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Additional safety risk to exceptionally approved drugs in Europe?

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The safety profile of new drugs is not well known at the time of market approval and serious safety issues are regularly identified for marketed drugs.
- Drugs intended to meet an unmet medical need can be approved for the market with less safety data than is usually required, using the Exceptional Circumstances and Conditional Approval applications in European Central procedure.
- It is unknown whether for drugs approved using Exceptional Circumstances and Conditional Approval procedures have an increased probability of serious safety issues identified post approval than for drugs approved through the standard procedures.

WHAT THIS STUDY ADDS

- Using the Exceptional Circumstances and Conditional Approval procedures does not lead to more post-marketing safety alerts or safety-related withdrawals when used for drugs with unmet medical needs.

AIMS

Regulatory requirements for new drugs have increased. Special approval procedures with priority assessment are possible for drugs with clear 'unmet medical need'. We question whether these Exceptional Circumstances (EC) or Conditional Approval (CA) procedures have led to a higher probability of serious safety issues.

METHODS

A retrospective cohort study was performed of new drugs approved in Europe between 1999 and 2009. The determinant was EC/CA *vs.* standard procedure approval. Outcome variables were frequency and timing of a first Direct Healthcare Professional Communication (DHPC). An association between approval procedure and the time from market approval to DHPC was assessed using Kaplan-Meyer survival analysis and Cox-regression to correct for covariates.

RESULTS

In total 289 new drugs were approved. Forty-six (16.4%) were approved under EC or CA, of which seven received a DHPC (15%). This was similar to the standard approval drugs (243), of which 33 received one or more DHPC (14%, $P = 0.77$). The probability of acquiring a DHPC for standard approval drugs *vs.* EC/CA drugs during 11-year follow-up is 22% (95% CI 14%, 29%) and 26% (95% CI 8%, 44%), respectively (log-rank $P = 0.726$). This difference remained not significant in the Cox-regression model: hazard ratio 0.94 (95% CI 0.40, 2.20). Only drug type was identified as a confounding covariate.

CONCLUSION

The EC/CA procedure is not associated with a higher probability of DHPCs despite limited clinical development data. These data do not support the view that early drug approval increases the risk of serious safety issues emerging after market approval.

Introduction

Increasingly, society has become aware that drugs not only cure or prevent diseases but also can lead to considerable patient harm. Adverse drug events, whether or not due to (in)correct use of drugs, have been estimated to be a leading cause of unplanned hospital admission [1, 2]. New drugs are allowed onto the market based on relatively limited knowledge of their benefit–risk profile due to inherent and well-known limitations in pre-approval clinical trials [3]. Those trials are typically performed in carefully selected patient populations not fully representing 'real world' patients, are of relatively short duration and are primarily developed to determine efficacy [4]. They are not powered to detect rare adverse events, adverse events with a high background incidence or those related to the disease [5]. It is therefore not surprising that both in Europe and the USA for approximately 10% of all marketed drugs, serious adverse drug events were identified post approval that had to be communicated to healthcare professionals or patients [6, 7]. Consistently, cardiovascular adverse events including QT prolongation and hepatotoxicity were leading causes for safety withdrawals of drugs [6, 7]. Acknowledging this situation, regulatory authorities have increased their pre-approval requirements over time. For example, thorough QT studies have become part of many new drug applications since QT prolongation and associated life-threatening arrhythmias have led to several drugs being withdrawn from the market [8, 9]. More recently, the debate on rosiglitazone has led the Food and Drug Administration (FDA) to step up its pre-approval requirements for new drugs for diabetes, to demonstrate absence of an excess risk of cardiovascular events [10]. The negative consequences are that drug development times may increase, as do costs that are estimated upward of $800m for the development of a new drug, limiting development of all but the most lucrative drugs [11].

This development may not be in the interests of patients with a shortage of available treatment options for their disease, such as HIV/AIDS, cancer and many orphan diseases with unmet medical need. This is why the FDA introduced the Accelerated Approval (AA) procedure in the USA and the European Medicines Agency (EMA) the Exceptional Circumstances (EC) or Conditional Approval (CA) procedures in Europe to approve drugs based on more limited clinical data sets. In Europe, the EC and CA procedures do not shorten the approval procedure itself, as is a common misconception. In the case of AA and CA procedures, companies are required to perform confirmatory studies post approval, whereas in the case of EC approval this is sometimes considered not realistic, e.g. due to the (extreme) rarity of the disease [12, 13]. However, an earlier effort by the FDA to streamline the regulatory process, the Prescription Drug User Fee Act (PDUFA) that restricted review times of new drugs, was criticized as it may have led to unsafe drugs being approved [14]. Since the EC procedure has been used since 1995 and the CA procedure since 2007, it seems opportune to evaluate whether these special approval procedures have led to more safety issues identified after the drugs were marketed.

