Sundhedsstyrelsen
Danish Health and Medicines Authority

ANNUAL REPORT FOR REPORTED PRODUCT DEFECTS AND WITHDRAWALS OF MEDICINES IN 2011

2012

Annual report for reported product defects and withdrawals of medicines in 2011

Danish Health and Medicines Authority

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1 Introduction

The Danish Health and Medicines Authority monitors and checks product defects of medicines on the Danish market to safeguard people as well as animals. In performing these activities, it may become necessary to withdraw medicines from the market if a product is of inconvenience to or could potentially harm consumers,

Pursuant to section 30 of the Danish executive order no. 824 of 1 August 2012 on the 'manufacturing and import of medicines and intermediary products', the Danish Health and Medicines Authority must be notified if a company considers that a product defect could lead to the withdrawal of a medicine from the Danish market or to supply difficulties. 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. The Danish Health and Medicines Authority must be notified regardless of whether a defect affects one single batch or the entire product.

In addition to the reports received from Danish companies, the Danish Health and Medicines Authority is also notified via the so-called 'Rapid Alert System' through which it receives warnings about product defects from foreign drug regulatory authorities. The Rapid Alert System covers countries in and outside the EU/EEA and enables Denmark to send out notifications about observed product defects. It is a global communication system, which contributes to minimising the spread of defective medicines in the legal supply chain.

The alerts are classified from I to III according to the severity of the defect. Class I defects are potentially life threatening and requires immediate action, and a rapid alert notification must be sent out to all countries in the Rapid Alert System. Class II defects could cause illness or mistreatment. Class III defects cover all other defects that may or may not pose a hazard to health.

The Danish Health and Medicines Authority thoroughly evaluates all reports and assesses in cooperation with the marketing authorisation holder or representative whether the product defect could lead to a withdrawal. This way, an efficient system for communication between company, authority and consumers is established.

A wide risk assessment is made to clarify if the product defect could have further implications for other medicines manufactured at the manufacturing site, if it could affect supply, or if there could be other consequences for the market.

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). All depending on what consequences the defect could have, it may be necessary to quarantine the medicine in question while the defect is being investigated.

Where critical product defects are concerned, the Danish Health and Medicines Authority places warnings on its website, www.dkma.dk, possibly in conjunction with a press release, or takes other steps to ensure the information reaches consumers.

2 Summary of findings in 2011

In 2011, 356 reports of medicinal product defects were registered, which is the highest number ever. The majority of the reports came from companies and other authorities and predominantly concerned defects on the package and packaging material and deviations from specifications. In addition, compliance checks of product labelling and package leaflets carried out by the Danish Health and Medicines Authority generated an increase in the number of reports.

About one third of all reports resulted in actual withdrawals of medicines from the Danish market, which is also more than the year before. Almost all withdrawals were effected based on reports from companies and from the Danish Health and Medicines Authority's own control system. The withdrawals were mainly caused by the defect types 'packaging, bottling/filling and labelling' as well as 'package defects'.

12 reports were caused by counterfeit medicines in the legal supply chain, primarily on non-European markets, but in 2011, we did see one counterfeit product on the Danish market, which resulted in a withdrawal.

