LÆGEMIDDEL STYRELSEN

DANISH MEDICINES AGENCY

Annual report for reported product defects and withdrawals of medicines in 2010

Introduction

The Danish Medicines Agency monitors and checks product defects of medicines on the Danish market to safeguard people as well as animals. If a product is of inconvenience to or may potentially harm consumers, it may be necessary to withdraw the medicine from the market.

The Danish Medicines Agency must be informed through *reports* if a company considers that a product defect could lead to the *withdrawal* of a medicine from the market. This is stipulated in section 30 of the Danish executive order no. 1242 of 12 December 2005 on the manufacturing and import of medicines and intermediary products. Section 30 also obliges all manufacturers to implement a system for registration and investigation of complaints and a system enabling the immediate withdrawal of medicines and intermediates at any time. Reporting to the Danish Medicines Agency must take place regardless of whether a defect affects one single batch or the entire product.

Via the so-called 'Rapid Alert System', the Danish Medicines Agency receives warnings about product defects from foreign drug regulatory authorities and reports new product defects at international level. The Rapid Alert System covers medicines in the legal supply chain only. The alerts are classified from I to III according to the severity of the defect. Class I defects are potentially life threatening and requires that a rapid alert notification must be sent to out all parties. Class II defects *could* cause illness or mistreatment and requires action within 24 hours. Class III defects cover all other defects that may or may not pose a hazard to health. Class III defects require action within two to three working days.

The Danish Medicines Agency thoroughly evaluates all reports and assesses in cooperation with the company, whether the product defect could lead to a withdrawal. Before a decision is made to withdraw a medicine, several aspects must be examined first. Is the medicine marketed in Denmark? Is it distributed to countries outside Denmark? Has it been clinically tested or dispensed via a special compassionate use permit? And so forth. It is also investigated to what extent the product defect presents a potential risk for patients, and how a potential withdrawal would affect consumers. Next, it is determined how far down the supply chain the product needs to be withdrawn (wholesaler, pharmacy, consumer). Where critical product defects are concerned, the Danish Medicines Agency places warnings on its website, www.dkma.dk.

Companies must comply with the rules on Good Manufacturing and Distribution Practice (GMP and GDP), which contribute to minimising potential defects during the manufacturing process and distribution of medicines. At inspections, we check whether companies comply with these rules. In addition, we regularly take in selected medicines, packages, labels, package leaflets and analyses for testing in the Danish Medicines Agency's laboratories. Both inspections of companies and tests performed in the Danish Medicines Agency's laboratories can lead to the withdrawal of medicines.

Summary of findings in 2010

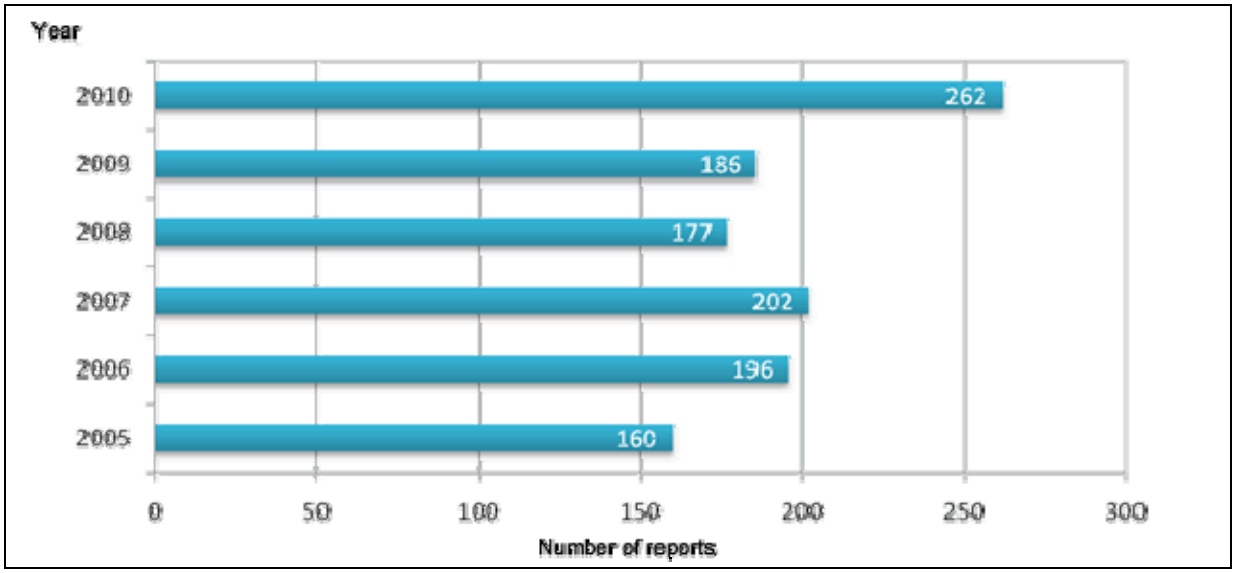
In 2010, the Danish Medicines Agency received a total of 262 reports on product defects involving medicines. This is the highest number of reports received within the past five years. The increase in the total number of reports is generated by a general increase across all types of product defects. Examples include more reports related to non-compliance with GMP, defects related to the product itself and variation applications ending with withdrawals. The majority of reports came from other authorities and companies. Eight of the 262 reports were caused by counterfeit medicines in the legal distribution chain, which, however, did not affect the Danish market. Furthermore, about 24 % of the reports resulted in medicines being withdrawn from the Danish market. The majority of the withdrawals were reported by companies and were primarily caused by 'packaging defects' and 'packaging, bottling/filling and labelling'.