Our study evaluates whether the early approval under EC or CA has led to a higher probability of new serious safety issues post approval than for drugs approved with the standard procedure of the EMA.

Methods

Study design and study population

A retrospective cohort study was performed including all new active substances approved under the European Centralized Procedure (CP) from 1 January 1999 to 31 December 2009, using a limited definition of new active substances, by excluding biosimilars as defined by Eichler *et al*. [15, 16]. The determinant was whether the drug product was approved using EC/CA or the standard procedure. Regulatory and scientific information on drugs was obtained from the European Public Assessment Report (EPAR), which is a summary report of the application. EPARs are issued for drugs that have received a marketing authorization under the European Centralized Procedure (CP). EPARs are publicly available and can be retrieved from the EMA website [17].

Outcome

The primary outcome was the identification of a first serious safety issue post approval. A serious safety issue was defined as an issue requiring regulatory risk communication in the form of a Direct Healthcare Professional Communication (DHPC) or a safety-related withdrawal of the marketing authorization.

A DHPC contains information aimed at ensuring safe and effective use of medicinal products. It is delivered directly to individual healthcare professionals by a Marketing Authorization Holder or by a Competent Authority. DHPCs issued for drugs approved with the European CP were retrieved from the Dutch Medicines Evaluation Board website [18]. We included European DHPCs issued from 1 January 1999 to 31 December 2009 and excluded DHPCs, where the safety issues were related to the administration of the drug, the pharmaceutical quality of the product or to malfunctioning in a device for the administration of the drug.

Time to DHPC or safety-related market withdrawal, defined as the time in months from the date of market approval to the date of a first DHPC or withdrawal, was assessed. Whether a withdrawal was safety-related or not, was determined from the EMA press release

regarding each drug withdrawal, as retrieved from the EMA website.

Covariates

Covariates were defined that could be considered as potential confounders. These were related to the drug, procedural issues and the clinical development and were obtained from the EPAR. The factors related to the drug were drug class [on anatomical therapeutic and chemical (ATC) code [19] ATC-2 level, where more than five drugs were approved through the EC or CA procedure], whether it was first in class (yes/no) and the type of drug (small molecule or biological including vaccines) as these might influence the likelihood of receiving EC or CA marketing authorization as well as potentially increase the risk of serious safety issues post approval. The procedural issue was orphan drug status (yes/no), because orphan drugs could be more prone to receiving EC or CA market approval and might be less prone to issuance of DHPCs. Another potentially important factor in the marketing authorization application dossier related to the clinical development process was the size of safety population (less than 1500 subjects, yes/no). EC/CA drugs can more often be approved with less than 1500 subjects exposed and drugs with smaller exposure in patients/healthy volunteers before approval may lead to more adverse drug reactions only being identified after approval. This number of 1500 has been specified by the E1 document published by the Internal Conference on Harmonization (ICH), agreement between USA, European and Japanese regulators, as a minimum number of subjects/patients who are expected to be exposed pre-approval to any new drug product [20].

Analysis

Differences between baseline characteristics were analysed using chi-square and are presented in Table 1. The probability for EC/CA and drugs approved with standard procedure to receive a DHPC or to be withdrawn for safety reasons was evaluated by Kaplan Meyer analysis correcting for follow-up duration and by the log-rank test. A follow-up duration of 11 years was deemed appropriate, as 73% of DHPCs are issued in the first 10 years after market approval [7].

Our study had 80% power at a 5% α-level to detect a difference of 10% between EC/CA and drugs approved with standard procedure of identifying safety-related issues requiring a DHPC during the 11-year follow-up. This is considering that 280 new drugs obtained marketing authorization during the study period and had a 20% baseline chance for acquiring a DHPC, which is approximately in between the estimation for biologicals (29%) [21] and for all drugs (10%) [6] during 10-year follow-up.