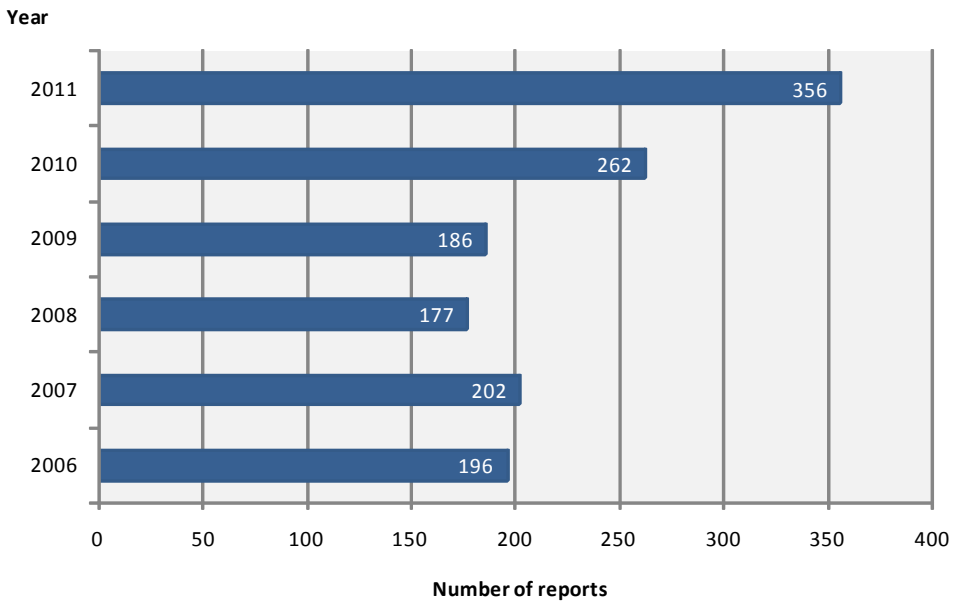
3 Reports

3.1 Number of reports

In 2011, we received a total of 356 reports on product defects involving medicines. Thus the increase in reports recorded in 2009 and 2010 continued into 2011.

Figure 1 shows the number of reports in the period 2006-2011. As illustrated, there were significantly more reports in 2011 compared to the previous years. From 2010 to 2011, the number of reports increased by 36 %.

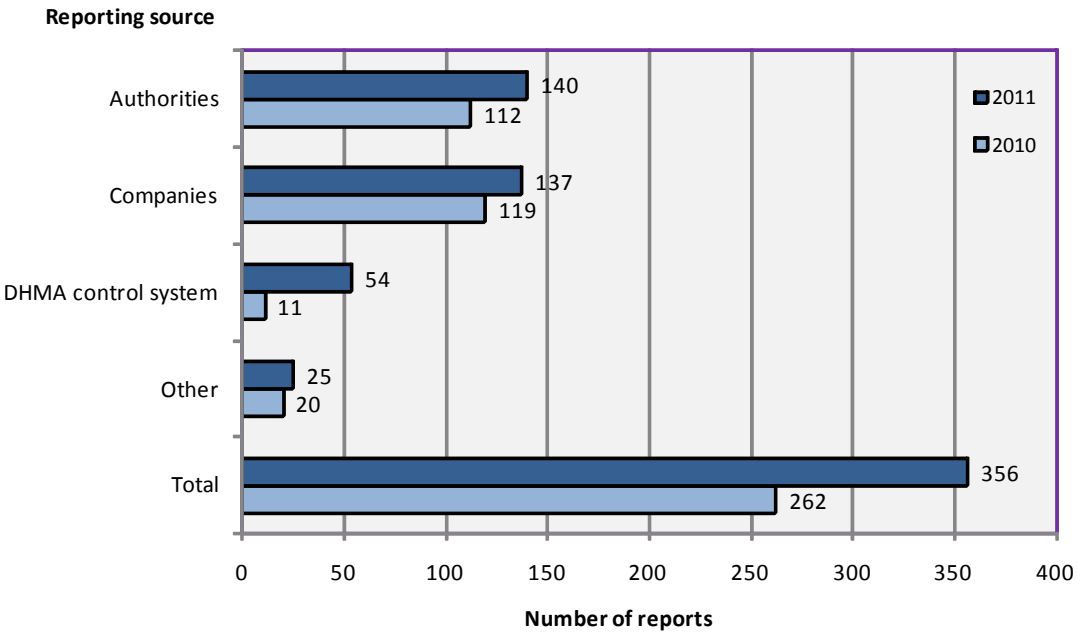
Figure 1. Number of reported product defects from 2006-2011



3.2 Reports broken down by reporting source

Figure 2 breaks down the reports received in 2011 and 2010 on reporting sources.

Figure 2. Reports broken down by reporting source



All sources submitted more reports in 2011 than in 2010. The majority of reports came from companies and authorities, which together accounted for about 80 % of all reports.

The category 'Other' covers complaints about medicines submitted by healthcare professionals, including pharmacies, and mostly involve defects related to the packaging material or the like. It also covers complaints received from citizens who have experienced problems with the effect of a medicine or its package.

The biggest increase was recorded for the reports generated by the Danish Health and Medicines Authority's compliance checks of labelling and package leaflets, which grew from 4 % in 2010 to 12 % in 2011.

In 2011, the Danish Health and Medicines Authority had particular focus on correct implementation of Braille on medicinal products. Spot checks were performed to check if the requirement effective from 2010 for Braille on Danish medicine packages had been observed. Marketing authorisation holders which had not put Braille on their medicine packages were ordered to withdraw the concerned medicines from the market.

