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ORIGINAL REPORT

Benefit-risk reassessment of medicines: a retrospective analysis of all safety-related referral procedures in Europe during 2001–2012

Jacoline C. Bouvy[1,2], Lotte Huinink[2] and Marie L. De Bruin[1]*

[1] *Division of Pharmacoepidemiology and Clinical Pharmacology, Faculty of Science, Utrecht University, Utrecht, The Netherlands*
[2] *Institute for Medical Technology Assessment (iMTA), Faculty of Health, Policy and Management, Erasmus University Rotterdam, Rotterdam, The Netherlands*

ABSTRACT

Purpose The aim of this study was to determine the outcomes and timing within the product life cycle of all benefit-risk reassessment procedures for marketed products that were completed by the committee for medicinal product for human use during 2001–2012.

Methods A cohort of all referral procedures for benefit-risk reassessment (Article 20, Article 31, Article 36, Article 107 procedures) for which committee for medicinal product for human use issued an opinion between 1 January 2001 and 31 December 2012 was created. The European Medicines Agency website and the Dutch Medicines Evaluation Board website were used to collect all data.

Results There were a total of 73 benefit-risk reassessments during the study period; 61 reassessments for a single product and 12 reassessments for multiple products or an entire product class. Nineteen reassessments resulted in the recommendation to remove the product from the market. On average, a benefit-risk reassessment was performed 18.7 years after the product was first marketed. Seventeen products were marketed 5 years or less when the reassessment procedure was completed; six of these products were subsequently removed from the market.

Conclusions The majority of all benefit-risk reassessments that were performed during the study period did not result in removing the product from the market, but rather, in confirming the positive benefit-risk of the product, conditional to changes to the product's marketing authorisation. About half of all products that were removed from the market during the 2000s had been marketed for more than 20 years.
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INTRODUCTION

In Europe, a market license for a new medicinal product is only granted when the product's benefit-risk profile is deemed positive by expert committees, which means that there is sufficient evidence in support of the product's quality, safety and efficacy. Such data originate from preclinical and clinical studies that are usually performed in limited and selected patient populations[1] and are designed to establish efficacy rather than safety. As a result, less frequent adverse drug reactions of the medicine, or those adverse drug reactions occurring only after long-term treatment, remain unobserved.[2] Therefore, the safety of medicines is monitored throughout the product life cycle, and the occurrence of unexpected or serious adverse events in the post-marketing setting may compel a reassessment of a product's benefit-risk profile. Until 2012, benefit-risk reassessments for all medicinal products that are authorised in the European Union (EU)—regardless of whether products are registered in all EU countries or only in a number of member states[3,4]—were performed by the committee for medicinal product for human use (CHMP), but since 2012, these reassessments are performed by the pharmacovigilance risk assessment committee (PRAC). During recent years, calls from industry, regulatory authorities and academics for a switch to a more rational and explicit decision-making procedure with regard to the benefit-risk assessment of medicines have been made[5–10] in order to improve the transparency and accountability of regulatory decision-making.

* Correspondence to: M. L. De Bruin, Division of Pharmacoepidemiology and Clinical Pharmacology, Faculty of Science, Utrecht University, Utrecht, The Netherlands. E-mail: m.l.debruin@uu.nl

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The natures of those safety (or efficacy) issues that trigger a benefit-risk reassessment procedure (a so-called referral procedure; Table 1) as well as the outcomes of these reassessments have not been systematically studied. Previous studies have assessed market withdrawals in the USA,[11] in the UK,[12,13] or more recently, safety withdrawals in the EU,[14] but to the best of our knowledge, no recent studies have assessed the outcomes of all benefit-risk reassessments—including those reassessments that do not result in a market withdrawal. Furthermore, most studies in the past have focused on new active substances or relatively newly marketed products, but it was found that the 20-year survival rate for medicines marketed since 1972 in the UK was 84%.[12] Therefore, it is important to study the benefit-risk reassessments of all marketed medicines, including those medicines that have been marketed for many years, as well as to consider all possible outcomes of such reassessments, and not merely focus on market withdrawals. The aim of this study, therefore, was to determine the outcomes and timing of all benefit-risk reassessment procedures that were performed by the European Medicines Agency (EMA) during 2001–2012.

METHODS

Benefit-risk reassessment procedures

When a benefit-risk reassessment procedure is started, a medicine—or a medicine class—is referred to the EMA such that (until July 2012) the committee for medicinal products for human use (CHMP) could make a harmonised recommendation regarding the product's benefit-risk in light of new evidence. Since July 2012, the PRAC performs all safety-related benefit-risk reassessments. Medicinal products in Europe can be authorised through two different pathways and are either centrally authorised products (authorised in entire EU by the EMA) or non-centrally authorised products (authorised in one or more member states by a national regulatory authority). As a result, there are different so-called referral procedures (Table 1), but the benefit-risk reassessment for all these procedures is essentially identical, and all reassessments were performed by the CHMP during the study period.