A multivariable Cox proportional hazard model (HR and 95% CI) was used to evaluate the association between approval type and time to first DHPC, correcting for confounding covariates ($P < 0.1$ in the chi-squared analyses). A sensitivity analysis was also performed including all covariates in the Cox model.

As the research did not involve any patient data or other confidential material, no ethics approval was necessary for the performing of the study.

Table 1

Approval procedures and issuance of a DHPC for new active substances (NAS) approved between 1 January 1999 and 31 December 2009 and drug, procedural issues and clinical development characteristics

	All NAS *n* (%)*	Approval EC/CA *n* (%)*	Standard *n* (%)*	*P***	DHPC Yes *n* (%)*	No *n* (%)*	*P***	HR (95% CI)***
Total	289 *(100)*	46 *(100)*	243 *(100)*		40 *(100)*	249 *(100)*		0.94 (0.40, 2,20)
Drug								
Drug classes (ATC-2 level§)				**<0.001**†			**0.014**	
Alimentary tract and Metabolism – other (A16)	*13 (5)*	*7 (15)*	*6 (3)*		*1 (3)*	*12 (5)*		0.57 (0.07, 4.43)
Direct acting antivirals (J05)	*19 (7)*	*8 (17)*	*11 (5)*		*7 (18)*	*12 (5)*		3.07 (1.28, 7.37)
Antineoplastics (L01)	*38 (13)*	*11 (24)*	*27 (11)*		*7 (18)*	*31 (12)*		1.62 (0.69, 3.83)
Other drug classes ‡	*219 (76)*	*20 (44)*	*199 (82)*		*25 (63)*	*194 (78)*		reference
First in class (y)	37 *(13)*	5 *(11)*	32 *(13)*	0.669	6 *(15)*	31 *(12)*	0.654	–
Biologicals (y)	109 *(38)*	14 *(30)*	95 *(39)*	0.266	13 *(33)*	96 *(39)*	0.463	–
Procedural issues								
Orphan drugs (y)	55 *(19)*	20 *(44)*	35 *(14)*	**<0.001**	7 *(18)*	48 *(19)*	0.790	–
Clinical development								
Safety population <1500 (y)¶	157 *(56)*	38 *(83)*	119 *(51)*	**<0.001**	23 *(59)*	134 *(56)*	0.694	–

*Percentages are expressed within NAS, approval type and DHPC (column). ***P* value of chi square, statistically significant values are presented in bold. ***Cox-proportional hazard ratio corrected for covariates presented. †Drug classes are selected to over-represent EC/CA procedure (≥five drugs registered through EC/CAA procedure). ‡All drugs that are not categorized on ATC-2 level as A16, J05 or L01. §Variable is categorical and ratio of values adds up to 100%, presented with numbers in italics. (y) Variable is dichotomous and value represents the 'yes'. ¶EPARs were not available for nine drugs, thus the size of the safety population could not be established for those nine drugs. The ratio presented is for the 280 NAS with EPARs available. CA, Conditional Approval; DHPC, Direct Healthcare Professional Communication (as proxy for safety issues) after excluding non-safety-related DHPCs; EC, Exceptional Circumstances.

Results

Of the 289 new drugs that obtained a marketing authorization between 1 January 1999 and 31 December 2009, 46 (16%) were approved under EC/CA, of which 38 were with EC approval and eight with CA. In the study period, two to 10 EC/CA drugs were approved annually, without any obvious pattern (Figure 1). Sixteen drugs were withdrawn from the market for commercial reasons, all approved with standard procedure. The medium follow-up of those withdrawn drugs was 45 months.

In total 74 DHPCs were issued for 49 of the 289 drugs included, with 16 drugs receiving more than one DHPC. Five drugs, all approved with standard procedure, were withdrawn because of safety concerns: inhaled insulin, efalizumab, rimonabant, valdecoxib and a combination vaccine (Hexavac™). Eleven DHPCs for nine drugs were excluded: for five drugs the safety issues were related to the administration of the drug, for three drugs to the pharmaceutical quality of the product and for one drug to a malfunction in a device for the administration of the drug. A list of all DHPCs is presented in Appendix 1. Of the 46 drugs with EC/CA approval, seven received a DHPC (15%) in comparison with 33 of 243 standard approvals (14%, $P = 0.77$). DHPCs for three EC approved drugs (drotecogin alfa, atazanavir and tenofovir) regarded lack of efficacy concerns in certain subpopulations. All other DHPCs concerned safety issues.

