ORIGINAL RESEARCH ARTICLE

Drug Saf 2010; 33 (6): 463-474
0114-5916/10/0006-0463/$49.95/0

A Decade of Safety-Related Regulatory Action in the Netherlands

A Retrospective Analysis of Direct Healthcare Professional Communications from 1999 to 2009

Peter G.M. Mol,[1,2] *Sabine M.J.M. Straus*,[2,3] *Sigrid Piening*,[1] *Jonie T.N. de Vries*,[1] *Pieter A. de Graeff*[1,2] and *Flora M. Haaijer-Ruskamp*[1]

1 University Medical Center Groningen, Groningen, the Netherlands
2 Dutch Medicines Evaluation Board, The Hague, the Netherlands
3 Department of Medical Informatics, Erasmus Medical Center, Rotterdam, the Netherlands

Abstract

Background: As pre-approval trials are inherently limited in assessing the complete benefit-risk profile of a new drug, serious safety issues may emerge once a drug gains widespread use after approval. Regulators face the dilemma of balancing timely market access with the need for complete data on risks. This challenge has led to a life-cycle approach but, so far, few data are available on post-approval safety issues requiring regulatory action.

Objective: The aim of this study is to determine the frequency, timing and nature of safety issues that necessitated safety-related regulatory action in the form of a Direct Healthcare Professional Communication (DHPC) issued by pharmaceutical companies in collaboration with the Dutch Medicines Evaluation Board during the past decade.

Methods: All DHPCs issued in the Netherlands from 1 January 1999 to 1 January 2009 were retrospectively collected from the national regulatory authorities. Elapsed time between the approval date and the issue of the DHPC was determined. Characteristics of the action including the nature of the safety issue (according to Medical Dictionary for Regulatory Activities [MedDRA®] terminology), type of drug and procedural aspects of the regulatory action taken were reviewed. DHPC characteristics were tabulated and explorative non-parametric tests were performed to study the effect of safety issue, drug class, drug type, orphan drug and first-in-class status on elapsed time from approval to the DHPC.

Results: 157 DHPCs were issued concerning 112 different active substances, approximately 9% (112/1200) of active substances available in the Netherlands in 2007. The number of DHPCs issued increased by 2.1 (95% CI 1.2, 3.1; $p < 0.001$) DHPCs per year over the past decade, reaching a total of 25 in 2008. The median time between approval and DHPC was 5.3 years (range 0.13–48 years). No significant trend in elapsed time to DHPC was observed in

relation to the studied years (p = 0.06). One-third of all DHPCs were issued in the first 3 years after approval, but 27% (n = 43/157) of the DHPCs were issued 10 or more years after approval. Timing of DHPCs differed depending on safety issue, drug class, drug type and orphan drug status. DHPCs mostly concerned adverse events in the system organ class of 'cardiac disorders' (15%), 'injury, poisoning and procedural complications' (13%) and 'general disorders and administration site conditions' (10%). In ten cases the drug was eventually withdrawn. Withdrawal occurred a median duration of 2.4 years after registration (range of 1.5–48 years) and was most frequently due to cardiac disorders (including QT interval prolongation; four occasions) and hepatobiliary disorders (two occasions).

Conclusions: In the past decade, the number of DHPCs has increased over time. This is likely caused by a multitude of factors: increased risk awareness by the public, media, regulators and other stakeholders; the type of drugs approved, such as orphan drugs and biologicals; and the regulatory process, including conditional approvals. The number of DHPCs may in the future increase further with the possibility of screening large epidemiological databases proactively for adverse drug events. Nine percent of all marketed drugs required a safety-related action. Regulatory action is taken shortly (<3 years) after market approval nearly as often as after intermediate (3–10 years) and long-term (>10 years) market exposure. These findings underline the need for risk management during the whole life cycle of a drug.

