European Medicines Agency
*Inspections*

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# Good Manufacturing Practice: An analysis of regulatory inspection findings in the centralised procedure

## 1. Executive Summary

An analysis is presented of the deficiencies reported following inspections requested by the CHMP/CVMP and carried out by the EEA Member States on behalf of the EMEA of manufacturers of medicinal products and starting materials in the EEA and third countries during the period 1995-2005. A total of 9465 deficiencies, comprising 193 critical (2%), 989 major (10%) and 8283 other deficiencies (88%) were recorded in the EMEA database during the 435 inspections carried out by EEA inspectors during the above referenced period.

The deficiencies reported following the GMP inspections of centralised products are classified by the EMEA GMP scientific administrators according to a list defined by the MHRA of 40 categories (see table 1). While providing less fine detail than an analysis based on the chapters, paragraphs and annexes of the EU GMP guide, this system gives sufficient detail to provide a meaningful analysis.

This document describes the classification system, the method used by the EMEA staff to enter the data, some top level examples of analysis and the potential value of this system in identifying areas of concern. The system allows more detailed examples which have not been included in this document (e.g. comparisons between findings in different sectors, e.g., EU vs. third countries manufacturers; trends in findings in different years).

The primary purpose of this document is to provide an indication of the most common failures to comply with the EU GMP guide, as recorded by the EMEA for centralised products.

## 2. Introduction

Different types of inspections (e.g. general GMP inspection, routine re-inspection, product related-inspection, 'for cause' inspection) may be requested by the CHMP and CVMP and carried out according to the activities of the manufacturers. The conduct of these inspections may vary according to the objectives and may focus for example on the general level of GMP (e.g. first inspection in a third country), or on manufacture of a specific medicinal product or process (e.g. product related inspection).

The wide diversity of facilities in terms of activities, lay-out or management structure together with the variety of products and production processes as well as analytical methods means that judgment by inspectors on-site of the degree of compliance with GMP is crucial for the quality of centralised products on the EEA market.

The manufacture of medicinal products in the European Economic Area (EEA) is governed by European directives and is subject to the holding of relevant authorisations in accordance with Article 40 of Directive 2001/83/EC and Article 44 of Directive 2001/82/EC. To obtain and retain a licence, a company is obliged to comply with the relevant principles and guidelines of GMP as laid down in EU

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rules. The supervisory authority of each Member State is obliged by means of repeated inspections to ensure that these requirements are met.

Compliance by an applicant or Marketing Authorisation holder with GMP and other provisions of a Marketing Authorisation for medicinal products for administration to humans and animals will be assessed by the EEA Inspectorates when the CHMP and/or CVMP considers this necessary. CHMP and/or CVMP may request inspections in the EEA and also in third countries (i.e countries outside the EEA without an operational MRA) and, in certain special circumstances, it may be appropriate for the inspector to be accompanied by a relevant assessor appointed by the (Co)-Rapporteurs.

In the case of a general GMP inspection, inspectors assess whether the manufacturer is compliance with GMP. GMP includes ensuring that all manufacturing operations are performed in accordance with the relevant marketing authorisation (Articles 5 of Directive 2003/94/EC and 91/412/EC). The inspector is also in a position to verify that the details relating to the manufacture and control of a product which were provided in the marketing authorisation application for that product are being adhered to in the manufacture of batches of that product for release onto the market in the EEA.

At the end of each inspection of a manufacturer the inspector conducts a closing meeting at which the deficiencies or failures to comply with GMP are presented formally to the representatives of the company (normally the technical management including the key personnel and preferably some or all of the senior management) and may be discussed. The final meeting is a significant part of the inspection. The deficiencies observed during the inspection should be discussed. Their importance should also be discussed so that deadlines for remedial actions may be fixed. In the case of serious deficiencies leading to possible serious risk for patients and/or animals, immediate action should be taken by the inspectors, which should involve the relevant Scientific Committee (CHMP or CVMP).

Subsequently these deficiencies are confirmed to the manufacturer in the draft inspection report or post-inspection letter. Any response from the manufacturer is considered in the final report and the process is completed with the issuing of the final report to the EMEA.