The mean follow-up duration, from the date of approval to a first DHPC, withdrawal or end of study period, for EC/CA and standard approved drugs, was 52 months (95% CI 42, 62) and 55 months (95% CI 50, 60), respectively. The Kaplan Meyer derived probability for drugs receiving a DHPC was similar for both types of approval processes (Figure 2; log-rank $P = 0.726$). At 3-year follow-up, drugs under EC/CA approval had a 7% (95% CI 0%, 15%) risk of receiving a DHPC, while standard approvals had a 10% (95% CI 6%, 14%) risk of receiving a DHPC. At 11-year follow-up, this risk was 26% (95% CI 8%, 44%) for EC/CA approved drugs and 22% (95% CI 14%, 29%) for standard approved drugs.

The unadjusted hazard ratio (HR) for EC/CA drugs to receive a DHPC during the follow-up was 1.16 (95% CI 0.51, 2.62). When correcting for confounders, the EC/CA drugs had a 0.94 (95% CI 0.40, 2.20) HR to receive a DHPC during the follow-up in the Cox proportional hazards model. From the confounders hypothesized to be present, the distribution of 'drug classes' (ATC-2 level) was significantly different between drugs approved under EC/CA and standard conditions ($P < 0.001$), as the drug classes were specifically selected to have more than five drugs licensed under EC/CA. As could be expected, EC/CA drugs were more likely to be orphan drugs (44%) than the drugs approved with the standard procedure (14%, $P < 0.001$) and more EC/CA drugs (83%) had safety populations that did not meet the ICH threshold of 1500 patients exposed to a new drug before approval than drugs approved with the standard procedure

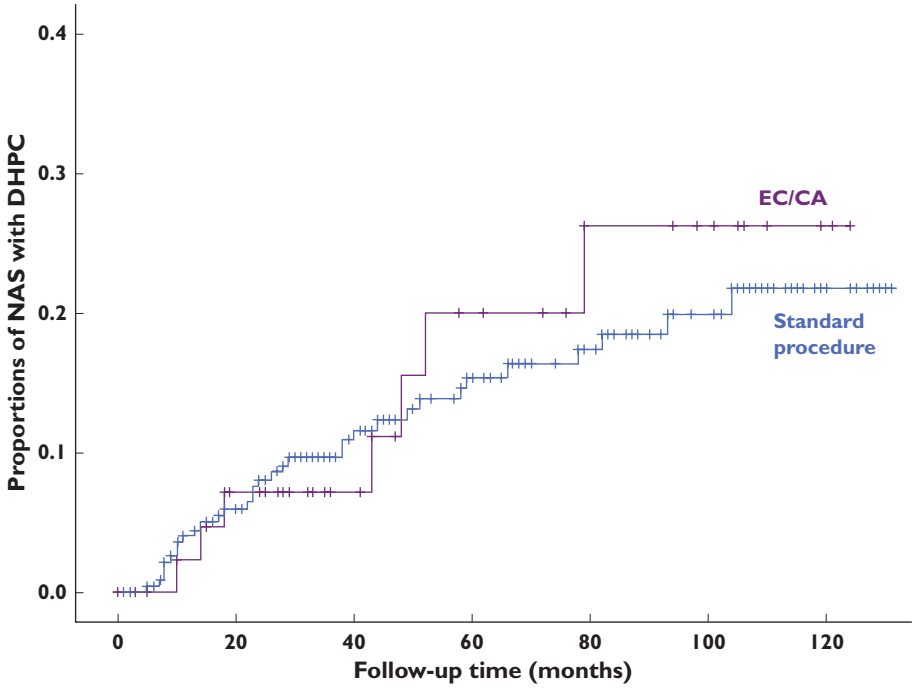

Figure 1

Proportion of new active substances (NAS) that obtained a marketing authorization between 1999 and 2009 under exceptional circumstances/conditional approval (EC/CA) or standard marketing authorizations with or without a Direct Healthcare Provider Communication (DHPC)