Background

Drug treatment has brought many benefits. Nevertheless, the same drugs that can be life-saving and improve quality of life can cause adverse reactions that are an important factor for hospitalization and morbidity.[1,2] Pre-approval trials, even when carefully designed and executed, are limited in their assessment of the full safety profile of a drug, and its complete benefit-risk profile can only be appreciated once a drug is approved and used in daily practice.[3] Well known shortcomings of pre-approval trials include lack of information on long-term effects, the selection of (relatively healthy) patients and exclusion of certain patient groups (e.g. pregnant women, the elderly or children), and a study design that is primarily meant to assess efficacy.[3-5] In addition, certain adverse events will be difficult to identify such as relatively rare adverse events, (e.g. rhabdomyolysis due to HMG-CoA reductase inhibitors ['statins']), adverse events that have a relatively high background incidence (e.g. rofecoxib and cardiovascular events) and events related to the disease (e.g. selective serotonin reuptake inhibitors and suicide).[6]

Regulators face the dilemma of balancing timely market access with the need for complete data on risks. This challenge has led to a life-cycle approach. Approval does not signal the end of drug development, but the start of continuous evaluation of both benefits and risks during the entire market life cycle of a drug. The approval of a drug is a critical juncture in a product's life cycle because it signals the start of broad 'uncontrolled' use.[6,7] It marks the beginning of another important stage in the product life when all stakeholders (regulators, the Marketing Authorization Holders, prescribing physicians, pharmacists, independent researchers, academia and also the patients) actively pursue and manage knowledge about benefits and risks.

The concept, need and key aspects of a holistic pharmacovigilance approach have been identified in earlier publications[8-11] The importance of a more proactive conduct of pharmacovigilance by putting in place measures that allow for the early detection, assessment, minimization and communication of risks of medicines throughout their life cycle has been widely accepted now.[8,9] In the EU, this has ultimately translated into the requirement to submit risk management plans when seeking market approval since November 2005. The aim of this requirement is "to ensure that the benefits of a particular medicine exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole".[5] An important part of the risk management and risk minimization in risk management plans is accurate and timely communication of identified safety risks.[12]

To date, little information is available on the frequency, nature and timing of safety-related regulatory actions. Two US studies show that 10% of drugs registered in the US between 1975 and 1999 required a safety-related action.[13,14] Recently it was shown that biologicals had a 14% probability of acquiring a first safety-related regulatory action within the first 3 years after market approval with a higher risk of a safety-related action in 'first-in-class' biologicals.[15] This relatively new class of drugs has immunomodulatory effects, resulting in potentially predictable infection-related adverse events that nevertheless still necessitated post-approval regulatory action. This led some to conclude that regulatory oversight is imperfect and should be improved.[16] However, an overall picture of recent safety-regulatory warnings for medicinal products, small molecules and biologicals, marketed in a non-US setting, is lacking. Differences between European and US healthcare systems and health perception may lead to different assessment of a drug's risk and to different regulatory action.[15,17]

The aim of this study is to determine the frequency, timing and nature of safety issues that necessitated safety-related regulatory action based on a Direct Healthcare Professional Communication (DHPC) in the Netherlands during the past decade.

Methods

This study focuses on drugs marketed in the Netherlands from 1 January 1999 to 1 January 2009, which, as of 2007, amounted to approximately 1200 unique active substances.[18] A major safety-related regulatory action taken in the Netherlands consists of a DHPC (formerly called a 'Dear Doctor letter') to inform healthcare providers of important drug-related safety issues and/or withdrawal of a drug for safety reasons. All DHPCs issued from 1 January 1999 to 1 January 2009 in the Netherlands were included in this study. Using the perspective of the DHPC enabled us to also evaluate urgent safety issues for drugs that had received market approval before the study period. Issued DHPCs were identified and retrieved from the Dutch Medicines Evaluation Board (CBG-MEB) website[19] and the Netherlands Health Care Inspectorate (IGZ) archive.[1] The date of issuance was used as the date of the safety-related regulatory action. Time between the approval date and DHPC and/or drug withdrawal was determined.

Characteristics of Safety Issues

For each DHPC, the characteristics of the procedural aspects, nature of the safety issue and drug(s) involved were extracted. The procedural aspects that were assessed included involvement of the European Medicines Agency, as explicitly mentioned in the DHPC, and the timing of the DHPC; whether it was the first safety-related regulatory action; or, where earlier DHPCs had occurred, (i) repeating the same issue, or (ii) describing a new safety issue for the same drug. Finally, per DHPC, a safety-related market withdrawal (yes/no) was recorded. The nature of the safety issue was classified according to the

1 The DHPCs from the Netherlands Health Care Inspectorate are not available online. The DHPCs retrieved during this study are available from the authors upon request.