In 2011, we also checked the package leaflets of antidepressants (SSRIs – selective serotonin reuptake inhibitors) to see if the information for pregnant and lactating women had been updated in compliance with the updated warnings for these products. The companies which had failed to update the package leaflets accordingly were ordered to withdraw the concerned SSRIs from the market.

3.3 Reports broken down by type of defect

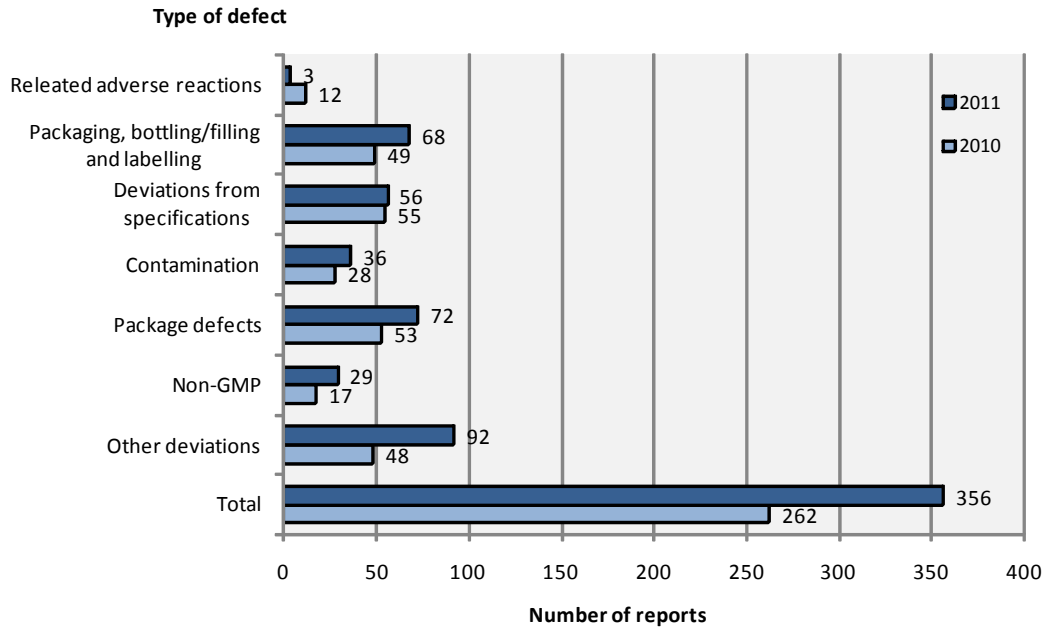
When the reports are registered at the Danish Health and Medicines Authority, they are distributed between six different types of defects.

The distribution for 2011 compared to 2010 is shown in figure 3. In 2011, the number of reports increased across all types of product defects, except for the category 'related adverse reactions', which fell on the year before.

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

The defect type 'Other deviations' break down evenly on the categories described in Box 1. 12 of these reports concerned counterfeit medicines, which is described in section 3.1.

Figure 3. Reports broken down by type of defect



29 reports were related to non-compliance with GMP, referring to companies having failed to observe the rules on Good Manufacturing Practice. 11 of these reports were also related to the suspension or withdrawal of the so-called ’Certificate of Suitability’ (CEP).

Active substance 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 Health and Medicines Authority 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 non-GMP compliant companies and suspended or withdrawn CEPs. However, most of the reports have not involved medicines or substances contained in medicines on the Danish market, and many of the reports referred to cases outside the EU/EEA.

However, situations in which a company is declared non-GMP compliant could have major consequences for the affected markets. This occurred in 2011 when the Danish Health and Medicines Authority was informed of a US-based manufacturer who was declared non-GMP compliant following an inspection carried out in the USA. The company supplied a number of medicines worldwide, and since many of them were characterised as essential in several countries, there was a lot of focus on maintaining supplies and, through joint efforts, finding alternative manufacturers and treatment options where possible.