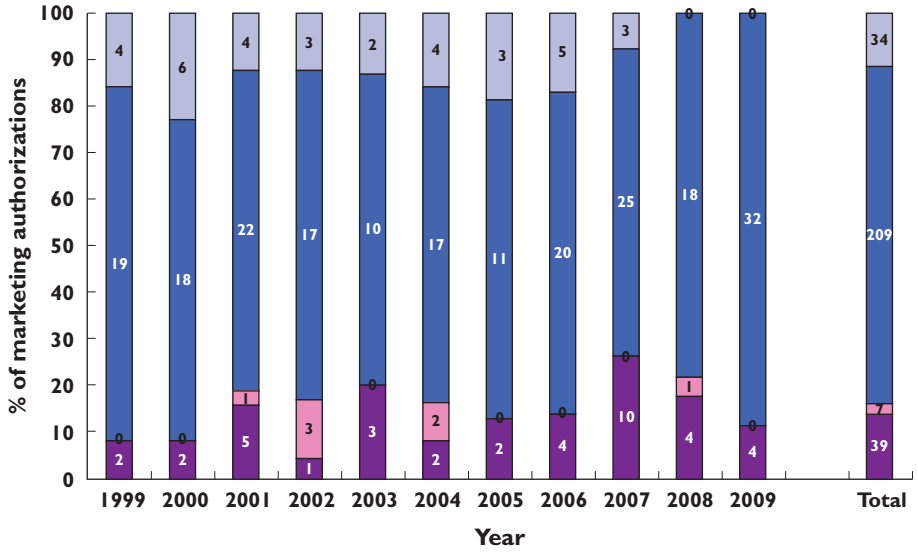

Figure 2

Proportion of new active substances authorized under exceptional circumstances/conditional approval (EC/CA) or standard conditions with a subsequent Direct Healthcare Provider Communication (DHPC)

(51%, $P < 0.001$). For nine drugs we were unable to retrieve the variable 'size of the safety population' as scientific discussion of the EPARs was no longer available on the EMA website. All these drugs have been withdrawn from the market. However, only drug class was associated with the issuance of a DHPC ($P = 0.014$) and was subsequently included in the Cox model as a potential confounder (Table 1). In the sensitivity analysis that incorporated all covariates, the results were similar. The approval procedure did, however, not affect the issuance of DHPCs. For example, 38% (three of eight) EC/CA and 36% (four of 11) HIV AIDS drugs approved with standard procedure received a DHPC. HIV/AIDS drugs had an increased risk of a DHPC, HR 3.07 (95% CI 1.28, 7.37) independent of the approval procedure.

Discussion

In the EU, drugs receiving approval through the EC or CA procedure have a similar probability of a first serious safety issue requiring a DHPC as drugs approved with standard procedure in our 11-year follow-up study, 26% and 22%, respectively. None of the EC/CA, but five of the drugs approved with standard procedure were withdrawn from the market because of safety concerns.

In this direct comparison of approval procedures, no association could be found between approval procedure and identification of serious safety issues post approval. Recent examples have shown the need for continuous monitoring of the benefit risk balance during the lifecycle of a drug [7]. This has led to a more proactive approach of pharmacovigilance through risk management plans. In the risk management plan, based on the knowledge of the drug's characteristics at the time of the approval, gaps in data are identified, companies are required to obtain additional data on benefits and risks of the drug in daily practice or in post-marketing trial settings [22, 23]. Since the EC/CA drugs have been approved on preliminary evidence, regulators usually require even stricter risk management plans [12, 13, 24]. This close follow-up is expected to be more sensitive in picking up important safety issues than routinely collecting spontaneous adverse drug reactions, which is the usual approach for drugs approved with the standard procedure. Balancing this effect of close follow-up is that EC/CA drugs are generally intended to treat rare diseases and not all European countries reimburse conditionally approved drugs. Therefore, the population exposed to these drugs post approval may still not be sufficiently large to detect less common adverse drug reactions. Heemstra *et al*. consider this a likely explanation for their observation of orphan drugs having fewer safety issues post approval than biologicals or (all) new drugs in cross-study comparisons [24]. Support for their explanation is that they observed an association of safety-related regulatory action for drug classes with the highest expected use, those orphan drugs used within oncology and gastroenterology and metabolic indications (ATC classes L01/L02 and A, respectively). In our study these drug classes and drugs to treat HIV/AIDS (ATC class J05) were also overrepresented in the EC/CA group. Moreover, drug classes and specifically those involving the HIV/AIDS drugs were shown to truly confound the results, for which we corrected in the Cox-proportional hazard model, as they also more frequently led to a DHPC. HIV/AIDS drugs are the most commonly used EC/CA drugs, which may indeed explain that rare but serious safety issues are picked up relatively