Medical Dictionary for Regulatory Activities (MedDRA® version 11.0) using preferred terms and aggregated at system organ class (SOC) level. If multiple safety issues were mentioned in the same DHPC, the main safety issue that prompted the safety communication was identified by the authors (PM, JdV, SS and PdG) by consensus, which was then included in the analysis.

Characteristics of the drugs, i.e. the anatomical therapeutic chemical (ATC) classification system code, registration process (registered by EU process or national process), drug type (small molecule or biological) and orphan drug (yes or no), were retrieved from websites of the European Medicines Agency,[20] CBG-MEB[19] and WHO.[21]

Data Analysis

The DHPCs were clustered by the year of issuance to assess a change in frequency over time. Regression analysis was used to evaluate a possible trend in the number of DHPCs per year. For drugs with more than one DHPC, each DHPC was counted as a separate event, while distinguishing first and repeated communicated safety issues. Because of a skewed distribution of elapsed time from approval to the date of DHPC, non-parametric statistics were used. Box-plots (medians with their interquartile ranges) were used to describe the time elapsed between approval and DHPC, and the Kruskal-Wallis test for trend was used to evaluate whether the median elapsed time changed during the study years. The Mann-Whitney U test was used to probe for a possible relationship between characteristics of the safety issues and elapsed time from approval to DHPC. All statistical analyses were conducted by using the statistical software package SPSS version 16 (SPSS Inc., Chicago, IL, USA).

Results

During the study period a total of 157 DHPCs were issued in the Netherlands concerning 112 different active substances, which represents approximately 9% (112/1200) of all active substances available in the Netherlands. The number of DHPCs issued increased by 2.1 (95% CI 1.2, 3.1; $p < 0.001$) DHPCs per year over the study period, reaching a total of 25 in 2008 (figure 1). This finding was robust when we corrected for an increasing number of active substances on the Dutch market (data not shown).

The median time between approval and a safety-related action was 5.3 years (range 0.13–48 years) [figure 2]. During the first 3 years of the study period, the time between approval to issuance of a DHPC was relatively short in comparison to later years (Kruskal-Wallis test; $p = 0.06$). One-third (51/157) of all DHPCs were issued in the first 3 years after market approval and 40% (63/157) between 3 and 10 years after approval. Notably, 27% (43/157) of DHPCs were issued for drugs granted market approval more than 10 years earlier, including six for drugs that had already been approved for 30 years or more.

Characteristics of the Safety Issues

With respect to the procedural issues, the involvement of the European Medicines Agency increased to approximately 90% in 2007 and 2008 from approximately 50% during the earlier years of our study period (figure 1). In 50 of 157 (32%)

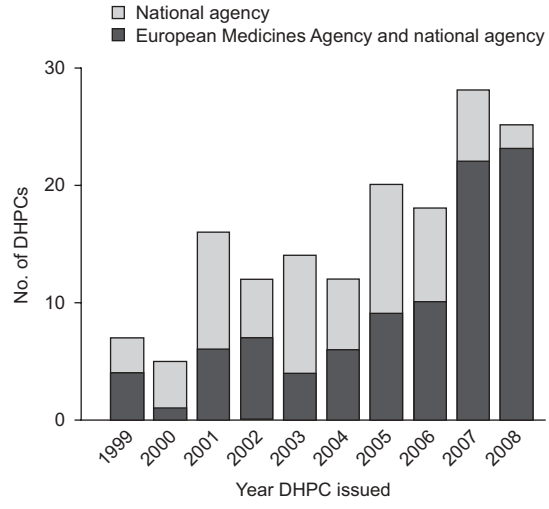

Fig. 1. Ten years of Direct Healthcare Professional Communications (DHPCs) in the Netherlands, 1 January 1999 to 1 January 2009. DHPCs are sent by the manufacturer in collaboration with the national agency or European Medicines Agency and national agency.

