European Medicines Agency
Inspections

London, 18 January 2007
Doc. Ref. EMEA/INS/GMP/23020/2007

An analysis of quality product defects in the centralised procedure

1. Executive Summary

An analysis is presented of the product quality defects reported on centrally authorised products in 2005. A total of 65 product defects were reported to the EMEA of which 20 resulted in product recalls (two recalls Class 1, four Class 2 and fourteen Class 3).

The paper describes the background and legal basis for the reporting of suspected product quality defects to the EMEA, how these are handled by the EMEA, and the main findings during 2005. It gives an indication of the most common product defects for centrally authorised products for both human and veterinary medicinal products.

This is the first analysis made by the EMEA. It is anticipated that further analysis and comparisons will be prepared on an annual basis.

2. Introduction and background

The EMEA's Inspections Sector receives and co-ordinates reports of suspected defects in centrally authorised medicinal products for human or veterinary use and co-ordinates the necessary actions.

Marketing Authorisation Holders (MAHs), manufacturers and importers are obliged to report to the EMEA any product defect in a centrally authorised product which could result in a recall or restriction on supply. In addition, Marketing Authorisation Holders are requested, in accordance with Regulation 726/2004, Articles 16(2) and 41(4), to inform the EMEA of any prohibition or restriction imposed by the competent authority of any country in which the medicinal product is placed on the market and of any other new information might influence the evaluation of the benefits and risks of the medicinal product concerned. This includes systematic information on warning letters issued by non-EEA regulatory authorities relating to manufacture problems.

Reports on suspected product defects should include:

- The product name
- The name of the manufacturer or parallel importer
- The strength and dosage form of the product
- The product licence number
- The batch number or numbers of the product
- The expiry date or dates of the product
- The nature of the defect
- The account of any action taken in consequence

Once the report is provided, the EMEA Inspections Sector co-ordinates the necessary actions with the Rapporteur and Supervisory Authority(ies). EMEA informs the MAH on the outcome of these

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 95
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

discussions and on the need for any regulatory action which may have been decided by the Rapporteur and Supervisory Authority(ies) or CxMP.

Where a defect is considered to be a risk to public or animal health, the MAH is requested to withdraw the affected centrally authorised product from the EU market and the Supervisory Authority issues a Rapid Alert in accordance with the procedure described in the Compilation of Community Procedures (*http://www.emea.europa.eu/Inspections/docs/CoCP/CoCP_RapidAlertProc.pdf*). The alert is classified from 1 to 3 depending upon the expected risk presented to the public or animal health by the defective product. This classification is internationally agreed upon for medicinal product recalls and is defined as follows:

- Class 1: the defect presents a life threatening or serious risk to health
- Class 2: the defect may cause mistreatment or harm to the patient or animal, but it is not life threatening or serious.
- Class 3: the defect is unlikely to cause harm to the patient, and the recall is carried out for other reasons, such as non-compliance with the MA or specification.

In the case of Class 1 recalls, a rapid alert notification must be sent to all EEA Member States, PIC/S, EDQM, WHO, FDA and MRA partners, irrespective of whether or not the batch was exported to that country. In most cases, Class 1 recalls should be to patient level, however, this may not be the appropriate action if alternative medicines are not available, so that an assessment by the Rapporteur of the overall risk to patients/animals must be conducted. Also, consideration has to be given to the difficulties of communicating to patients since Marketing Authorisation Holders may need to arrange press releases and advertising campaigns.

Class 2 rapid alert notifications should be sent only to those EEA Member States, PIC/S, EDQM, WHO and MRA partners to which it is known, or believed, that the batch has been distributed. In identifying those countries, due consideration should be given to parallel distribution and import arrangements and the free trade between wholesale distributors within the EEA. In the case of parallel imports where there is difficulty in establishing the traceability of batches, consideration should be given to notifying all Member States through the Rapid Alert System. Class 3 recalls are not notified through the Rapid Alert System.

For Class 2 and 3 recalls, recall to patient level is rarely required for this level or risk, since lack of the product may present a greater risk to the patient than continuing treatment. Occasionally Class 2 or 3 recalls can be carried out just to wholesaler level in circumstances such as where stocks are unlikely to be found further down the supply chain and the level or risk is sufficient low.