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 or batches thereof.**
- **Packaging, bottling/filling and labelling: Defects occurring during packaging or repackaging of a medicine, e.g. if the wrong strength of a product has been placed into a package (mix-up), or if the package leaflet is missing or has errors.**
- **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 Health and Medicines Authority, e.g. the specifications for shelf life and solubility.**
- **Contamination: Contamination include defects or sterility failure occurring during the manufacturing of the medicine or the active substance where impurities, for some reason or other, have entered the medicine.**
- **Package defects: Defects that typically occur in connection with the labelling of the package, e.g. incorrect batch number, expiry date or lack of Braille. In addition, this type of defect covers physical/technical defects such as leaking containers.**
- **Other defects: Other defects typically concern reports of counterfeit medicines, authorised variation applications and the suspension of marketing authorisations leading to withdrawals. Cases of supply problems and defects on the product itself, e.g. precipitation, also fall under this category.**

3.4 Counterfeit medicines

Via the Rapid Alert System, we have received a steady number of reports of counterfeit medicines found in the legal supply chain. 2007 was, however, a peak year, and in 2011 we once again saw an increase in the total number of reports received, cf. table 1. The increase may be ascribed partly to overall increased focus on counterfeit medicines in the past couple of years with consequent increased reporting tendency and partly to a real increase in the number of counterfeits globally.

Table 1. Number of reports of counterfeit medicines in the period 2006-2011

	2006	2007	2008	2009	2010	2011
Counterfeit medicines	8	19	3	6	8	12

In 2011, the Danish Health and Medicines Authority (then the Danish Medicines Agency) received the first ever report of a counterfeit medicine that had entered the legal supply chain in Denmark. As a result, the medicine was recalled from patients. The other 11 reports did not involve the Danish market.

In response to requests for increased focus on counterfeit medicines, a new directive (2011/62/EU) has been implemented. It puts focus on a number of new measures in the legal supply chain. The first part of the new directive must be implemented into Danish law by 1 January 2013.

4 Withdrawals

4.1 Number of withdrawals

29 % of the 356 product defects reported to the Danish Health and Medicines Authority in 2011 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 couple of years and is at the highest level seen over the period 2006-2011.

The increase in the total number of reports is matched by an increase in number of withdrawals.103 withdrawals in 2011 is the highest number of withdrawals over the six-year period.

Table 2. Number of withdrawals from 2006-2011

	2006	2007	2008	2009	2010	2011
Number of reports	196	202	177	186	262	356
Number of withdrawals	55	57	41	46	64	103
Withdrawals in per cent	28%	28%	23%	25%	24%	29%

4.2 Withdrawals broken down by reporting source

Table 3 shows the distribution of the 103 withdrawals in 2011 by reporting source.

Table 3. Reports resulting in withdrawals broken down by reporting source in 2008-2011

	2008	2009	2010	2011
Company	29	29	42	54
Foreign authority	8	5	18	6
Danish Health and Medicines Authority's control system	3	8	3	39
Other	1	4	1	4
Total	**41**	**46**	**64**	103

In 2011, the majority of withdrawals were generated by reports from companies and the control system of the then Danish Medicines Agency. Compared to previous years, reports from these sources have increased with a marked increase in withdrawals effected based on reports from the Danish Health and Medicines Authority's control system. This is offset by a drop in withdrawals effected based on reports from foreign authorities. One of the most significant explanations for this is that the majority of these reports did not involve medicines distributed to the Danish market.

4.3 Reports broken down by type of defect

The causes of the 103 withdrawals in 2011 are shown in figure 4 and compared to 2010. In 2011, the majority of withdrawals were caused by the defect types 'packaging, bottling, filling and labelling' and 'package defects'. This is because 2011 saw a general increase in this type of reports and because the Danish Health and Medicines Authority's has had particular focus in the areas involving compliance checks of package leaflets and labelling.

The withdrawals classified under 'other defects' were among other things caused by defects on the product itself or on the basis of authorised variation applications. In addition, there was an increase in withdrawals effected based on deviations from specifications.

Combined, defects related to the packaging material (packaging, bottling/filling and labelling) or package (package defects) accounted for more than half of withdrawals in 2011. Withdrawals that are effected based on these types of defects rarely imply that there is a real patient risk, nor does it mean that there is anything wrong with the medicine itself. The withdrawals are effected pursuant to the Danish executive order on labelling, or on the basis of risk of confusion or difficulties with using the medicine. Companies therefore play a key role in reducing these errors via thorough reviews and through updates of packaging material, package leaflet and packaging design.

Figure 4. Withdrawals broken down by type of defect