Cohort

We created a cohort of all benefit-risk reassessments (i.e. referrals) of medicinal products that were triggered by safety and/or effectiveness concerns and that were finalised (i.e. a CHMP opinion was issued) between 1 January 2001 and 31 December 2012 (Figure 1). We scanned the minutes of all monthly CHMP meetings during the study period—that are publicly available on the EMA website—to identify all products that were subjected to an Article 20, Article 31, Article 36 or Article 107 referral procedure (Table 1 and Figure 1). Subsequently, the referral database—available on the EMA website as well—was used to check the list compiled based on the CHMP minutes in order to identify any inconsistencies and/or missing information. Furthermore, the EMA kindly provided a list of referral procedures for CAPs upon request in a personal communication. We organised all procedures by international nonproprietary name (INN) and differentiated between procedures in which one INN was evaluated (single INN reassessments), and procedures in which multiple INNs or a whole class of products were evaluated

Table 1. Types of referral procedures in Europe

Referral procedure	Description of procedure
Article 20 Reg. (EC) 726/2004	This type of referral is triggered for medicines authorised via the centralised procedure in case of manufacturing or safety issues. The procedure is organised by product name level; this means that if one INN is registered under different brand names and formulations, each form of the product will have a separate procedure.
Article 31 Dir. 2001/83/EC	This type of referral is triggered when the interest of the community is involved, following concerns relating to the quality, safety or efficacy of a medicine not authorised through the centralised procedure. The procedure is organised by INN level or by product class level.
Article 36 Dir. 2001/83/EC	This referral applied for products that were authorised through the non-centralised route. It was triggered when a Member State considered that action (variation, suspension or withdrawal) was needed on the grounds of the need to protect public health. This procedure has been replaced by Art. 107i and Art. 31. The procedure is organised by INN level or by product class level.
Article 107 Dir. 2001/83/EC	This referral was triggered when a Member State varied, suspended or revoked the MA for a medicine in its territory because of a safety issue. This procedure has been replaced by Art. 107i in July 2012. The procedure is organised by INN level or by product class level.
Article 107i Dir. 2010/84/EU (Amd.)	This referral is triggered when a Member State or the European Commission consider that urgent action is necessary because of a safety issue. This procedure applicable for both centrally and non-centrally authorised products and is implemented per July 2012. The procedure is organised by INN level or by product class level.

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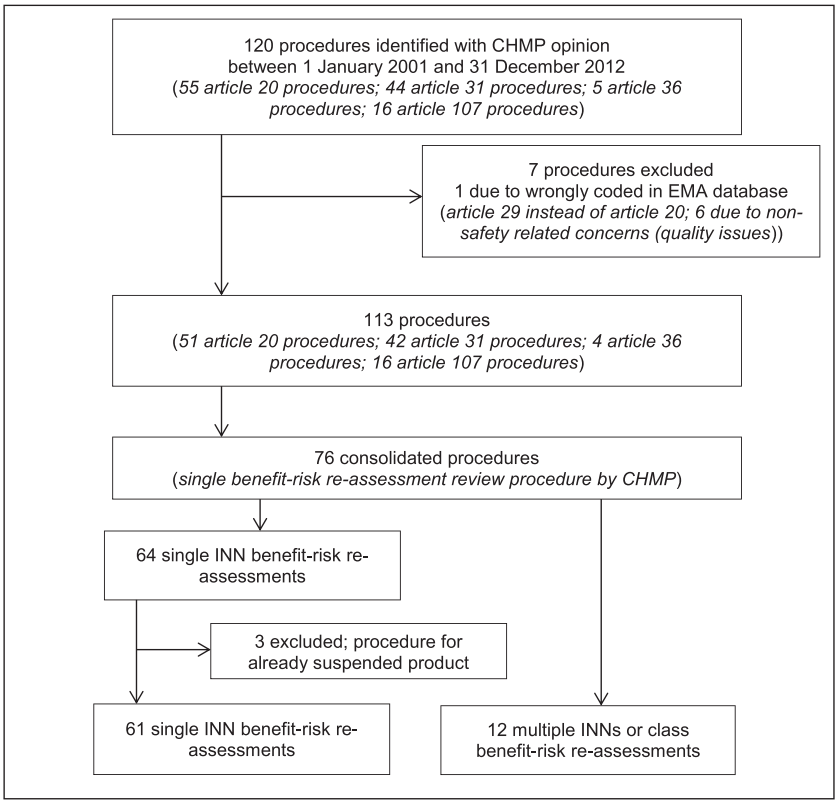

CHMP Committee for Medicinal Products for Human Use; EMA European Medicines Agency; INN International Nonproprietary Name.