2. Method

Product defects are classified by the EMEA using the classification in table 1.

No	Category
1	Chemical cross-contamination
2	Coring problems (particles)
3	Counterfeit
4	Deviation from Marketing Authorisation (MA)
5	Dissolution test results
6	FDA Warning Letter
7	GMP inspections observations
8	Handling error

9	Microbiological cross-contamination
10	Official Medicines Control Laboratory Out Of Specification (OMCL OOS)
11	Out of Specification (OOS)
12	Product Information Literature
13	Ancillary materials
14	Parallel Distribution
15	Pharmacovigilance
16	Stability testing
17	Sterility assurance

Table 1. List of categories in alphabetical order of deficiencies used by the EMEA to classify product defects

3. Findings

Data from 65 product defects reported by manufacturers, MAHs and competent authorities, of which 20 resulted in product recalls (30%) has been analysed. A summary of the recalls in each category is recorded in table 2.

Type of Recall	Number	Incidence (%)
Class 1	2	10
Class 2	4	20
Class 3	14	70

Table 2. Ranking of total recalls in 2005

It can be observed that Class 1 recalls (10% of the total recalls versus 90% for Class 2 and Class 3 recalls) are fortunately the less frequent ones and represented only 3% of the overall product defects in 2005.

In addition to this classification based on the type of recall, the EMEA has classified the product defects based on the list in table 1. The results are summarised in table 3.

No	Category	Number	Incidence (%)
1	Product Information Literature	14	23.1
2	Deviation from MA	10	15.4
3	Ancillary materials	9	13.8
4	OOS	8	12.3
5	GMP inspection findings	4	6.2
6	Coring problems	4	6.2
7	Parallel distribution	3	4.6

8	Chemical cross-contamination	2	3.1
9	Dissolution test	2	3.1
10	OMCL OOS	2	3.1
11	Pharmacovigilance	1	1.5
12	FDA Warning Letter	1	1.5
13	Handling error	1	1.5
14	Stability testing	1	1.5
15	Sterility Assurance	1	1.5
16	Microbiological cross-contamination	1	1.5
17	Counterfeit	0	0.0

Table 3. Ranking of total product defects in 2005 using the EMEA classification

The most reported product defect in 2005 was due to mistakes in the Product Information Literature (package leaflet, outer package, etc) with 23% of the total. Examples are the following: wrong shelf-life and batch number, wrong blue box, etc. These product defects[1] normally are associated with class 2 recalls. It should be stressed that this kind of issue ruins the efforts of the whole upstream manufacturing chain leading the authorities to request recalls of batches that are technically speaking safe and of good quality but that carry out a risk of misuse because of the wrong Product Information Literature attached to it. From this observation it may be worth putting even more focus on reviewing the labelling / packaging / release procedures and processes during GMP inspections of pharmaceutical manufacturers.

The second most significant product defect (15.3%) is connected with deviations of the Marketing Authorisation. The 10 cases reported in 2005 were associated mainly with one MAH for several centrally authorized products. No recalls were considered necessary.

The third most significant category (13.8% of the total) corresponds to problems with the packaging material (e.g. medical device). This is a typical problem identified with biological and sterile products and no recalls are normally associated. The fourth category (Out of Specification) is a typical defect leading to recalls. The classification of the recall depends on the type of specification. These first 4categories represent a total of two thirds of the product defects reported.

Finally, the Class 1 defects reported in 2005 corresponded to 'Microbiological cross-contamination' and serious 'GMP inspection findings' observed during the course of the inspections.

4. Conclusion

This is the first time that the EMEA has prepared an analysis of reported product defects to centrally authorised medicinal products, with the result that only limited information is available. However, the analysis performed in 2005 gives some indicators of the main defects reported. This analysis complements other similar analyses from other regulatory bodies and may therefore be helpful for Inspectors, National Competent Authorities, manufacturers and MAHs in identifying the main areas where there is room for improvement.

Further analysis to be performed in the coming years will give a clearer picture to all parties involved of the main areas where quality improvements may be needed. Results will be used to analyse trends,

[1] Wrong name of the medicinal product, active substance or strength are normally Class 1 defects. These examples were not reported in 2005.

to identify the need for revision of the EU GMP guide, or for example, to monitor differences between different groups of manufacturers, etc.