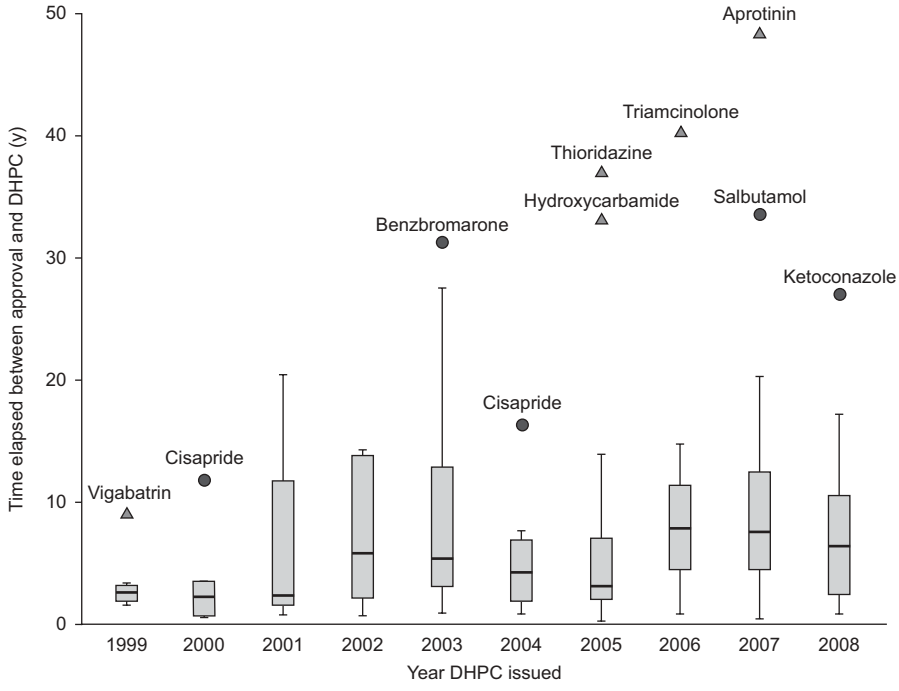

Fig. 2. Elapsed time from drug approval to publication of a Direct Healthcare Professional Communication (DHPC) [1 January 1999 to 1 January 2009] shown as box and whisker plots: the box indicates the interquartile range (IQR) [25–75%], the horizontal bar the median, whiskers (T-bars) represent 90% of reported values and outliers (>1.5×IQR) are represented by circles (1.5–3×IQR) and triangles (>3×IQR).

cases, a DHPC was issued more than once for the same drug; 27 (17%) repeated a previously identified safety issue and 23 (15%) communicated a new safety issue. In ten cases the drug was withdrawn from the Dutch market because of identified major safety concerns; these drugs were on the market for a median duration of 2.4 years (range 1.5–48 years) [table I].

The most frequently communicated safety issues concerned the following SOCs: 'cardiac disorders' (15%); 'injury, poisoning and procedural complications' (13%); and 'general disorders and administration site conditions' (10%). Of the 24 DHPCs that were sent out for cardiac disorders, ten (42%) concerned one class of drugs, i.e. the cyclo-oxygenase-2 selective inhibitors ('coxibs') [see appendix, Supplemental Digital Content 1, http://links.adisonline.com/DSZ/A26]. Seven DHPCs concerned QT interval prolongation that in the MedDRA® is classified in the category 'investigations'. In the category of 'injury, poisoning and procedural complications', nine of a total of 20 DHPCs were related to incorrect drug use (e.g. administration and dosing errors). Six DHPCs contained warnings for the increased risk of fetal malformation after exposure during pregnancy. The SOC 'general disorders and administration site conditions' included warnings about reduction or lack of efficacy (n = 8) or an increased risk of a fatal outcome (n = 5) when used in specific patient populations.

The safety issues that led to withdrawal of the ten drugs were cardiac disorders (rofecoxib and valdecoxib), QT interval prolongation (grepafloxacin and thioridazine), hepatobiliary disease (nefazodone and trovafloxacin) or related to various SOCs (cerivastatin and rhabdomyolysis, aprotinin and death, inhaled human insulin and lung carcinoma, and rimonabant and depression) [table I and appendix (Supplemental Digital Content 1)].