1. Reports

1.1 Number of reported product defects

In 2010, we received a total of 262 reports on product defects involving medicines. Figure 1 shows the number of reports in the period 2006-2010. As illustrated, there was a significant increase in reports in 2010 compared to the previous year.

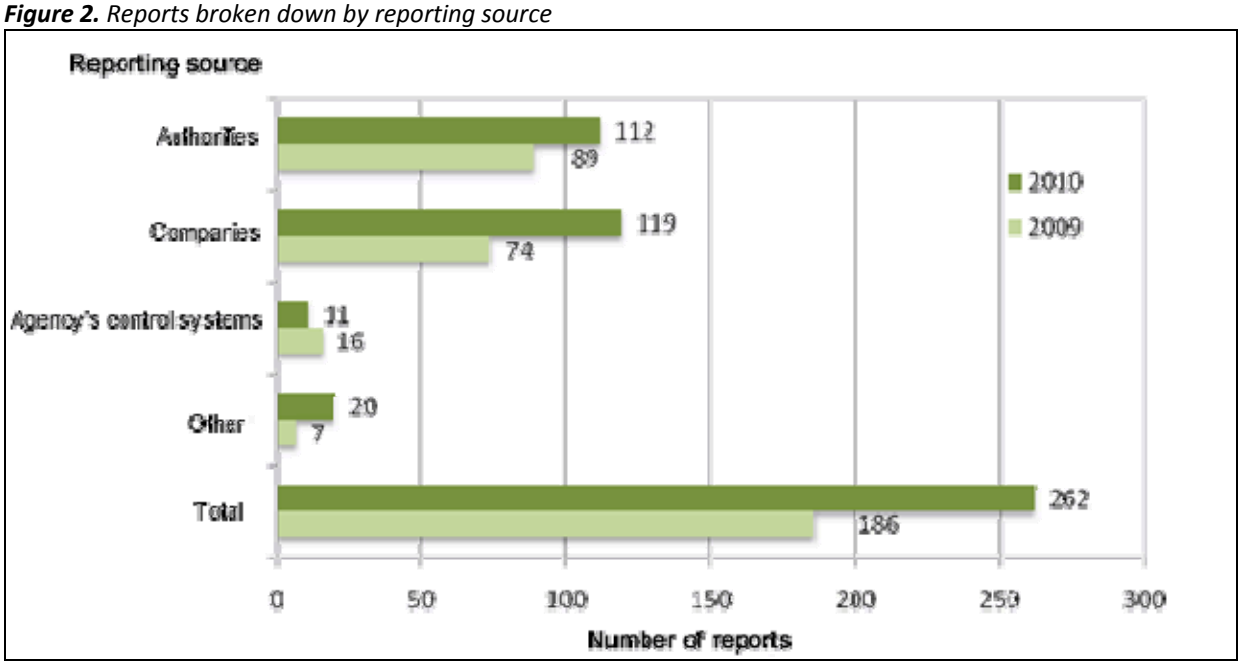
Figure 1. *Number of reports involving product defects from 2006-2010*



1.2 Reports broken down by source

Figure 2 breaks down the 262 reports submitted to the Danish Medicines Agency in 2010 and 2009 on reporting sources.