Figure 1. Data selection

(class reassessments). We excluded new procedures that were performed for a product that was already suspended (i.e. not marketed) at the start of the procedure.

A referral procedure for a marketed product can have four possible types of outcomes: the CHMP can recommend to (i) maintain the marketing authorisation of the product without any changes; recommend to (ii) change the conditions of the product's marketing authorisation; recommend the (iii) suspension of the marketing authorisation of the product until new evidence for the product's positive benefit-risk is generated; or recommend the (iv) revocation of a product's marketing authorisation. We collected all CHMP decisions, as well as the reasons for the reassessment, from the publicly available referral assessment reports (www.ema.europa.eu). Other data that we collected included the date of the first market authorisation for all products that underwent a reassessment, as well as the year in which the CHMP Opinion was issued. In 22% of cases, the date of first marketing authorisation was not stated in the assessment reports. In these instances, we extracted the date of the first marketing authorisation in the Netherlands from the website of the Dutch Medicines Evaluation Board (www.cbg-meb.nl). In a number of cases, no exact year of first authorisation was given, but only the decade was stated (e.g. has been available in member states since the 1960s). In such cases, we used the decade's middle year (e.g. 1965) as an approximation for the year of first marketing authorisation in an EU country.

RESULTS

Outcomes of benefit-risk reassessments

We identified a total of 120 referral procedures with a CHMP opinion that was issued between 1 January 2001 and 31 December 2012 and excluded seven procedures because of misclassification, resulting in 113 procedures in total (Figure 1). As multiple procedures can be started for the same active ingredient simultaneously and such procedures are combined in one CHMP review, there were 73 consolidated procedures, composed of 61 single INN benefit-risk reassessments and 12 reassessments where either a number of different INNs or an entire medicine class were reviewed for the same safety issue (Figure 1).

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The most common decision ($N=39$; 64% of all single INN reassessments) made by the CHMP following a benefit-risk reassessment was to allow the product to remain on the market, but under the condition that changes to the product's marketing authorisation would be made (Table 2). In only two cases (3%) did, the CHMP decide to maintain the marketing authorisation of a product without any changes. Furthermore, in 16% ($N=10$) of the single INN reassessments, the CHMP decided to suspend the product's marketing authorisation. Finally, in 16% ($N=10$) of the single INN reassessments, the CHMP decided either to revoke the product's marketing authorisation, or the market authorisation holder decided to withdraw the product before the reassessment was finalised. One out of the 12 (8.3%) class benefit-risk reassessments resulted in the suspension of one of the products in the class, and although none of the class reassessments resulted in the revocation of a marketing authorisation by the CHMP, in one case, two of the products belonging to the class that was reassessed were voluntarily withdrawn by the manufacturers before the reassessment procedure was finalised.

Single international nonproprietary name benefit-risk reassessments

The average number of years that passed between first marketing authorisation and the reassessment for single products was 18.8 year (median 13.0 years; $N=59$). On average, the timing of a benefit-risk reassessment that resulted in the decision to maintain the marketing authorisation without any changes was 30 years after market entry ($N=2$; Table 2). The average time between first authorisation and the end of the reassessment was 15.8 years ($N=38$; median 13.0 years) for the products that required a change to the conditions of the marketing authorisation. Furthermore, 10 of these products had been marketed 5 years or less at the time of the reassessment, and 16 products had been marketed 10 years or less. The products that were withdrawn from the market following a benefit-risk reassessment had been marketed on average for 27.4 years ($N=9$; median 35 years), and the suspended products had been marketed for 20.3 years ($N=10$; median 12 years) (Table 2).

There were 17 products in total for which a benefit-risk reassessment procedure was finalised within the first 5 years of the marketing authorisation (Table 2). Three products were withdrawn, and three products were suspended, but 11 of these newly marketed products were allowed to remain on the market; for one product, the CHMP decided that no change to the marketing authorisation was necessary, and 10 products required a change to the conditions of the marketing authorisation. One of the products with a first benefit-risk reassessment 4 years after the first marketing authorisation (sibutramine; marketed in 1999, first referral in 2002) was eventually withdrawn from the market in 2010, 11 years after the first marketing authorisation.