Three drug classes (ATC level 1) were responsible for more than half of all DHPCs:

Table I. Characteristics of Direct Healthcare Professional Communications (DHPCs) issued in the Netherlands (1 January 1999 to 1 January 2009)

Characteristic	DHPCs [n (%)]	Median time to DHPC [y (interquartile range)]	No. of drugs withdrawn
All	157 (100)	5.3 (2.3–10.5)	10
Adverse event with ≥5 DHPCs by SOC			
Blood and lymphatic system disorders	9 (6)	6.8 (3.2–13.0)	0
Cardiac disorders	24 (15)	3.6 (2.0–8.0)	2
General disorders and administration site conditions	15 (10)	4.5 (3.1–7.4)	1
Hepatobiliary disorders	9 (6)	5.3 (1.9–8.6)	2
Infections and infestations	10 (6)	2.8 (1.4–8.8)	0
Injury, poisoning and procedural complications	20 (13)	9.1 (4.8–12.2)	
Investigations[a]	7 (5)	13.8 (10.1–16.1)[b]	2
Musculoskeletal and connective tissue disorders	7 (5)	1.9 (1.6–6.5)	1
Nervous system disorders	10 (6)	4.9 (0.8–11.3)	1
Psychiatric disorders	7 (5)	2.1 (1.1–2.9)[b]	0
Renal and urinary disorders	5 (3)	6.2 (4.1–12.6)	0
Skin and subcutaneous tissue disorders	8 (5)	7.3 (4.8–10.1)	0
Other warnings	26 (17)	5.9 (2.3–12.8)	1
Drug class with ≥5 DHPCs (ATC code)			
Alimentary tract and metabolism (A)	16 (10)	6.0 (2.4–9.5)	2
antidiabetes drugs (A10)	5	5.5 (4.8–6.5)	1
Blood and blood forming organs (B)	13 (8)	5.6 (3.6–13.7)	1
antithrombotic agents (B01)	7	3.6 (3.1–7.7)	0
Cardiovascular system (C)	5 (3)	1.9 (1.8–12.8)	1
Genitourinary system and sex hormones (G)	5 (3)	15.8 (12.4–20.3)[b]	0
Anti-infectives for systemic use (J)	29 (18)	4.5 (2.0–6.4)	2
antibacterials for systemic use (J01)	5	4.4 (2.0–5.3)	2
antivirals for systemic use (J05)	22	4.3 (1.5–6.4)	0
Antineoplastic and immunomodulating agents (L)	27 (17)	3.0 (1.5–6.8)[b]	0
antineoplastic agents (L01)	10	4.6 (2.3–8.8)	0
immunosuppressants (L04)	16	2.2 (1.3–4.5)[b]	0
Musculoskeletal system (M)	20 (13)	3.1 (1.9–4.9)	2
anti-inflammatory and anti-rheumatic products (M01: coxibs)	13	2.8 (1.9–4.8)	2
drugs for treatment of bone diseases (M05)	5	3.2 (1.9–4.3)	0
Nervous system (N)	28 (18)	8.8 (2.8–12.7)	2
antiepileptics (N03)	6	9.3 (7.1–10.4)	1
anti-parkinson drugs (N04)	5	8.6 (2.9 – 13.8)	0
psychoanaleptics (N06: e.g. antidepressants)	8	5.8 (2.5–12. 5)	0
Various (contrast agents)	7 (5)	7.1 (3.2–12.6)	0
Other ATC classes	7 (5)	Not calculated[c]	0
Drug type		$p = 0.051$[d]	
Biological	29 (18)	3.3 (2.1–6.6)	1
Small molecule	128 (82)	5.8 (2.3–11.5)	9
Orphan drug		$p = 0.007$[d]	
Yes	8 (5)	2.0 (1.0–3.9)[b]	0
No	149 (95)	5.5 (2.4–10.9)	10

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Table I. Contd

Characteristic	DHPCs [n (%)]	Median time to DHPC [y (interquartile range)]	No. of drugs withdrawn
First-in-class drug		p = 0.299[d]	
Yes	24 (16)	5.6 (2.4–13.6)	3
No	131 (85)	5.3 (2.1–10.2)	7

a All were QT interval prolongation.

b Time to DHPC was significantly different for particular variables in comparison with all other variables.

c Not calculated because of the small number and unrelated classes of drugs in this group.

d p-Value was calculated with Mann-Whitney U test and considered significant when $p \leq 0.05$.

ATC = Anatomical Therapeutic Chemical; **SOC** = system organ class.