If the outcome of the inspection is that the manufacturer is non-compliant, the CHMP and/or CVMP can take any necessary regulatory action, which may involve suspension or revocation of the Marketing Authorisation. If the non-compliant manufacturer is in the EEA, the relevant supervisory authority may also suspend or revoke the manufacturing authorisation. The action taken by the relevant authorities (i.e. supervisory authority and/or CHMP/CVMP) will depend upon the nature and the extent of non-compliance.

## 3. Method

The Inspections Sector developed a Microsoft Access GMP Database in 1999 to provide a management tool for the GMP Inspections of centrally authorised products (CAP) in the context of central marketing authorisation applications[1]. This database has a functionality permitting the analysis of deficiencies reported by the EEA inspectors which provides a valuable tool in identifying those practices of manufacturers which are of greater concern.

Classification of GMP deficiencies are described in the Compilation of Community Procedures[2]. Deficiencies are classified as “critical”, “major” and “other significant deficiencies”. A critical GMP failure occurs when a practice could give rise to a product which could or would be harmful to the patient or animal, or which has produced a harmful product. A combination of major deficiencies, which indicates a serious system failure, may also be classified as a critical deficiency.

[1] While parts of this database are accessible by the Member States using a secure Internet connection in read-only mode, it was agreed by the Ad-hoc meeting of GMP inspection services not to make available those parts related to the analysis of the deficiencies

[2] http://www.emea.eu.int/Inspections/docs/335103en.pdf

A deficiency may be classified as major for the following reasons:

- A non-critical deficiency which has produced or may produce a product, which does not comply with its marketing authorisation; *or*
- A non-critical deficiency which indicates a major deviation from EU GMP; *or*
- (within EU) A non-critical deficiency which indicates a major deviation from the terms of the manufacturing authorisation; *or*
- A non-critical deficiency which indicates a failure to carry out satisfactory procedures for release of batches or (within EU) a failure of the Qualified Person to fulfill his legal duties; *or*
- A combination of several "other" deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such.

Deficiencies which are classified as "other" represent deficiencies which cannot be classified as critical or major, possibly because of lack of information, but which nevertheless indicate departures from GMP. They are not necessarily of a minor nature and are essentially unclassified.

The final inspection report refers each deficiency to the relevant chapter and paragraph of the EU GMP guide. However, this system is not practical to use for analysis from a statistical point of view because the guide often refers to a particular aspect of GMP in more than one place (e.g. finished product testing may be found in more than 20 references of the GMP guide). The difficulty could be avoided by structuring the system differently, so that one deficiency belongs to one single category.