In the majority of the single INN assessments, the positive benefit-risk profile of the product was confirmed (Table 3). In two cases, the MA was maintained without any changes, and in 39 reassessments, the recommendation that the MA needed to be changed was made. Table 3 lists all these benefit-risk reassessments, including the year of first MA, the trigger for the reassessment procedure and the classification of the adverse event that triggered the referral (MedDRA system organ class (SOC)). The triggers were general disorders and administration site conditions (nine reassessments), cardiac disorders (eight reassessments);,hepatobiliary disorders (six reassessments); nervous system disorders (five reassessments); neoplasms benign, malignant and unspecified (five reassessments); gastrointestinal disorders (three reassessments); skin and subcutaneous disorders (three reassessments); immune system disorders (two reassessments); congenital, familial and genetic disorders (two reassessments); vascular

Table 2. Outcomes of all benefit-risk reassessments during 2001–2012

	Maintain MA	Change MA	Withdraw MA	Suspend MA	Total
Number of single INN reassessments:	2	39	10	10	61
Reassessments within 6 years of first MA	1	10	3	3	17
Years between first MA—referral, mean	30.0	15.8*	27.4†	20.3	18.4‡
Years between first MA—referral, median	30.0	13.0*	35.0†	12.0	13.0‡
Number of class reassessments	0	10	1	1	12

MA, marketing authorization; INN, international nonproprietary name.
*$N=38$; one date could not be retrieved.
†$N=9$; one date could not be retrieved.
‡$N=59$; two dates missing.

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Table 3. All single INN assessments that resulted in the recommendation to maintain or change the MA ($N = 41$)

Product	Year referral	Outcome	Year first MA	Suspected ADR	SOC
Rotavirus vaccine (Rotarix)	2010	Maintain	2006	Contamination PCV-1 virus	General disorders and administration site conditions
Pholcodine	2011	Maintain	1955	IgE-sensitisation to neuromuscular blocking agents resulting in increased risk anaphylactic reactions	Immune system disorders
Cisapride	2001	Change	1988	QT-prolongation: risk severe arrhythmia	Cardiac disorders
Calcitonin	2002	Change	1973	Doubt efficacy	General disorders and administration site conditions
Bupropion	2002	Change	1999	Seizure and fatalities	Nervous system disorders
Sibutramine	2002	Change	1999	Two-fatal cases due to cardiovascular events	Cardiac disorders
Loratadine (+ pseudoephedrine)	2003	Change	1989	Hypospadias in newborn when used during pregnancy	Congenital, familial and genetic disorders
Nimesulide	2003	Change	1985	Serious liver problems	Hepatobiliary disorders
Paroxetine	2004	Change	1991	Suicidal behaviour adolescents	Psychiatric disorders
Gadobutrol	2006	Change	2000	Doubt efficacy	General disorders and administration site conditions
Hepatitis B vaccine	2006	Change	—	Reassess benefits	General disorders and administration site conditions
Bicalutamide	2007	Change	1995	Cardiovascular complications	Cardiac disorders
Nimesulide	2007	Change	1985	Serious liver problems	Hepatobiliary disorders
Piroxicam	2007	Change	1991	Gastrointestinal side effects	Gastrointestinal disorders
Etoricoxib	2008	Change	2002	Cardiovascular risks	Cardiac disorders
Moxifloxacin	2008	Change	2002	Hepatotoxicity	Hepatobiliary disorders
Norfloxacin	2008	Change	1985	Reassess benefits	Administration site conditions
Methylphenidate	2009	Change	1982	Cardiovascular and cerebrovascular events in children	Cardiac and Nervous system disorders
Valproate	2009	Change	1965	Doubt efficacy in manic episodes	General disorders and administration site conditions
Becaplermin (gel)	2010	Change	1999	Increased risk cancer	Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Bevacizumab (systemic)	2010	Change	2005	Doubt efficacy in combination therapy	General disorders and administration site conditions
Ketoprofen topical	2010	Change	1978	Skin photosensitivity	Skin and subcutaneous tissue disorders
Modafinil	2010	Change	1992	Neuropsychiatric disorders + skin hypersensitivity	Psychiatric and Skin and subcutaneous tissue disorders
Natalizumab	2010	Change	2006	PML after >2 years of use (1 : 1000)	Infections and infestations
Saquinavir	2010	Change	1996	QT-prolongation: risk severe arrhythmia	Cardiac disorders
Somatropin	2011	Change	1985	Increased mortality	General disorders and administration site conditions
Dexrazoxane	2011	Change	2006	Risk cancer (AML, MSD) in paediatric patients	Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Dronedarone	2011	Change	2009	Liver-, lung- and cardiovascular events	Cardiac, Hepatobiliary, and Respiratory, thoracic and mediastinal disorders
Lenalidomide	2011	Change	2007	Increased risk cancer (secondary)	Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Nimesulide	2011	Change	1985	Gastrointestinal + hepatic safety concerns	Gastrointestinal and Hepatobiliary disorders
Pioglitazone (and combinations)	2011	Change	2000	Increased risk cancer (bladder)	Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Orlistat	2012	Change	1998	Severe hepatotoxicity (rare)	Hepatobiliary disorders
Calcitonin	2012	Change	1973	Increased risk cancer	Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Doripenem	2012	Change	2008	Not effective at currently approved dose	General disorders and administration site conditions
Fibrin sealants	2012	Change	1997	Risk air embolism	Vascular disorders
Fingolimod	2012	Change	2011	Cardiovascular risks	Cardiac disorders
Influenza vaccine	2012	Change	2008	Narcolepsy children and adolescents	Nervous system disorders
MMRV vaccine	2012	Change	2004	Risk congenital rubella syndrome = malformations newborn	Congenital, familial and genetic disorders
Strontium ranelate	2012	Change	2004	Cardiovascular + skin reactions	Vascular and Skin and subcutaneous tissue disorders
Tolperisone	2012	Change	1960	Gastrointestinal + neurological events; hypersensitivity	Gastrointestinal, Immune system, and Nervous system disorders
Trimetazidine	2012	Change	1970	Worsening Parkinson	Nervous system disorders