'anti-infectives for systemic use' (18%), 'anti-neoplastic and immunomodulating agents' (17%) and 'nervous system' drugs (18%). The time to communicate safety issues differed depending on the SOC category. Psychiatric safety issues were communicated significantly earlier than other SOC categories (median time 2.1 years; $p = 0.015$ Mann-Whitney U-test), whereas safety concerns related to QT interval prolongation were communicated late in the life cycle of a drug (median time 13.8 years; $p = 0.012$). Timing of communication of safety issues also differed for the different drug classes, with early reporting for immunosuppressants (median of 2.2 years) and late reporting for genitourinary system drugs and sex hormones (median of 15.8 years) [table I]. Also, timing was influenced by the orphan drug status ($p = 0.007$) and drug type; biologicals in particular were associated with rapidly issued DHPCs ($p = 0.051$). Whether the drug was first-in-class or not had no effect.

Discussion

The issuance of DHPCs is an important indicator for post-approval safety issues. In the past decade, the number of DHPCs issued has increased, but no significant trend in time elapsed between approval and the safety-related regulatory action was observed. The involvement of the European Medicines Agency increased to approximately 90% in 2007 and 2008, from approximately 50% during the earlier study years. Some suggest that regulators have become more risk averse, in particular after the rofecoxib (Vioxx®) affair.[22-24] This may explain the increase in number of safety-related actions as observed after withdrawal of rofecoxib from the market in October 2004. The ensuing media attention may have amplified the risk awareness of the general public,[23,25] which in turn may have affected regulator's and industry's response to new drug safety issues. Fear of litigation, especially in the US, may have been another factor leading to increased risk communication.[16,26] Although, for example, in the triazolam (Halcion®) case, courts did play an important role in the handling and unravelling of its central nerve system toxicity (aggression, amnesia, etc.) by the healthcare society as a whole,[27] individual law suits for financial compensation are not common practice in the Netherlands. In Europe, litigation is probably a less relevant factor, although between-nation differences exist. In the future, the number of DHPCs is expected to increase further by the pressure put on regulators to strengthen their pharmacovigilance activities.[22] Initiatives, such as the 'Sentinel Project' in the US, to actively and systematically search in (multiple) large epidemiological databases for hitherto unknown adverse drug events will likely increase the number of required regulatory risk communications,[28] albeit at the risk of generating false positive signals.[29] Safety-related regulatory action by a DHPC was necessary for 9% of marketed drugs in the Netherlands, comparable with what has happened in the US during the last quarter of the past century.[13]

Considering all products, the median time from approval to DHPC is 5.3 years, and one-third of all DHPCs occur during the first 3 years

after market approval. These findings, in particular the latter, are not unexpected as, at the time of market approval, the safety profile of a new drug has not been fully established. Early after approval, patient exposure increases exponentially and thus the power to detect adverse drug reactions increases dramatically. It is more remarkable that in this study one-quarter of all DHPCs are issued for drugs that are already 10 or more years on the market. A DHPC was issued 40 years after market approval to announce the market suspension of aprotinin after the observation that mortality increased in patients treated with this drug.[30,31] The nearly equal distribution of DHPCs issued shortly (<3 years) after market approval, and after intermediate (3–10 years) and long-term (>10 years) market exposure implies that risk management should be maintained throughout the life cycle.

Timing of DHPCs may differ between safety issue, drug class, drug type and orphan drug status. Timing is relatively fast, as discussed, for orphan drugs, immunologicals and possibly biologicals, perhaps because of the knowledge at the time of approval and the way these drugs are subsequently monitored. Our observation that DHPCs for biologicals are issued approximately 2.5 years earlier after approval than for small molecules underlines their specific status. Reasons for this may be their complex production process, limited predictability of preclinical data, high potential for immunogenicity and often the small patient populations studied. This may justify specific risk management strategies, such as patient registries and obligatory post-marketing observational studies.[32] These findings may be biased as these products belong to a relatively new class of agents, with orphan drug regulation only coming into effect in the year 2000 in the EU.[33] Our findings seem to be in line with those of Giezen et al.[15]

Safety issues from the SOC 'psychiatric disorders' are communicated significantly sooner after approval than for other drugs in our study, but this may be driven by the attention for rimonabant (three DHPCs), for which depression-related adverse events received considerable attention during the registration process.[34] The first of three DHPCs for rimonabant was issued even before the drug was marketed in the Netherlands. Some of the attention may have been caused by the fact that rimonabant did not get market approval in the US. In contrast, drugs in the ATC class 'genitourinary system and sex hormones' received DHPCs late in their drug's life cycle. This may have been the consequence of small increases in relative risk of either very low baseline risk events (for example venous thrombotic events for second-generation oral contraceptives)[35] or high background risk events (breast cancer in postmenopausal women using hormone replacement therapy)[36,37] where the safety concerns were only picked up once very large exposed groups could be evaluated in well defined epidemiological or clinical studies.