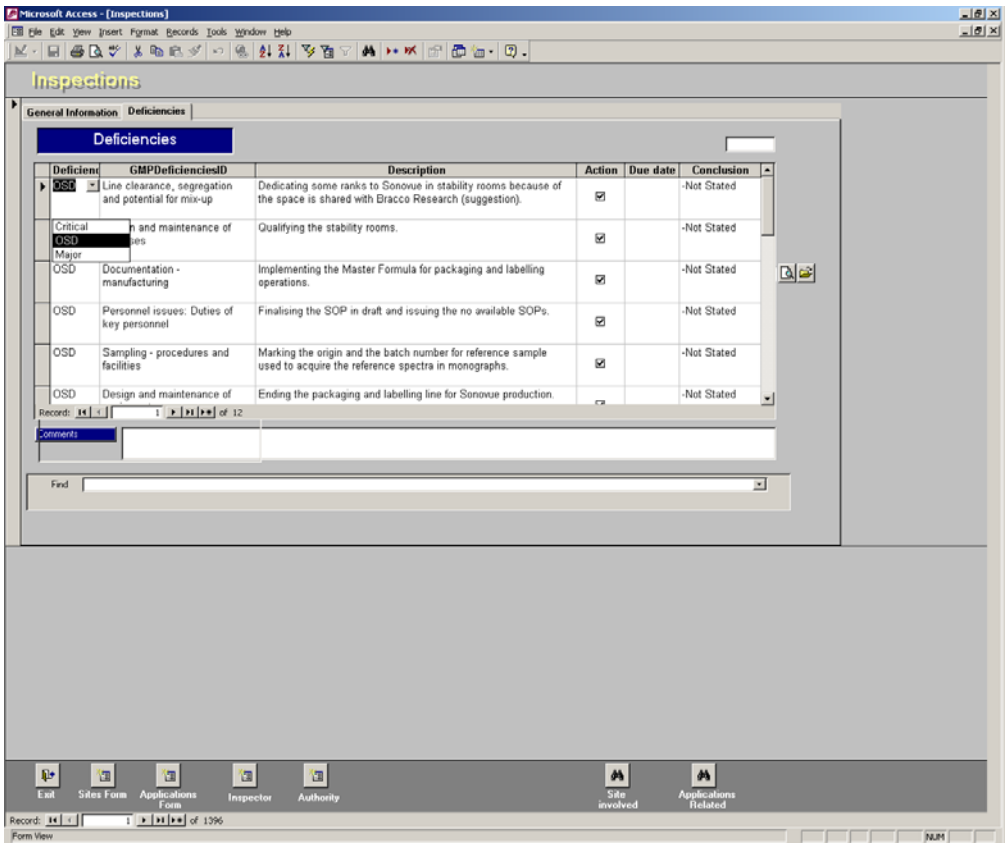
The EMEA Inspections Sector maintains a GMP database with all deficiencies (critical, major and other) listed in the final inspection reports. Data can be retrieved and analysed in a number of formats depending on the search criteria used. The EMEA with the MHRA has developed a simpler classification with 40 categories (see table 1) to avoid the above problem from a statistical point of view.

All deficiencies are recorded in the database and classified as listed in the inspection report in accordance with the critical, major and other classification (see picture 1). The EMEA Inspections Sector makes a second classification of the deficiencies using the 40 new categories (see picture 2).

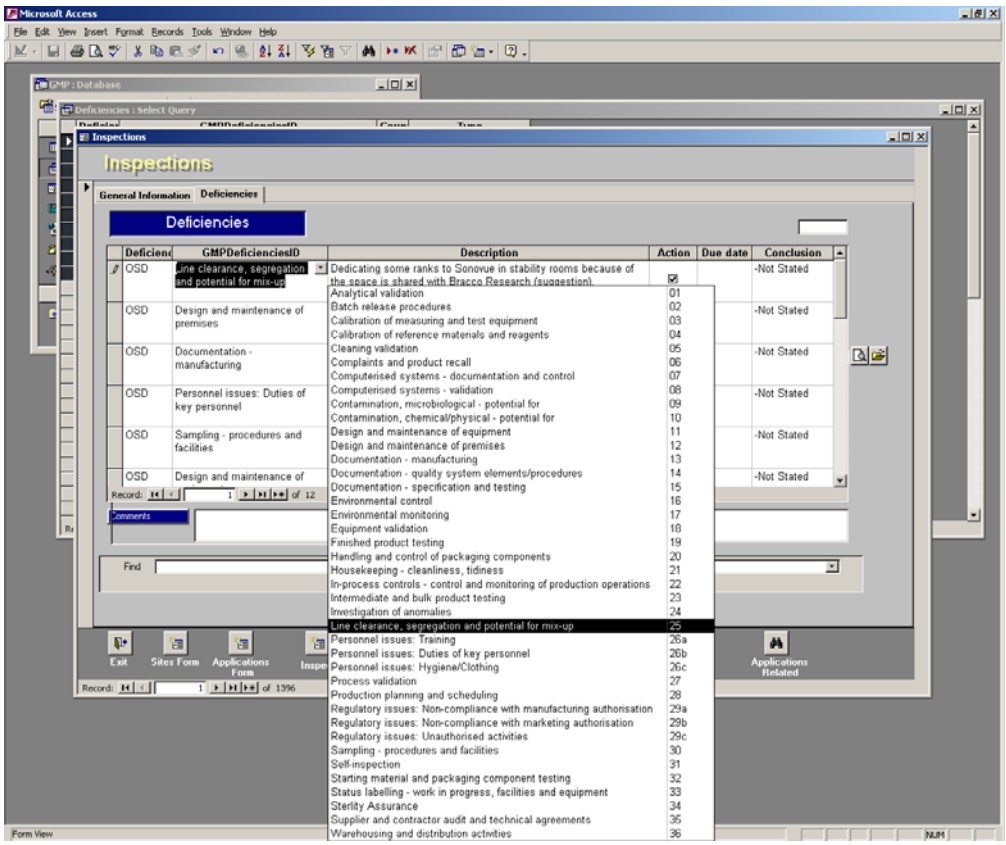
Findings of the analysis of the deficiencies for 1995/2005 are given in the next section. Comparisons are made between findings in different sectors, i.e., active substance vs. finished product manufacturing sites; EEA vs. third country manufacturers. Only inspections carried out by EEA inspectors on behalf of the EMEA are recorded.