early. Our data, however, also showed that for both HIV/AIDS and anti-cancer (data not shown) drugs, the approval procedure did not predict whether serious safety issues were identified more readily post approval. Unfortunately, data on drug usage could not be obtained. Many of the EC and CA licensed drugs are used in a hospital setting and hospital drug consumption data are not readily available in the Netherlands or for the EU as a whole. Also, reimbursement is different across EU countries and associated prescription data difficult to obtain. This needs further study, perhaps in a setting where comprehensive total drug usage is available. Our results are in line with Richey *et al*. [25], who concluded that anti-cancer drugs approved with the accelerated approval were safe because none was withdrawn. They also confirm the more limited analyses by Boon *et al*. [26]. However, Boon *et al*. included in their assessment all withdrawals, not discriminating between withdrawals due to safety issues and withdrawals for commercial reasons.

Our finding that EC/CA drugs that were approved with more limited clinical data sets are as safe as drugs approved with the standard procedure seems at odds with the current societal demand for more pre-approval ascertainment of harms and benefits of new drugs [10, 11, 27, 28]. This finding has important societal implications. The request for large-scale outcome studies, for example, for new drugs for diabetes may already be prohibitive even in a field with a large target population. Therefore, it is reassuring to learn that EC/CA registration with limited clinical data sets seems to have been safe in the past decade for drugs with high unmet medical need.

Reassuringly, only three DHPCs were issued because of efficacy concerns from confirmatory trials, indicating that the objective to allow early access of potentially effective drugs meets its expectations.

Although we showed in an earlier study that approximately 10% of all marketed drugs throughout their lifecycle required safety-related regulatory action [7], we found in this study that for more recently approved drugs within 11 years after that approval, the probability of requiring a DHPC is 26%. This is higher than reported earlier by Lasser *et al*. [6] but in line with Giezen *et al*., who reported similar probabilities for biologicals [21]. Lasser *et al*. included all drugs on the market in the USA from 1975 to 1999, while the study done by Giezen *et al*. was more recent and included only biological drugs approved in Europe and the USA between 1995 and 2007. Our finding is consistent with the increasing trend of regulatory risk communications (DHPCs) per year that we observed in our earlier study [7]. The difference between our results and Giezen *et al*.'s on one hand, and those of Lasser *et al*. on the other, could be due to increasing risk awareness, or to the implementation of more sensitive pharmacovigilance tools.

With this apparent growing risk awareness, it was remarkable that 51% of all drugs with regular authorization did not meet the ICH guideline of at least 1500 subjects exposed to the drug in pre-approval trials (safety population), in particular because this ratio is rather constant throughout the study period (data not shown). It would be a topic of future research to explore why the safety population is so limited in the marketing authorization procedure. However, one must keep in mind that the safety requirements in the EU and ICH guidelines are merely a guide. A complete cure for a rapidly fatal disease would require relatively few patients, while, to establish clinical benefit and an absence of harm, for a new surrogate endpoint may take many thousand patient years.

Limitations of the study

Direct Healthcare Professional Communications might not be the most sensitive proxy for safety issues and could be handled or perceived differently for EC/CA drugs addressing 'unmet medical needs'. The acceptability of serious safety issues in the overall benefit/risk balance may be higher and could have a higher threshold for issuing a DHPC resulting in less strong safety-related regulatory action, such as a change in the Summary of Product Characteristics. However, this does not become apparent when the observed safety issues reported for EC/CA are considered *vs*. those for regularly approved drugs (Appendix 1). Furthermore, the DHPC is recommended as the risk communication tool to guarantee continued safe use of a drug [29]. Other studies have used the DHPC as the most important proxy of serious safety issues [6, 21, 24]. It is the best we have as an overall measure that is going through a careful evaluation procedure at the EU level.

We cannot be completely sure that drugs withdrawn from the market for commercial reasons do not also have a safety issue prompting the company's decision to withdraw the drug. However, in the reported cases the EMA press releases explicitly mentioned either that safety concerns were not the reason for withdrawal or that commercial reasons prompted the withdrawal.

As mentioned, EC/CA drugs are used in relatively small patient populations, which reduces the chance of finding rare adverse events. Therefore, our conclusion for the EC/CA procedure does not imply that this procedure would be appropriate for all drugs.

In conclusion, our study showed that the risk of receiving a DHPC is similar for those drugs licensed using EC and CA and the drugs that were licensed using the standard procedure in the past 11 years in the EU.

