HCP reports between the two periods, that is, the period of IRR and a four year period after IRR.

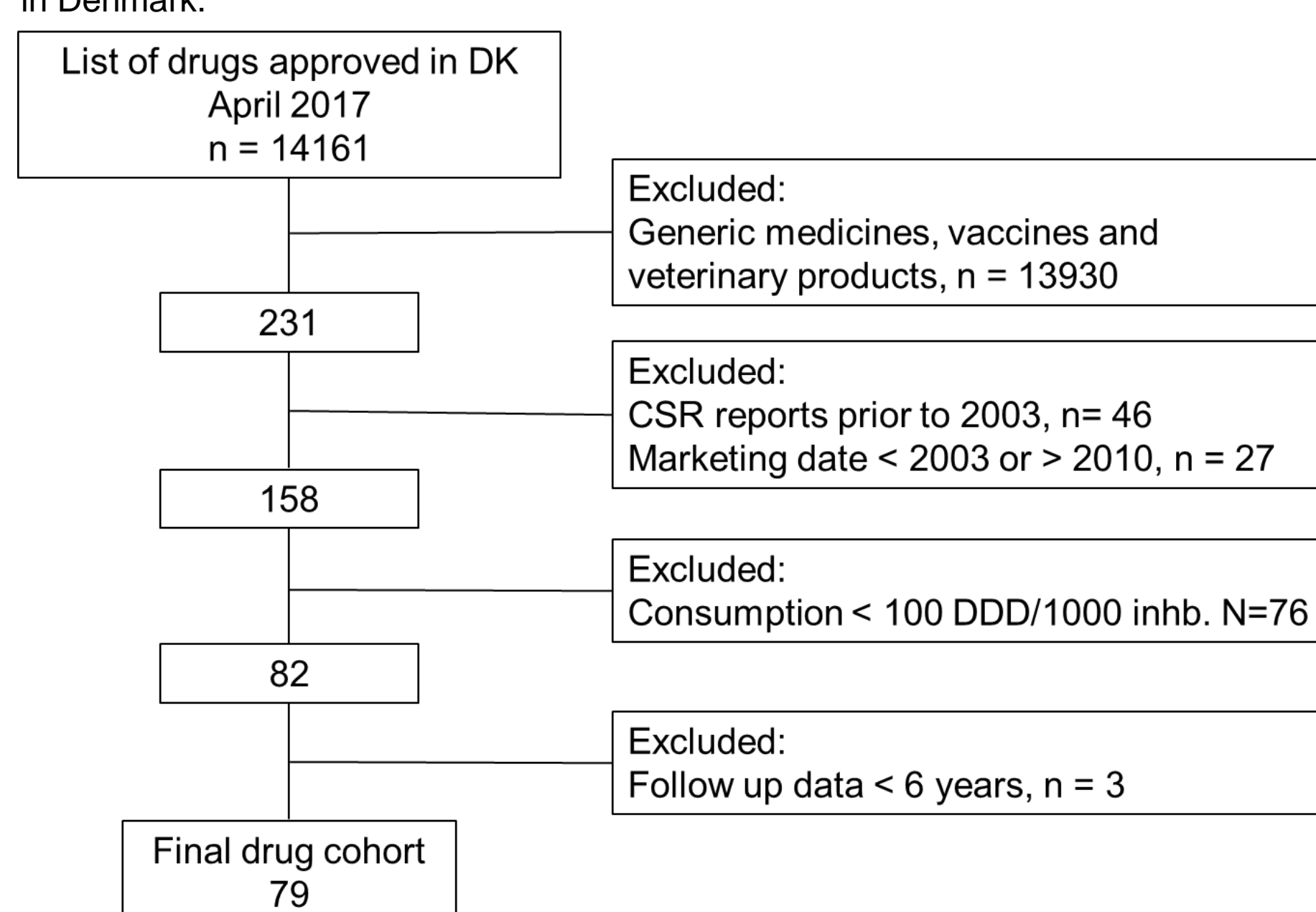
Mann-Whitney U test was performed to determine difference in ADR reporting rates between the two periods.

Results of the two knowledge about IRR questions were dichotomised into correct and non-correct answers. Number of correct answers and non-correct answers are provided.

Results

A total of 79 drugs were identified (Figure 1). For the 79 drugs marketed in Denmark between 2003 and 2010, a total of 6714 spontaneous ADR reports corresponding to 994 spontaneous ADRs were reported during the IRR period (mean 6.3 report per year per drug, median 1 report per year per drug) and 2849 ADR reports in the four years following IRR (mean 9.0 reports per year per drug, median 2.5 reports per year per drug). General characteristics of ADR reports are presented in Table 1.

Figure 1. Flow diagram of included and excluded pharmaceutical products marketed in Denmark.