| No | Category of GMP deficiency | No | Category of GMP deficiency |
|---|---|---|---|
| 1 | Analytical validation | 21 | Housekeeping - cleanliness, tidiness |
| 2 | Batch release procedures | 22 | In-process controls - control and monitoring of production operations |
| 3 | Calibration of measuring and test equipment | 23 | Intermediate and bulk product testing |
| 4 | Calibration of reference materials and reagents | 24 | Investigation of anomalies |
| 5 | Cleaning validation | 25 | Line clearance, segregation and potential for mix-up |
| 6 | Complaints and product recall | 26 | Personnel issues: Duties of key personnel |
| 7 | Computerised systems - documentation and control | 27 | Personnel issues: Hygiene/Clothing |
| 8 | Computerised systems - validation | 28 | Personnel issues: Training |
| 9 | Contamination, chemical/physical - potential for | 29 | Process validation |
| 10 | Contamination, microbiological - potential for | 30 | Production planning and scheduling |
| 11 | Design and maintenance of equipment | 31 | Regulatory issues: Non-compliance with manufacturing authorisation |
| 12 | Design and maintenance of premises | 32 | Regulatory issues: Non-compliance with marketing authorisation |
| 13 | Documentation - manufacturing | 33 | Regulatory issues: Unauthorised activities |
| 14 | Documentation - quality system elements/procedures | 34 | Sampling - procedures and facilities |
| 15 | Documentation - specification and testing | 35 | Self-inspection |
| 16 | Environmental control | 36 | Starting material and packaging component testing |
| 17 | Environmental monitoring | 37 | Status labelling - work in progress, facilities and equipment |
| 18 | Equipment qualification | 38 | Sterility Assurance |
| 19 | Finished product testing | 39 | Supplier and contractor audit and technical agreements |
| 20 | Handling and control of packaging components | 40 | Warehousing and distribution activities |

**Table 1. List of categories of deficiencies used in EMEA GMP database.**




**Picture 1. The deficiencies as listed in the inspection report are entered in the database in the third column and classified (see column 1) as critical, major and 'other significant deficiencies' (OSD).**




**Picture 2. The EMEA Inspections Sector reclassifies each deficiency in accordance with the 40 category list (column 2)**

## 4. Findings

Data from 435 inspections, comprising 255 pre-approval, 132 routine, 29 variations and 9 'for cause' inspections has been analysed. 316 inspections of finished product manufacturers and 119 of active ingredient manufacturers, comprising 35 manufacturers in the EEA and 400 in third countries[3], were recorded. A total of 9465 deficiencies, comprising 193 critical (2%) , 989 major (10%) and 8283 other deficiencies (88%) were recorded during these inspections. A summary of these deficiencies in each category is recorded in table 2, where the deficiencies of active substance manufacturers vs. finished product manufacturers and EEA manufacturers vs. third country manufacturers can be distinguished.