MA, marketing authorization; ADR, adverse drug reaction; SOC, system organ class.
The nature of the changes to the conditions of the marketing authorization for each referral procedure can be found in publicly available documents on the EMA website.

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disorders (two reassessments); psychiatric disorders (two reassessments); respiratory disorders (onw reassessment); infections and infestations (one reassessment).

Suspended and withdrawn products

Twenty-two benefit-risk reassessments resulted in the suspension or revocation of the product's marketing authorisation (Table 4). As for two of these products, the suspension was lifted as the result of new evidence, and it follows that for 19 out of 73 benefit-risk assessments performed the outcome was the removal of the product from the market—decided either by the CHMP or through a voluntary withdrawal of the product(s) by the market authorisation holder.

The majority of the 19 suspended or withdrawn products for which we could retrieve the date of first marketing authorisation had been marketed for 10 years or more when the product was removed from the market, and nine products had been marketed for more than 20 years (Figure 2), whereas six products were removed from the market within the first 5 years of their market introduction.

DISCUSSION

In the majority of all benefit-risk reassessment procedures completed by CHMP between 1 January 2001 and 31 December 2012, it was concluded that the product's benefit-risk profile remained positive, but that changes to the conditions of the marketing authorisation were necessary. The results of this study demonstrate that the majority of products for which concerns over product safety or efficacy arose post-authorisation were allowed to remain on the market conditional to changes to the product's marketing authorisation. In addition, about half of the products that were removed from the market during the study period had been marketed for more than 20 years.

Our study has several limitations. All data were manually extracted from documents available through the EMA website. Even though our data cover a long time period, our findings are not necessarily predictive for future benefit-risk reassessments by regulatory authorities, especially because PRAC now performs all safety referrals. A preliminary analysis of all the referrals that have been finalised in PRAC during its first 18 months of operation, however, shows a similar proportion of outcomes (approximately 30% withdrawals, and 70% label changes).[15] As we intended to study the outcomes of benefit-risk reassessment procedures, we did not include any cases where products were withdrawn for other reasons such a market withdrawals due to commercial reasons. We also did not include safety reviews that were performed in the context of a periodic safety update report that will occur more frequently and might result in label changes. We did not assess the nature of the condition changes to a product's MA, but some changes could be more 'severe' than others and range from adding information on a safety issue to the product's label to restricting the patient indication. Notwithstanding, we included all benefit-risk reassessments that have been performed during a 12-year period and have also included those procedures where a product was not withdrawn from the market. Therefore, our study provides a more complete picture of how CHMP made decisions regarding the benefit-risk of medicines during a 12-year period.

An analysis of the market withdrawals of new molecular entities in the USA during 1980–2009 found that the average time until withdrawal was 5.9 years.[11] Another study that assessed safety withdrawals in the UK during 1971–1992 found that the average time until withdrawal was 58 months (4.8 years)[13] and a third study found that the average time until withdrawal of a new active substance from the UK market during 1972–1994 was 4.9 years.[12] While safety withdrawals only concerned a subset of the regulatory outcomes we studied, we found an average time until withdrawal of 27.4 years for the 10 products that were withdrawn from the market during the 2000s as a result of a referral procedure. Although our sample differs in a number of ways from those used in the previous studies, notwithstanding, these differences indicate that the types of products that were removed from the market from the 1970s until the 1990s were mostly newly marketed products, whereas the majority of products that were removed from the market during the 2000s after a referral procedure were products that had already been marketed for many years. A number of other publications have reported timing to market withdrawals in various regions,[16–18] but none of these publications used very similar samples, making it problematic to compare our findings. Comparing timings of products that were withdrawn in the USA during the same years as covered by our study could be an area of future research.