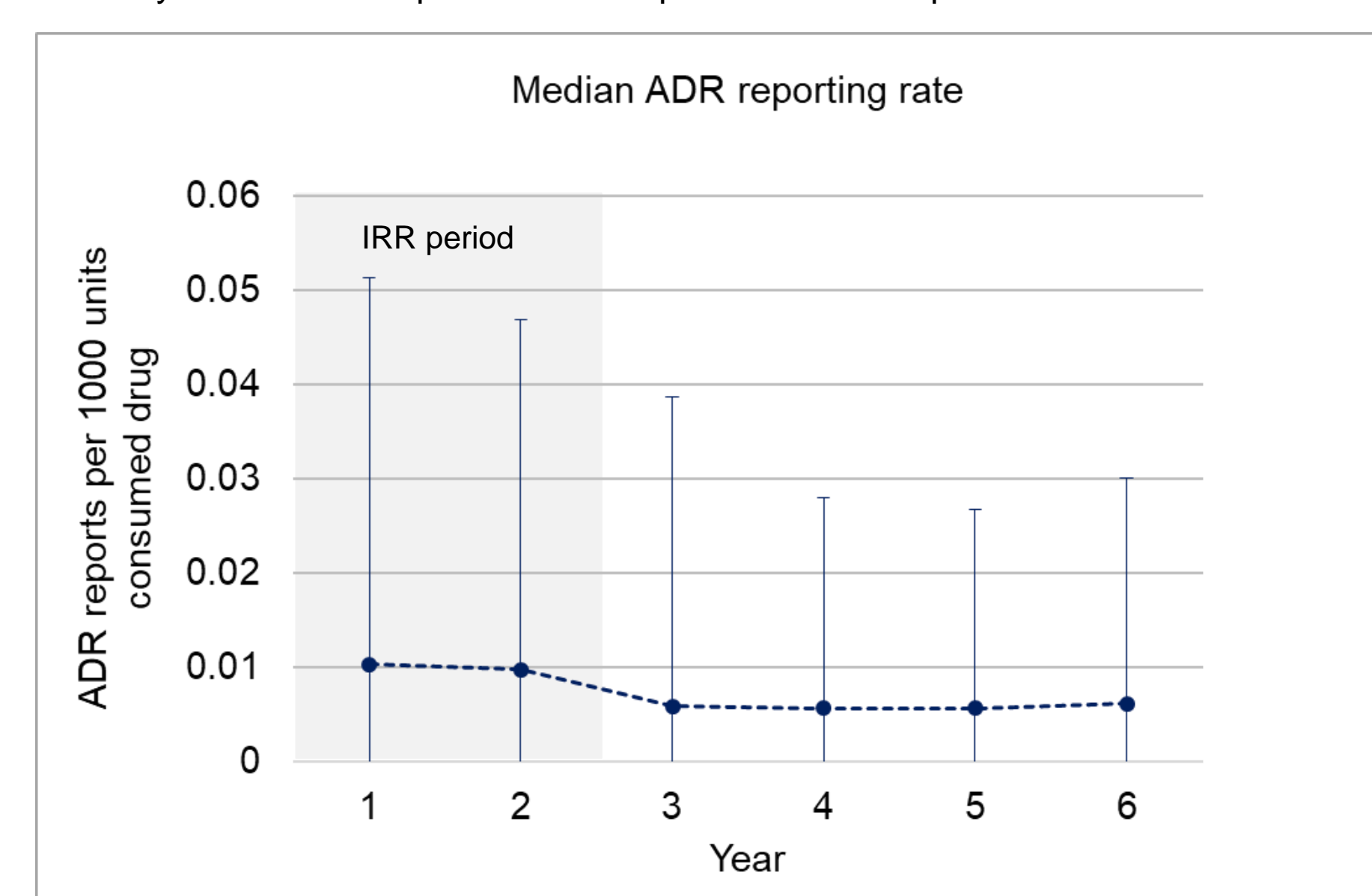


A significant difference between the distribution of non-serious and serious reports for the two periods was found 577 non-serious reports vs. 417 serious reports during IRR, and 1484 non-serious vs. 1365 serious in the four year after IRR ($X = 10.287, df = 1, p < .01$). The distribution between HCP reporting and other reporting (such as patients) also differs between periods, with 92.6 % of reports being from HCP during IRR and only 85.4% from HCP in the period after ($X = 33.289, df = 1, p < 0.001$).

Table 1. General characteristics of ADR reports during the Intensified Reporting Requirement (IRR) period and the four year period after IRR.

	IRR period N (%)	After IRR period N (%)
ADR reports	994	2849
Serious	417 (42.0)	1365 (47.9)
Non-serious	577 (50.0)	1484 (52.1)
HCP reporting	920 (92.6)	2433 (85.4)
Other	74 (7.4)	416 (14.6)

Figure 2. Median yearly ADR rate [ADR reports per 1000 units consumed drug], for the six years of follow-up. Error bars represent 1 and 3 quartile.



The median ADR report rate during the IRR period was 16.7 reports per 1000 units consumed (mean 45.2 reports per 1000 units consumed). In the four year period after IRR the median ADR report rate was 6.6 reports per 1000 units consumed (mean 24.6 reports per 1000 units consumed), there was no statistical significant difference between the ADR report rate in the two periods ($W = 3238, p = 0.05459$).

The survey was distributed to 120 physicians attending one of the 3 courses held in May and June 2017. A total of 87 physicians participated, 13 were excluded due to insufficient completion of the questionnaire. See Table 2 for general overview of responses among the 74 included participants

Table 2. General overview of questionnaire replies.

	Year medical experience			All (n = 74)
	0-5 (n = 37)	5-10 (n = 30)	>10 (n = 7)	
Definition of IRR				
Correct	21	19	4	44
False	16	21	3	30
Where to find list on drugs under IRR				
Correct	25	20	2	47
False	12	10	5	27

More than half of physicians 44 of 74 (59.5%) correctly defined the IRR requirements as 'During the first two years after a medicine has been marketed in Denmark all potential ADRs should be reported'. More than half of the physicians 47 of 84 (63.5%) also correctly identified the DKMA webpage as the place to find the list of drugs under IRR at a given time. Thirty-two of the 74 responders (43.2%) were correct in both questions.

Conclusion

Reporting of ADRs while drugs are under IRR was not higher than the period after, even when adjusting for consumption. However, there was a difference in the seriousness of the ADRs between the two periods, as well as in HCP reporting. The lack of knowledge of IRR among physicians might contribute to our results.

The law of IRR does not seem to have the intended effect, and other measures to ensure reporting in the two years after marketing should be explored