| | **Active ingredient** | **Finished Product** | **EEA** | **Third country** |
|---|---|---|---|---|
| **Number of inspections** | 119 | 316 | 35 | 400 |
| **Number of critical deficiencies** | 34 (1.65%) | 159 (2.13%) | 55 (7.50%) | 138 (1.57%) |
| **Number of major deficiencies** | 321 (15.52%) | 682 (9.15%) | 26 (3.54%) | 977 (11.12%) |
| **Number of other significant deficiencies** | 1712 (82.83%) | 6611 (88.71%) | 653 (88.96%) | 7670 (87.31%) |
| **Total deficiencies** | 2067 | 7452 | 734 | 8785 |
| **Average deficiencies per inspection** | 17 | 23 | 21 | 22 |

**Table 2. Deficiencies found in 1995/2005 by different categories (active ingredient vs. finished product, and EEA vs. third country).**

It is interesting to point out that there is an average of 2% critical GMP deficiencies for all categories except for EEA manufacturers, where the average figure is 7.5%. The most plausible reason for this is that inspections in the EEA in the context of the centralised products are 'product-related' inspections where the (Co)-Rapporteurs have already identified some concerns for the adherence of the manufacturer to the marketing authorisation dossier. These inspections are normally problem oriented and the significant high number of critical deficiencies generally confirms the initial suspicions of the (Co)-Rapporteurs and justify the value of this kind of inspections.

The rest of the results in table 2 shows constant values across all categories of deficiencies and the average number of deficiencies per inspection (around 20).

Table 3 shows the 40 categories of GMP deficiencies and the number of deficiencies (critical, major and others) recorded for all manufacturing sites during the period 1995/2005, together with the incidence of reporting of each category as a percentage of the total number of deficiencies

**Concerns over documentation (quality systems and procedures) head the list by a significant margin, representing 14.1% of the total number of deficiencies. However, if all deficiencies relating to documentation (see rows 1, 4 and 6) were grouped together, they would make up 24% of the total. This is a significantly high value meaning that one out of every four deficiencies observed relates to a problem with documentation.**

[3] 68 of the inspections carried out in third countries correspond to current MRA partners countries, which were performed before the finalisation of the agreement.

| No | Category of GMP deficiency | Number | Incidence (%) |
|---|---|---|---|
| 1 | Documentation - quality system elements/procedures | 1341 | 14.1 |
| 2 | Design and maintenance of premises | 634 | 6.7 |
| 3 | Design and maintenance of equipment | 594 | 6.2 |
| 4 | Documentation - manufacturing | 526 | 5.5 |
| 5 | Contamination, microbiological - potential for | 463 | 4.9 |
| 6 | Documentation - specification and testing | 432 | 4.5 |
| 7 | Status labelling - work in progress, facilities and equipment | 371 | 3.9 |
| 8 | Environmental monitoring | 323 | 3.4 |
| 9 | Process validation | 317 | 3.3 |
| 10 | Sampling - procedures and facilities | 297 | 3.1 |
| 11 | Supplier and contractor audit and technical agreements | 296 | 3.1 |
| 12 | Equipment validation | 288 | 3.0 |
| 13 | Personnel issues: Hygiene/Clothing | 266 | 2.8 |
| 14 | Personnel issues: Duties of key personnel | 258 | 2.7 |
| 15 | Contamination, chemical/physical - potential for | 256 | 2.7 |
| 16 | Housekeeping - cleanliness, tidiness | 243 | 2.6 |
| 17 | Line clearance, segregation and potential for mix-up | 238 | 2.5 |
| 18 | Personnel issues: Training | 205 | 2.2 |
| 19 | Calibration of measuring and test equipment | 202 | 2.1 |
| 20 | Sterility Assurance | 194 | 2.0 |
| 21 | Environmental control | 192 | 2.0 |
| 22 | Regulatory issues: Unauthorised activities | 176 | 1.8 |
| 23 | Cleaning validation | 173 | 1.8 |
| 24 | Investigation of anomalies | 164 | 1.7 |
| 25 | In-process controls - control and monitoring of production operations | 153 | 1.6 |
| 26 | Starting material and packaging component testing | 121 | 1.3 |
| 27 | Batch release procedures | 118 | 1.2 |
| 28 | Regulatory issues: Non-compliance with marketing authorisation | 113 | 1.2 |
| 29 | Warehousing and distribution activities | 104 | 1.1 |
| 30 | Self-inspection | 91 | 1.0 |
| 31 | Analytical validation | 83 | 0.9 |
| 32 | Computerised systems - documentation and control | 64 | 0.7 |
| 33 | Complaints and product recall | 47 | 0.5 |
| 34 | Handling and control of packaging components | 38 | 0.4 |
| 35 | Finished product testing | 36 | 0.4 |
| 36 | Calibration of reference materials and reagents | 28 | 0.3 |
| 37 | Computerised systems - validation | 27 | 0.3 |
| 38 | Intermediate and bulk product testing | 18 | 0.2 |
| 39 | Regulatory issues: Non-compliance with manufacturing authorisation | 18 | 0.2 |
| 40 | Production planning and scheduling | 11 | 0.1 |
| Total number of deficiencies | | 9519 | |