Unlike many studies that have focused on safety withdrawals of medicines, we assessed all possible outcomes of benefit-risk reassessments and found that although newly marketed medicines (marketed 5 years or less) were still regularly subjected to a reassessment of the product's benefit-risk in light of new safety

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Table 4. All reassessments that ended in the recommendation to suspend or withdraw the MA ($N = 20$)

INN	ATC code	Year referral	Outcome	Year MA	Indication	Reasons for start of referral procedure	SOC
Cerivastatin	C10AA06	2002	Revoked	1998	Hyperlipidaemia	CHMP review found cerivastatin was effective in the treatment of hyperlipidaemia but did not present a specific therapeutic benefit in relation to comparable compounds and there were concerns related to the risk of rhabdomyolysis.	Musculoskeletal and connective tissue disorders
COX II inhibitors	M01AH	2005	Only refecoxib voluntarily withdrawn	—	Rheumatoid arthiritis; osteoarthritis	Clinical trial data for rofecoxib revealed a risk of thrombotic cardiovascular events and resulted in the worldwide withdrawal of rofecoxib in 2004. Subsequently, other COX II inhibitors were reviewed by CHMP and were found to have positive benefit-risk profiles.	Cardiac disorders
Clobutinol	R05DB03	2007	Voluntarily withdrawn	1961	Cough	CHMP review started after suspended in Germany in 2007due to cardiovascular safety (QT prolongation). MAH decided to withdraw its product voluntarily from all markets worldwide.	Cardiac disorders
Lumiracoxib	M01AH06	2007	Revoked	2005	Rheumatoid arthritis; osteoarthritis	CHMP review stated after UK assessment of reports of liver problems.	Hepatobiliary disorders
Veralipride	N05AL06	2007	Revoked	1979	Hot flushes	CHMP review following reports of serious side effects including depression and anxiety that resulted in product withdrawn in Spain in 2005.	Psychiatric disorders
Dextropropoxyphene	N02AC04	2009	Non-parental form revoked and parental form suspended	1970	Acute + chronic pain	CHMP review started after concerns for some years over the risk of death from overdose—resulted in safety reviews in several member states but these have led to different conclusions. CHMP concluded that the benefits of non-parenteral forms of product do not outweigh their risks and recommended their withdrawal. CHMP noted that safety was less of a concern for the parenteral form. Therefore, the marketing authorisations for the parenteral form of product were suspended until further data are available to show that the benefits outweigh the risks.	Injury, poisoning and procedural complications
Iodocasein/thiamine	A11	2009	Revoked	1955	Obesity	CHMP review started after Italy suspended product in 2009 because of serious cases of hyperthyroidism and thyrotoxicosis. Product was only marketed in Italy.	Endocrine disorders
Propacetamol (powder for injection)	N02BE05	2009	Outcome procedure not clear, likely withdrawn	—	Pain + fever	CHMP review started after product was withdrawn in France because of the risk of serious hypersensitivity reactions, cases of thrombosis and administration site reactions. Information is missing from referral database, not clear what outcome of referral was. Product was only marketed in France.	Immune system disorders
Benfluorex	A10BX06	2010	Revoked	1974	Hyperlipidaemia/ diabetes	In 2007 indication withdrawn for use in patients with high blood levels of triglycerides. Safety review in 2009 by France resulted in suspension, after reports of cardiac valvulopathy (thickening of the heart valves) and pulmonary arterial hypertension. Suspension in Portugal followed, therefore CHMP started review.	Cardiac and respiratory disorders
Bufexamac	M02AA09	2010	Revoked	1975	Topical NSAID	CHMP started review after product was withdrawn in Germany because of allergic contact reactions. CHMP noted that the data to support the effectiveness of bufexamac were very limited. Most of the studies dated from the original development of bufexamac in the 1970s and 1980s were of a lower standard than that expected today. Because of this, no evidence of the effectiveness of bufexamac could be derived from them. In addition, when looking at the few more recent, controlled studies, the CHMP noted that the effectiveness of bufexamac had not been shown.	Skin and subcutaneous tissue disorders