The use of EC and CA should be continued, as it is valuable in allowing earlier entry to the market for eligible drugs that are mostly intended for rare diseases, without an apparent increased risk of unexpected serious side effects.

Competing Interests

Dr Eichler is the senior medical officer of the European Medicines Agency. Dr Mol, Dr de Graeff and Dr Straus work

for the Dutch Medicines Evaluation Board. The views expressed in this article are the personal views of the author(s) and may not be understood or quoted as being made on behalf of or reflecting the position of the Dutch MEB, the European Medicines Agency or one of its committees or working parties.

None of the authors has any conflict of interest to declare.

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Contributors

All authors contributed to the study design and data interpretation. AHA and PGMM performed the search and review of EPARs and DHPCs. All authors contributed to the final draft of the article and had full access to all of the data.

Appendix 1
Drugs with safety issues

Drug name	ATC	Approved	Warning	System organ class	Time to DHPC (years)
Standard approval					
Rimonabant*	A08AX01	June 2006	Depression	Psychiatric disorders	1.1
			Depression	Psychiatric disorders	2.1
			Depression	Psychiatric disorders	2.4
Insulin human (inhalation)*	A10AF01	January 2006	Lung carcinoma cell type unspecified recurrent	Respiratory, thoracic and mediastinal disorders	2.4
Rosiglitazone	A10BG02	July 2000	Macular oedema	Eye disorders	5.5
			Fracture	Musculoskeletal and connective tissue disorders	6.6
Pioglitazone	A10BG03	October 2000	Fracture	Musculoskeletal and connective tissue disorders	6.5
Eptifibatide	B01AC16	July 1999	Drug therapy changed	Surgical and medical procedures	7.7
Tipranavir	J05AE09	October 2005	Haemorrhage intracranial	Nervous system disorders	0.8
Abacavir	J05AF06	July 1999	Drug hypersensitivity	Immune system disorders	8.7
			Myocardial infarction	Cardiac disorders	8.8
Entecavir	J05AF10	June 2006	Pathogen resistance	Infections and infestations	0.7
Telbivudine	J05AF11	April 2007	Neuropathy peripheral	Nervous system disorders	0.8
Diptheria, tetanus, acellular pertussis, poliomyelitis, hepatitis B and haemophilus influenza type B vaccine*	J07CA	October 2000	Drug ineffective	General disorders and administration site conditions	4.9
Trastuzumab	L01XC03	August 2000	Cardiotoxicity	Cardiac disorders	0.8
			Cardiotoxicity	Cardiac disorders	1.7
Bevacizumab	L01XC07	January 2005	Tracheo-oesophageal fistula	Congenital, familial and genetic disorders	2.3
			Eye disorder	Eye disorders	4.1
Imatinib mesilate	L01XE01	November 2001	Urinary bladder adenoma	Renal and urinary disorders	3.4
			Cardiac failure	Cardiac disorders	5.1
Temsirolimus	L01XE09	November 2007	Anaphylactic reaction	Vascular disorders	1.2
Erlotinib	L01XX34	September 2005	Gastrointestinal perforation	Gastrointestinal disorders	3.7
Sirolimus	L04AA10	March 2001	Bronchial anastomosis complication	Respiratory, thoracic and mediastinal disorders	1.9
Efalizumab*	L04AA21	September 2004	Progressive multifocal leukoencephalopathy	Nervous system disorders	4.4
Etanercept	L04AB01	February 2000	Blood disorder	Blood and lymphatic system disorders	0.7
			Infection	Infections and infestations	3.0