**Table 3. Ranking of total GMP deficiencies for 1995/2005**

### 4.1. Critical deficiencies

Table 4 shows the total of critical GMP deficiencies found in the same period.

| No | Category of GMP deficiency | Number | Incidence (%) |
|---|---|---|---|
| 1 | Design and maintenance of premises | 31 | 16.1 |
| 2 | Contamination, microbiological - potential for | 20 | 10.4 |
| 3 | Contamination, chemical/physical - potential for | 17 | 8.8 |
| 4 | Documentation - quality system elements/procedures | 16 | 8.3 |
| 5 | Process validation | 12 | 6.2 |
| 6 | Housekeeping - cleanliness, tidiness | 12 | 6.2 |
| 7 | Personnel issues: Hygiene/Clothing | 11 | 5.7 |
| 8 | Environmental control | 10 | 5.2 |
| 9 | Personnel issues: Training | 8 | 4.1 |
| 10 | Sterility Assurance | 8 | 4.1 |
| 11 | Environmental monitoring | 7 | 3.6 |
| 12 | Design and maintenance of equipment | 6 | 3.1 |
| 13 | Batch release procedures | 5 | 2.6 |
| 14 | Documentation - specification and testing | 5 | 2.6 |
| 15 | Documentation - manufacturing | 4 | 2.1 |
| 16 | Status labelling - work in progress, facilities and equipment | 4 | 2.1 |
| 17 | Handling and control of packaging components | 3 | 1.6 |
| 18 | In-process controls - control and monitoring of production operations | 3 | 1.6 |
| 19 | Line clearance, segregation and potential for mix-up | 2 | 1.0 |
| 20 | Computerised systems - validation | 2 | 1.0 |
| 21 | Investigation of anomalies | 2 | 1.0 |
| 22 | Sampling - procedures and facilities | 1 | 0.5 |
| 23 | Cleaning validation | 1 | 0.5 |
| 24 | Personnel issues: Duties of key personnel | 1 | 0.5 |
| 25 | Regulatory issues: Non-compliance with manufacturing authorisation | 1 | 0.5 |
| 26 | Regulatory issues: Non-compliance with marketing authorisation | 1 | 0.5 |
| Total number of deficiencies | | 193 | |

**Table 4. Ranking of critical GMP deficiencies for 1995/2005**

It is interesting to note the differences between the nature and number of critical deficiencies of table 4 compared with the total number of deficiencies in table 3. Design and maintenance of premises is the greatest concern, followed by potential risk of cross-contamination (microbiological and chemical). Deficiencies relating to documentation are in lower positions, which indicate that these deficiencies are not considered to have consequences potentially harmful to patients or animals (definition of critical deficiencies).

If we group together the deficiencies related to potential cross-contamination (defined in the EU guide as "*contamination of a material or a product with another material or product, and including microbiological contamination*"), these would make a total of 19.2%. This represents the main concern of critical GMP deficiencies observed, which very often have concluded in negative inspection reports.