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Lacosamide (syrup)	N03AX18	2011	Syrup revoked, tablets remain available	2008	Epilepsy	2011, Quality defect in several batches of product that could not be solved.	General disorders and administration site conditions
Carisoprodol	M03BA02	2007	Suspended	1959	Short-term lower back pain	CHMP review started after suspended in Norway in 2007 because of increased risk of abuse and addiction and risk of causing intoxication and psychomotor impairmen. Conditions for lifting suspension: Data demonstrating that the products can be used safely taking into account information on intoxications from poison centres in Europe. Data demonstrating convincing efficacy and safety derived from appropriately designed clinical trials (including an active comparator) and data justifying the proposed dose	Psychiatric disorders
Rimonabant	A08AX01	2008	Suspended; voluntarily withdrawn in 2009	2006	Obesity	Possible risk of depression was known at MA, but data post-marketing experience and ongoing clinical trials indicated that serious psychiatric disorders may be more common than in the clinical trials used in the initial assessment of the medicine. Therefore, CHMP review started and product was suspended. In 2008, MAH voluntarily withdrew product.	Psychiatric disorders
Efalizumab	L04AA21	2009	Withdrawn voluntarily after suspension	2004	Psoriasis	Review at request of the EC following reports of serious side effects, including three-confirmed cases of PML in patients who had taken Raptiva for more than 3 years. In 2009, MAH decided to voluntarily withdraw the product, as it did not intend to conduct the clinical trials necessary to fulfil the requirements for lifting the suspension.	Infections and infestations
Fentanyl (transdermal)	N02AB03	2009	Suspended; non-renewal of MA in 2011	2006	Pain	MAH recalled all systems from the EU in 2008 as a precautionary measure due to quality defect resulting in the risk of overdose. Conditions for lifting suspension: Suspended until MAH can robustly demonstrate the quality of the product.	Injury, poisoning and procedural complications
Rosiglitazone (and combinations)	A10BG02	2010	Suspended	2000	Diabetes mellitus type II	Since its first authorisation, rosiglitazone had been recognised to be associated with fluid retention and increased risk of heart failure and its cardiovascular safety was kept under close review. Recent data from clinical trials and post-marketing data supported an increased cardiovascular risk of rosiglitazone and resulted in CHMP review. Conditions for lifting suspension: Convincing and robust data to identify a patient population in which the clinical benefits of rosiglitazone-containing products clearly outweighs the risks.	Cardiac disorders
Sibutramine	A08AA10	2010	Suspended	1999	Obesity	Sibutramine previously reviewed in 1999 and 2002, following concerns over its safety, especially cardiovascular side effects (increased blood pressure and heart rate). As a result of these reviews, in 2002, a study was started to investigate these risks. Study was stopped prematurely because of increased cardiovascular problems in treatment group as compared with placebo. Conditions for lifting suspension:	Cardiac disorders

(*Continues*)

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Table 4. (Continued)

INN	ATC code	Year referral	Outcome	Year MA	Indication	Reasons for start of referral procedure	SOC
						Convincing data to identify a patient population in which sustained and clinically important efficacy of sibutramine-containing products can be demonstrated, and in which the benefit clearly outweighs its risks.	
Modified-release opioids	N02A	2010	One of the products was suspended (Ethirfin)	2005	Pain	Review was started after concerns that the active substance in the capsules could be released too quickly if the capsules are taken with alcohol, leading to side effects such as respiratory depression (and inhibition of breathing). Market authorisation for Ethirfin was not renewed in 2010 after product was suspended.	Respiratory, thoracic and mediastinal disorders
Buflomedil	CO4AX20	2011	Suspended	1975	PAOD	CHMP review started after product suspended in France in 2011 because of serious and sometimes fatal neurological disorders (convulsions + status epilepticus) and cardiac disorders. Conditions for lifting suspension: Convincing data to identify a patient population in which the benefits of buflomedil clearly outweigh its identified risks.	Nervous system and cardiac disorders
Meprobamate	N05BC01	2012	Suspended	1970	Anxiolytic	CHMP review started after suspended 2011 in France due to safety risks including confusion, loss of consciousness, risk of addiction and cases of overdose leading to coma or death. Conditions for lifting suspension: Convincing data to identify a patient population in which the benefits of meprobamate clearly outweigh its identified risks.	Psychiatric disorders

INN, international nonproprietary name; ATC, anatomical therapeutic chemical classification system; MA, marketing authorization; SOC, system organ class, CHMP, committee for medicinal product for human use; EU, European Union; PAOD, peripheral arterial occlusive disease; NSAID, nonsteroidal anti-inflammatory drug; MAH, marketing authorisation holder.