Appendix 1

Continued

Drug name	ATC	Approved	Warning	System organ class	Time to DHPC (years)
Infliximab	L04AC03	August 1999	Tuberculosis	Infections and infestations	1.4
			Cardiac failure	Cardiac disorders	2.2
			Infection	Infections and infestations	2.5
			Lymphoma	Blood and lymphatic system disorders	6.8
Leflunomide	L04AA13	September 1999	Hepatitis	Hepatobiliary disorders	1.5
Anakinra	L04AC03	March 2002	Infection	Infections and infestations	0.9
Efalizumab	L04AA21	September 2004	Progressive multifocal leukoencephalopathy	Infections and infestations	4.1
Natalizumab	L04AA23	June 2006	Progressive multifocal leukoencephalopathy	Infections and infestations	2.1
Adalimumab	L04AB04	September 2003	Hepatosplenic T-cell lymphoma	Blood and lymphatic system disorders	4.9
Lenalidomide	L04AX04	June 2007	Maternal drugs affecting foetus	Injury, poisoning and procedural complications	0.4
			Teratogenicity	Congenital, familial and genetic disorders	1.2
Valdecoxib*	M01AH03	March 2003	Cardiovascular disorder	Cardiac disorders	1.7
			Cardiovascular disorder	Cardiac disorders	1.8
			Cardiovascular disorder	Cardiac disorders	1.9
			Cardiovascular disorder	Cardiac disorders	2.1
Parecoxib	M01AH04	March 2002	Hypersensitivity	Immune system disorders	0.6
			Cardiovascular disorder	Cardiac disorders	2.8
			Cardiovascular disorder	Cardiac disorders	2.9
Zoledronic acid	M05BA08	March 2001	Osteonecrosis	Musculoskeletal and connective tissue disorders	4.3
Dibotermin alfa	M05BC01	October 2002	Oedema	Metabolism and nutrition disorders	1.9
			Effusion	General disorders and administration site conditions	4.5
Strontium ranelate	M05BX03	September 2004	Drug rash with eosinophilia and systemic symptoms	Blood and lymphatic system disorders	3.2
Aripiprazole	N05AX12	June 2004	Cerebrovascular disorder	Nervous system disorders	0.7
Verteporfin	S01LA01	July 2000	Macular degeneration	Eye disorders	6.8
Deferasirox	V03AC03	August 2006	Hepatic failure	Hepatobiliary disorders	1.9
Sulphur hexafluoride	V08DA05	March 2001	Cardiovascular disorder	Cardiac disorders	3.2
			Photosensitivity allergic reaction	Skin and subcutaneous tissue disorders	3.6
EC/CA approval					
Miglustat	A16AX06	November 2002	Ulcerative colitis	Gastrointestinal disorders	4.4
Drotrecogin alfa	B01AD10	August 2002	Drug ineffective for unapproved indication	General disorders and administration site conditions	3.6
Atazanavir	J05AE08	March 2004	Drug effect decreased	General disorders and administration site conditions	0.8
Tenofovir	J05AF07	February 2002	Drug effect decreased	General disorders and administration site conditions	1.5
			Drug effect decreased	General disorders and administration site conditions	3.1
			Renal disorder	Renal and urinary disorders	4.1
			Renal failure	Renal and urinary disorders	6.2
Etravirine	J05AG04	August 2008	Epidermal necrosis	Skin and subcutaneous tissue disorders	1.2
Alemtuzumab	L01XC04	July 2001	Death	General disorders and administration site conditions	6.6
Bortezomib	L01XX32	April 2004	Pericarditis	Cardiac disorders	4.0
DHPCs exluded					
Agalsidase alfa	A16AB03	August 2001	Drug dispensing error	Injury, poisoning and procedural complications	7.5

Appendix 1

Continued

Drug name	ATC	Approved	Warning	System organ class	Time to DHPC (years)
Protein C algasidase beta	A16AB04	August 2001	Product contamination	General disorders and administration site conditions	7.9
			Product contamination	General disorders and administration site conditions	8.2
Alglucosidase alfa	A16AB07	March 2006	Product quality issue	General disorders and administration site conditions	2.8
Tenecteplase	B01AD11	February 2001	Device leakage	Injury, poisoning and procedural complications	0.7
Bivalirudin	B01AE06	September 2004	Incorrect dose administered	Injury, poisoning and procedural complications	3.1
Moroctocog alfa	B02BD02	April 1999	Circumstance or information capable of leading to medication error	Injury, poisoning and procedural complications	4.1
Thyrotropin alfa	H01AB01	March 2000	Product contamination	General disorders and administration site conditions	9.8
Lopinavir/ritonavir	J05AE06	March 2001	Circumstance or information capable of leading to medication error	Injury, poisoning and procedural complications	5.5
			Incorrect dose administered	Injury, poisoning and procedural complications	6.4
Levetiracetam	N03AX14	September 2000	Incorrect dose administered	Injury, poisoning and procedural complications	7.1

*Drug product was eventually withdrawn from the market due to safety reasons. ATC, Anatomical Therapeutic Chemical classification of the WHO; DHPC, Direct Healthcare Professional Communication.

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