Tables 5 and 6 list the top 20 categories for major and other significant GMP deficiencies. As described above, deficiencies related to documentation increases in the ranking as long as the deficiency is categorised with a lower risk (major and minor), so that these deficiencies are not normally considered

as having potentially harmful consequences. In a similar way, other categories with a high percentage of critical deficiencies (e.g. cross-contamination, design and maintenance of premises) is in a lower place in the ranking when the deficiency is considered 'major' or 'other'.

| No | Category of GMP deficiency | Number | Incidence (%) |
|---|---|---|---|
| 1 | Contamination, microbiological - potential for | 112 | 11.2 |
| 2 | Documentation - quality system elements/procedures | 102 | 10.2 |
| 3 | Regulatory issues: Unauthorised activities | 66 | 6.6 |
| 4 | Design and maintenance of premises | 59 | 5.9 |
| 5 | Regulatory issues: Non-compliance with marketing authorisation | 55 | 5.5 |
| 6 | Sterility Assurance | 53 | 5.3 |
| 7 | Documentation - manufacturing | 50 | 5.0 |
| 8 | Documentation - specification and testing | 46 | 4.6 |
| 9 | Equipment validation | 43 | 4.3 |
| 10 | Design and maintenance of equipment | 36 | 3.6 |
| 11 | Personnel issues: Duties of key personnel | 35 | 3.5 |
| 12 | Supplier and contractor audit and technical agreements | 34 | 3.4 |
| 13 | Contamination, chemical/physical - potential for | 33 | 3.3 |
| 14 | Process validation | 33 | 3.3 |
| 15 | Environmental monitoring | 25 | 2.5 |
| 16 | Personnel issues: Hygiene/Clothing | 25 | 2.5 |
| 17 | Investigation of anomalies | 22 | 2.2 |
| 18 | In-process controls - control and monitoring of production operations | 18 | 1.8 |
| 19 | Line clearance, segregation and potential for mix-up | 18 | 1.8 |
| 20 | Personnel issues: Training | 17 | 1.7 |

**Table 5. Ranking of the top 20 major GMP deficiencies for 1995/2005**

| No | Category of GMP deficiency | Number | Incidence (%) |
|---|---|---|---|
| 1 | Documentation - quality system elements/procedures | 1223 | 14.7 |
| 2 | Design and maintenance of equipment | 552 | 6.6 |
| 3 | Design and maintenance of premises | 544 | 6.5 |
| 4 | Documentation - manufacturing | 472 | 5.7 |
| 5 | Documentation - specification and testing | 381 | 4.6 |
| 6 | Status labelling - work in progress, facilities and equipment | 352 | 4.2 |
| 7 | Contamination, microbiological - potential for | 331 | 4.0 |
| 8 | Environmental monitoring | 291 | 3.5 |
| 9 | Sampling - procedures and facilities | 282 | 3.4 |
| 10 | Process validation | 272 | 3.3 |
| 11 | Supplier and contractor audit and technical agreements | 262 | 3.1 |
| 12 | Equipment validation | 245 | 2.9 |
| 13 | Personnel issues: Hygiene/Clothing | 230 | 2.8 |
| 14 | Housekeeping - cleanliness, tidiness | 228 | 2.7 |
| 15 | Personnel issues: Duties of key personnel | 222 | 2.7 |
| 16 | Line clearance, segregation and potential for mix-up | 218 | 2.6 |
| 17 | Contamination, chemical/physical - potential for | 206 | 2.5 |
| 18 | Calibration of measuring and test equipment | 195 | 2.3 |
| 19 | Personnel issues: Training | 180 | 2.2 |
| 20 | Environmental control | 168 | 2.0 |

**Table 6. Ranking of the top 20 other significant GMP deficiencies for 1995/2005**

### 4.2. Comparison of deficiencies in Finished Product Manufacturer versus Active Substance Manufacturer

An analysis of the critical deficiencies observed in finished product manufacturers compared with active substance manufacturers was also performed. Table 7 shows the top 10 critical GMP deficiencies cited most frequently during 1995/2005 for both manufacturers of active substances and finished products.