Figure 2. *Reports broken down by reporting source*



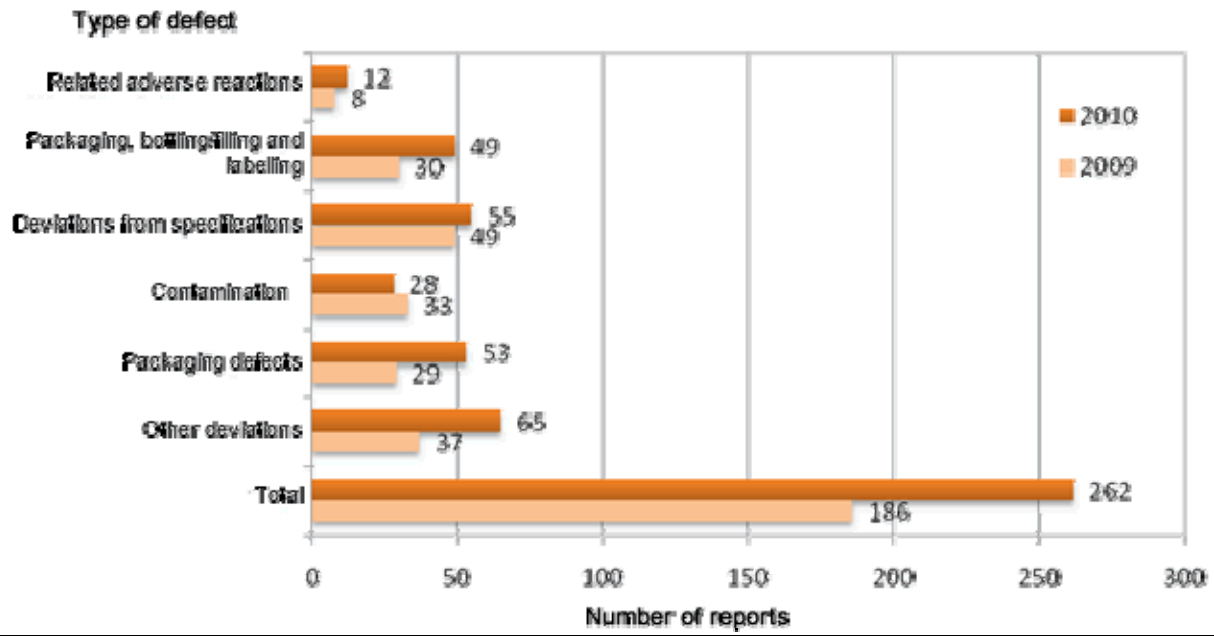
Compared to 2009, an increase has occurred in the number of reports submitted by authorities and companies as well as other sources (patients, doctors and pharmacies). In contrast, there was a fall in the number of reports originating from the Danish Medicines Agency's own control and licensing systems. The majority of reports come from companies and authorities, which together account for 88 % of all reports.

1.3 Reports broken down by type of defect

When the reports are registered at the Danish Medicines Agency, they are distributed on six different types of defects. The distribution for 2010 compared to 2009 is shown in figure 3. 2010 saw an overall increase in the number of reports received for all types of product defects with the exception of 'contamination', which fell slightly on the year before. The number of reports involving the defect types 'packaging defect' and 'other' increased significantly.

The different types of defects are described in Box 1 below.

Figure 3. *Reports broken down by type of defect*



Box. 1. *Types of defects*

- **Adverse reactions related to a product defect:** If a product defect of a given product causes an adverse reaction, it is assessed whether or not this should lead to the withdrawal of the medicine in question.
- **Packaging, bottling/filling and labelling:** Defects occurring during packaging or repackaging of a medicine, e.g. the placing of the wrong strength of a product into a package.
- **Deviations from specifications:** Defects related to cases where the manufacturer observes that a given medicine does not meet the medicinal product's specifications approved by the Danish Medicines Agency, e.g. the shelf life specifications.
- **Contamination:** Contamination defects include cases where impurities, for some reason or other, have entered the medicine during the manufacturing of the medicine or active substance.
- **Packaging defects:** Defects that typically occur in connection with the printing of the packaging material, for example a missing or incorrect expiry date. This type of defect also covers physical/technical defects such as leaking containers.
- **Other deviations:** Other deviations typically concern reports of non-compliance with GMP, counterfeit medicines, authorised variation applications and the suspension of marketing authorisations leading to withdrawals, as well as defects related to the product itself, e.g. precipitation, lack of sterility, etc.