As found elsewhere,[13,38,39] regulatory action is also most frequently taken for safety issues concerning cardiac disorders, even when considering that 42% of the DHPCs issued in the past decade are related to one drug class (the coxibs) only. These ten letters addressed the same issue: an increased risk of thrombotic adverse events (myocardial infarction and cerebrovascular accident) that is shared by all coxibs and led to the withdrawal of two of these agents. The wide uptake of these new drugs and the 'channelling effect' leading to treatment of more vulnerable patient groups with co-existent gastrointestinal and cardiovascular risk factors may have aggravated their harmful impact.[40] It is an example of the vulnerability of our ageing society to the inherent limits of the drug approval process, where the benefit-risk profile is established in narrowly defined, relatively young patient populations followed for relatively short periods that do not always reflect daily practice, where often elderly people with multiple comorbid diseases are treated for long periods of time.[3,5,22] Some safety concerns may dominate a certain time period, and extrapolation from older studies should be made with care. Clustering of safety issues in time may in part be due to such class effects but may also result in a spillover into a periodical focus on specific safety issues. Moreover, once a safety issue is identified, professional and mass media attention may result in

exaggerated reporting of the specific adverse event.[41,42] Nevertheless, cardiovascular safety of drugs has been a consistent concern over a longer period of time.[13,38,39]

Half of the safety issues involving the SOC 'injury, poisoning and procedural complications' were the result of erroneous drug use. Although such issues may not be an intrinsic toxic effect of a drug *per se*, medication errors have been shown to lead to considerable patient harm.[1,2,43] The prevention of medication errors by healthcare professionals has gained considerable momentum. Industry and regulators can contribute to this by bringing safe and practical drug formulations to the market, e.g. right size drug vials, appropriate inhalation devices, etc.

In our study, antivirals were largely responsible for regulatory safety actions in the SOC 'general disorders and administration site conditions'. They have been specifically found to have reduced efficacy when used in unapproved drug combinations to treat complex HIV patients. DHPCs were issued for antineoplastic agents nearly as frequently as for immunosuppressants. The issues are often related to potentially predictable but in clinical practice more difficult-to-manage infections and infestations. A considerable number of these agents belong to the biologicals that have been extensively discussed elsewhere.[15] Typically these agents are approved with relatively small safety databases. This appears to be generally accepted because they are indicated for life-threatening conditions where alternative treatments are lacking.[44] Some are formally approved under conditional or exceptional circumstances, allowing fast approval with limited safety databases.[45] Regular reassessment is often required of the developing benefit-risk profile after the drugs are granted provisional approval. This approach could explain the relatively early issuance of DHPCs after approval for immunosuppressants, but probably also for biologicals and orphan drugs since many of these are registered under similar conditions with proactive pharmacovigilance activities immediately after approval.

In the Netherlands, as elsewhere,[13,38,39] hepatotoxicity and QT interval prolongation were important safety issues that, despite repeated DHPCs, led to eventual withdrawal of drugs from the market. In the case of troglitazone, it was shown that recommendations to monitor hepatic function closely were poorly taken up despite repeated risk communication, and the drug could not be kept on the market.[46-48] In the case of corrected QT (QTc) interval prolongation, particularly when the risk was aggravated by drug-drug interactions (DDIs), risk communication failed to achieve consistently satisfactory changes in prescribing behaviour. Some authors demonstrated that contraindicated concomitant drug use with cisapride was reduced,[49,50] mostly after repeated risk mitigation strategies, but others did not.[51,52] The size of the effect was influenced by the format and explicitness of the warning, specifying contraindicated medication versus contraindicated drug classes.[53] Repeated drug warnings and automated pharmacy DDI alerts led to a *relative* reduction in co-dispensing of contraindicated drugs with cisapride in the Netherlands, but on an *absolute* level that effect was offset by an increased subsequent overall concomitant contraindicated use of fluconazole and clarithromycin.[54] In view of the recurrent nature of serious QT issues, regulators established more stringent guidelines in 2005 to assess the QT/QTc prolonging effects of a drug pre-approval.[55] The recommended 'thorough QT/QTc studies' have since become part of an increasing number of new drug application files.[56] Thus, it may come as no surprise that in our study, the same safety concern occurred in 17% of all DHPCs, indicating a possible lack of effect of the earlier warning. This may even be an underestimation as we did not have access to DHPCs issued before 1999. Therefore, the number of repeated DHPCs, especially of older drugs, may be an underestimation. The effectiveness of DHPCs in achieving the desired clinical behaviour has been questioned.[46-48,51,57] Additional measures and repetition may be required and the communication should be targeted to the situation.[58] In some cases, laboratory (biomarkers) or clinical adverse events were already present in the registration files of some drugs such as cerivastatin (creatinine kinase elevations indicative of muscle degradation and possibly myopathy),[59,60] nefazodone (abnormal liver function tests)[61] and rimonabant