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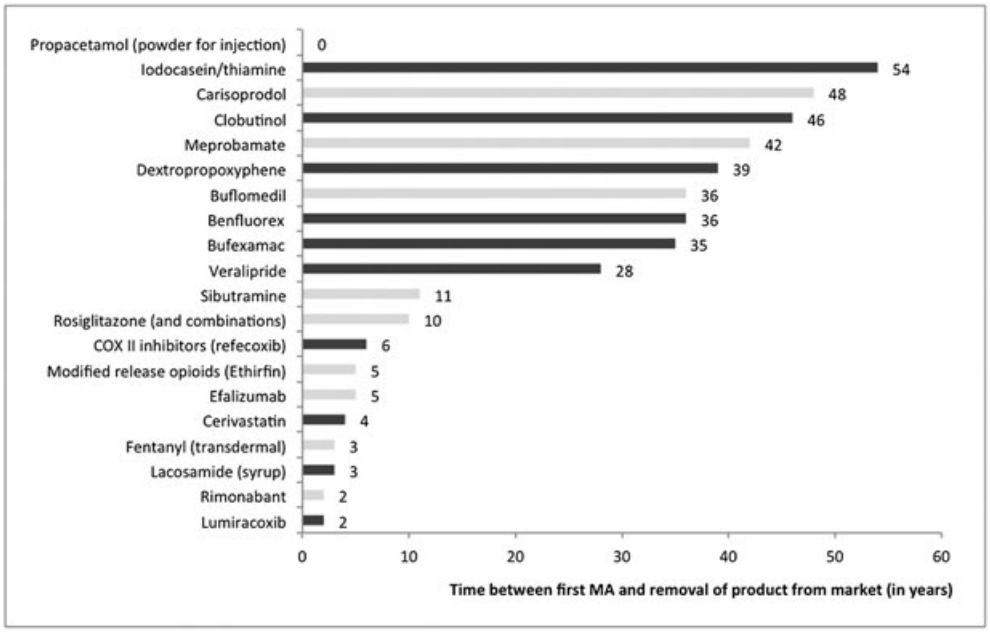

The dark bars indicate market withdrawals/revocations; the light bars indicate suspensions. If a product was suspended but was subsequently withdrawn voluntarily or the market license was not renewed, it is indicated as withdrawn as well. Therefore, the dark bars indicate those products that were still suspended as of November 2014. Total suspensions were 10 products; 2 suspensions were lifted and are not included in the figure. All suspended products (8) therefore refer to products that were still suspended on 1st September 2014. One suspension was lifted in a class referral (aprotinin). Missing data regarding first MA date propacetamol (powder for injection) which was withdrawn but therefore is not included in this figure.

Figure 2. Time (in years) elapsed between first marketing authorisation and suspension or withdrawal of product

information, in the majority of these cases CHMP decided that the benefit-risk profile of the product remained positive. The triggers for most of the benefit-risk reassessments that did not result in the recommendation to suspend or revoke the MA of the product could still be classified as serious safety issues (see Table 3 for an overview of all triggers). We did not include any potential determinants into our analysis that could explain why some products were considered to have a positive benefit-risk whereas others were found to have a negative benefit-risk (Table 4), but it is likely that the effectiveness of the product and the number of alternative treatment options available to patients were taken into account in the benefit-risk reassessment.

A recent study of safety withdrawals during 2002–2011 from EU markets found that the time between first authorisation and market withdrawal was 23.7 years on average, confirming our findings. This could mean that regulatory standards for market approval have increased since the 1990s, such that unsafe products no longer receive market approval. Alternatively, this finding could also mean that regulatory tolerability of safety risks has shifted as nowadays the tools to better manage the benefit-risk of such products are available. In addition, this finding also demonstrates that there are two distinct cases of a safety withdrawal: first, the withdrawal of a new product due to unforeseen safety issues and, second, the withdrawal of a product after having been marketed for many years. This finding indicates that important benefit-risk assessments are made well into the life cycle of medicines and not merely in the first few years after marketing authorisation.

Our results indicate that the majority of products that were removed from the EU market during the 2000s after a benefit-risk reassessment procedure had been marketing for more than 5 years. Furthermore, most of the benefit-risk reassessments that were performed during the study period did not result in removing the product from the market, but rather, in confirming the positive benefit-risk of the product, conditional to changes in the product's marketing authorisation. Finally, compared with

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previous studies, our results indicate that the number of products that are removed from the market because of safety reasons shortly after market introduction might have decreased compared with the 1970–1990s.

CONFLICT OF INTEREST STATEMENT

No funding was received for the work reported in this paper. All authors report no conflict of interest.

The results reported in this paper have not been published previously, nor have they been presented at scientific meetings or conferences.

Key Messages:

- As the safety profile of medicines is usually incomplete at market entry, the safety of medicines is monitored throughout the product lifecycle. If necessary, the benefit-risk profile of a marketed medicine will be reassessed by the committee for medicinal product for human use.
- During 2001–2012, there were a total of 73 benefit-risk reassessment procedures for either a single medicinal product or a product class. The majority of these procedures did not result in the removal of the medicine from the market, but rather, in confirming the positive benefit-risk profile, conditional to changes to the marketing authorization. Furthermore, the majority of products that were removed from the market were at the end of their lifecycle and not at the beginning.

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