The product defects classified as 'other' increased from 37 reports in 2009 to 65 reports in 2010. 17 of the 65 reports were related to non-compliance with GMP, implying that the companies have failed to observe the rules on Good Manufacturing Practice. Furthermore, seven of the reports categorised as non-compliance with GMP were related to the suspension or withdrawal of the so-called 'Certificate of Suitability' (CEP).

Manufacturers can apply to the European Directorate for the Quality of Medicines and Healthcare (EDQM) for issuance of a CEP. CEPs are issued for substances of the European Pharmacopoeia, and a CEP thus certifies that the manufacturing of the product in question lives up to defined quality standards.

The EDQM regularly updates changes to the status of CEPs on its website. If the EDQM withdraws or suspends a CEP, the marketing authorisation holder must take the necessary measures to ensure that active substances from the concerned active substance manufacturer are not used, either permanently or for a defined period. When the Danish Medicines Agency receives information about the suspension or withdrawal of a CEP, it is published on www.dkma.dk. In the last couple of years, we have seen an increase in the number of reports concerning CEPs, with a total of 13 reports in 2010.

1.5 Counterfeit medicines

In the period 2004-2007, the Rapid Alert System transmitted an increasing number of warnings about counterfeit medicines found in the legitimate supply chain globally, cf. table 1. After a considerable decline in counterfeit medicines in 2008, we once again recorded a small increase in 2009 and 2010, see table 1. The increase could be a result of intensified focus on counterfeits coupled with a rise in the number of reports submitted to the Danish Medicines Agency.

The Danish Medicines Agency has not received information about or observed any counterfeit medicines in the legitimate supply chain in Denmark so far.

Table 1. *Number of reports of counterfeit medicines in the period 2004-2010.*

	2004	2005	2006	2007	2008	2009	2010
Counterfeit medicines	2	3	8	19	3	6	8

As part of our activities to prevent counterfeit medicines from reaching consumers, the Danish Medicines Agency has set up a network consisting of authorities, industrial associations, scientific organisations and all links in the supply chain. The network participants meet biannually and initiate local and cross-cutting preventive measures. The network has produced guidelines for pharmaceutical companies and pharmacies in efforts to prevent counterfeit medicines from entering the legal supply chain.

In connection with the Danish Medicines Agency's work in the interdepartmental 'Network against Copyright Piracy', structured dialogue has been opened with the industry on the combat of counterfeit products in general, which also includes counterfeit medicines.

In order to facilitate the reporting procedure for companies comprised by the reporting duty of section 43B of the Danish Medicines Act (act no. 1180 of 12 December 2005), we have placed an electronic reporting form on our website (in Danish only). The reporting duty was implemented by amendment of the Danish Medicines Act on 1 July 2008. It obligates marketing authorisation holders pursuant to section 7 and

holders of a company authorisation pursuant to section 39(1) to report any discovery of counterfeit medicines to the Danish Medicines Agency.

The Danish Medicines Agency participates in the European cooperation between drug regulatory authorities in the EU, which exchanges information about illegal, including counterfeit, medicines distributed in the ***illegal*** supply chain in Europe. This could concern pharmaceuticals sold illegally via the internet, which could be related to a multitude of countries. We investigate such information if it seems to be related to Denmark and sanctioning measures are required. In circumstances that may be penalised under the Danish Medicines Act, the Danish Medicines Agency makes decisions regarding the liable party and refers, according to the circumstances, cases to the police for imposition of legal penalties. In addition we publish warnings on our website whenever it is necessary to inform Danish consumers.

In 2010, the Danish Medicines Agency made it possible to anonymously report violations of the Danish Medicines Act via our website (under the so-called 'whistle blowing scheme'). The scheme can, for example, be used to submit information about suspected illegal activities involving counterfeit medicines.

2. Withdrawals

2.1 Number of withdrawals

24 % of the 262 product defects reported to the Danish Medicines Agency in 2010 resulted in actual withdrawals of medicines from the Danish market.

As can be seen from Table 2, the total number of reports has increased in the past two years and is at the highest level seen over the period 2004-2010. We also recorded an increase in the number of withdrawals. 64 withdrawals puts 2010 in front seen over the past seven years.