(depression in trial population).[34] Whether these drugs were withdrawn in a timely manner because of proper follow up of identified safety signals, or should not have been approved in the first place, is a matter of debate. The currently required risk management plans for new drugs offer the opportunity to systematically follow up potential safety concerns after approval that otherwise may have gone undetected or would have resulted in the drug not being approved.

A limitation of our study is that only DHPCs issued in the Netherlands were evaluated. However, the European Medicines Agency is increasingly involved (>90% in 2008) in the decision to send a DHPC. Some countries may nevertheless be more proactive or respond to local safety concerns by issuing additional DHPCs. Our results could thus deviate from the situation in other European countries. A second limitation is that only safety issues linked to DHPCs and drug withdrawal were evaluated. Other forms of safety-related action, such as changes in the drug label (Summary of Product Characteristics) only are outside the scope of this study. Third, because of our study design we cannot compare characteristics of drugs with and without a DHPC; however, DHPCs were issued for drugs across almost the whole ATC spectrum. Finally, not all drugs are marketed immediately after approval. Unfortunately we did not have data on the exact date a drug was launched on the market and thus our results may overestimate elapsed time between widespread prescribing of a drug and the emergence of major safety concerns and subsequent DHPC. A recent letter by Tavassoli and Montastruc[62] suggests that more innovative drugs with 'improved actual benefit' over already available therapy lead to exaggerated early reporting of still unfamiliar adverse drug events because of higher uptake shortly after marketing. This could lead to a 'distorted' faster time to DHPC than would be expected on the lag time between approval and marketing only.

Conclusions

In the past decade the number of DHPCs issued in the Netherlands has increased. This is likely caused by a multitude of factors: increased risk awareness by the public, media, regulators and other stakeholders; the type of drugs approved, such as orphan drugs and biologicals; and the regulatory process, including conditional approvals. The number of DHPCs may, in the future, increase further because of the possibility of screening large epidemiological databases proactively for adverse drug events. Overall, 9% of all drugs on the market required a safety-related action. Some safety concerns will dominate a certain time period and issues may cluster in time as they are related to a certain drug class. Nevertheless, cardiovascular safety concerns, QT interval prolongation and hepatotoxicity seem to be recurrent findings over time. These may result in additional requirements for the pre-approval clinical programme. In the future, rare adverse drug events may be identified earlier because of more powerful pharmacovigilance tools. Issuance of DHPCs during the period of our study was almost equally distributed over the post-marketing life cycle. These findings underline the need for risk management during the whole life cycle of a drug.

Acknowledgements

This study is published in the framework of a larger project on the effectiveness of regulatory risk communication. This research project is supported by an unconditional grant from the Dutch Medicines Evaluation Board (MEB). The authors who are also (part-time) employees of the MEB (Peter Mol, Sabine Straus and Pieter de Graeff) express that the opinions presented in this paper are their personal opinion and do not necessarily reflect those of the MEB. All authors report that they do not have any conflicts of interest.

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Correspondence: Dr *Peter G.M. Mol*, Department of Clinical Pharmacology, FB 20, Graduate School of Medicine, University Medical Center Groningen, University of Groningen, P.O. Box 197, 9700 AD Groningen, the Netherlands.
E-mail: p.g.m.mol@med.umcg.nl