Table 2. *Number of withdrawals from 2004-2010*

	2004	2005	2006	2007	2008	2009	2010
Number of reports	143	160	196	202	177	186	262
Number of withdrawals	58	58	55	57	41	46	64
Withdrawals in per cent	41%	36%	28%	28%	23%	25%	24%

2.2 Withdrawals broken down by reporting source

Table 3 shows the distribution of the 64 withdrawals in 2010 on reporting source.

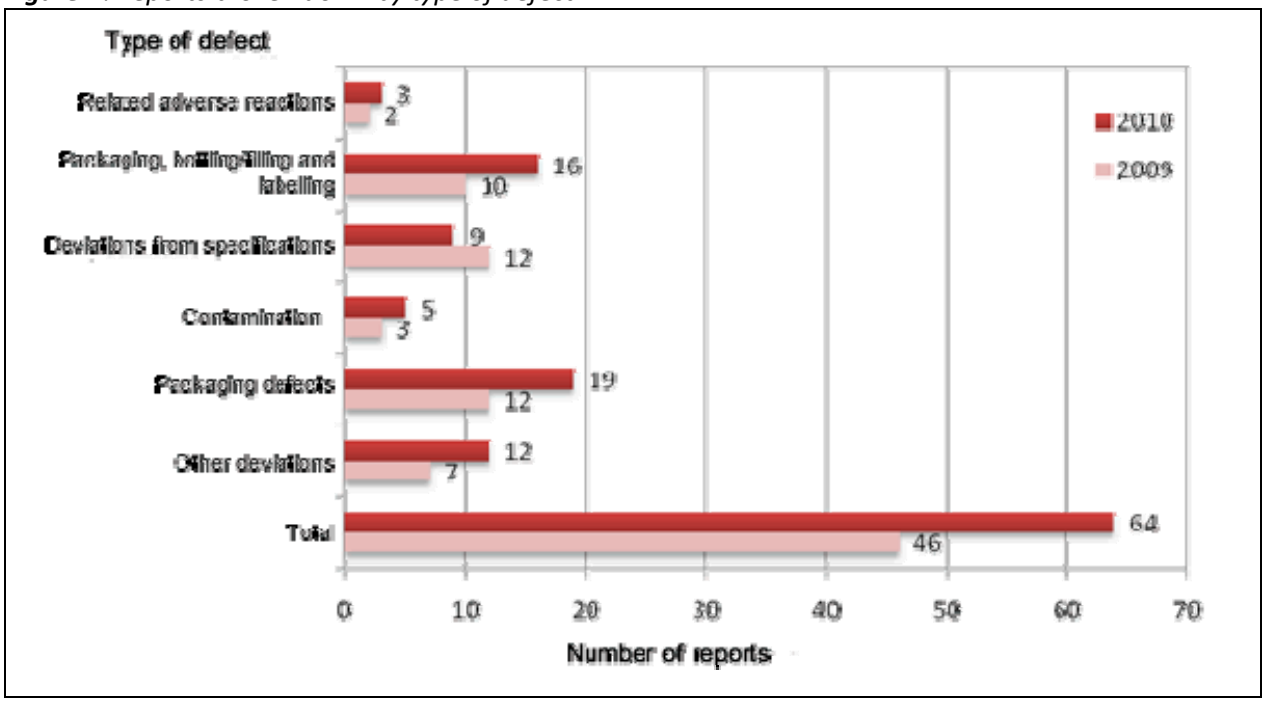
Table 3. *Reports resulting in withdrawals broken down by reporting source in 2007-2010*

	2007	2008	2009	2010
Company	47	29	29	42
Foreign authority	4	8	5	18
Danish Medicines Agency's control system	5	3	8	3
Other	1	1	4	1
Total	**57**	**41**	**46**	**64**

In 2010, the majority of withdrawals were generated by reports from companies and foreign authorities, which is significantly more than the year before. In contrast, the number of withdrawals generated by reports from the Danish Medicines Agency's own control system and other sources (patients, doctors, pharmacies) fell on the year before.

The causes of the 64 withdrawals in 2010 are shown in figure 4. In 2010, the majority of the withdrawals were caused by 'packaging defects' and 'packaging, bottling/filling and labelling'.
Two out of the 12 withdrawals classified as 'other' were CEP related and thus related to non-compliance with GMP. The other withdrawals classified with the product type 'other' were caused by defects on the product itself, e.g. precipitation or related to variation applications leading to the withdrawal of the product.

Figure 4. *Reports broken down by type of defect*



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