| | Finished product manufacturers | | Active ingredient manufacturers | |
|---|---|---|---|---|
| Category of GMP deficiency | Ranking | Incidence (%) | Ranking | Incidence (%) |
| Design and maintenance of premises | 1 | 17.6 | 4 | 8.8 |
| Contamination, chemical/physical - potential for | 2 | 10.1 | 8 | 2.9 |
| Contamination, microbiological - potential for | 3 | 9.4 | 2 | 14.7 |
| Documentation - quality system elements/procedures | 4 | 7.5 | 3 | 11.8 |
| Housekeeping - cleanliness, tidiness | 5 | 6.9 | 12 | 2.9 |
| Personnel issues: Hygiene/Clothing | 6 | 5.7 | 7 | 5.9 |
| Environmental control | 7 | 5.0 | 6 | 5.9 |
| Personnel issues: Training | 8 | 5.0 | - | - |
| Sterlity Assurance | 9 | 4.4 | 17 | 2.9 |
| Environmental monitoring | 10 | 3.8 | 9 | 2.9 |
| Process validation | 11 | 3.8 | 1 | 17.6 |
| Design and maintenance of equipment | 12 | 3.8 | - | - |

**Table 7. Comparison of the ranking of the top 10 critical GMP deficiencies between manufacturers of finished product vs. active ingredient.**

159 critical deficiencies (1.65% of the total deficiencies) in 316 inspections of manufacturers of finished products and 34 critical deficiencies (2.13% of the total) in 119 inspections for manufacturers of active substance were observed in the last 10 years by EEA inspectors.

Until 30 October 2005, the applicable legislation[4] was based on the assumption that pharmaceutical manufacture began when preparing a medicinal product from its components (active substance(s) and excipients) and its packaging materials, and no GMP requirement was applicable to the manufacture of these components or starting materials. However, biological medicinal products were considered an exception to this general rule and it was agreed that their manufacture begins earlier, i.e. when preparing the active substance from the source material (e.g. working cell banks)[5]. Given the importance of any step in the manufacturing process for the quality of the end product, the complete manufacturing process for a biological medicinal product has been subject to inspection by the EEA Inspectorates on behalf of the EMEA. Nevertheless, these inspections were focussed essentially on the process during which the biological active substance is manufactured (i.e. product related inspection).

[4] The legal basis for the regulation of medicinal products for Human and Veterinary use is determined by the Community Directives 2001/83/EC and 2001/82/EC. These Directives were amended, correspondingly, by Directives 2004/27/EC and Directive 2004/28/EC to, inter alia, permit the inspection by Competent Authorities, under certain circumstances, of manufacturer of active substances.

[5] In the new legislative environment, biological active substances continue to be routinely inspected on the same grounds, and other active substances may be inspected under certain circumstances

The above interpretation explains the difference between the critical deficiencies observed in both categories. Analysis of the findings for active substances manufacturers is relatively justified (e.g. process validation heads the list by a significant margin) due to the specific product/process related focus of the inspection. As described in section 4, more serious deficiencies are usually observed on product/process related inspections. On the other hand, the ranking for critical deficiencies of finished product manufacturers follows the usual ranking for general GMP inspections.

### 4.3. Comparison of deficiencies in the manufacture of sterile products versus non-sterile

Table 8 makes a comparison between manufacturers of sterile products vs. non-sterile products. The average numbers of deficiencies observed in each category of these manufacturers were similar (20 for non-sterile vs. 23 for sterile). However, the deficiencies are distributed in a different manner, showing more higher risk deficiencies (critical and major) for manufacturers of sterile products. This may be explained by the higher complexity of the sterile processes.

| | **Non-sterile** | **Sterile** |
|---|---|---|
| **Number of inspections** | 186 | 249 |
| **Number of critical deficiencies** | 33 (0.88%) | 160 (2.77%) |
| **Number of major deficiencies** | 251 (6.72%) | 752 (13.00%) |
| **Number of other significant deficiencies** | 3451 (92.40%) | 4872 (84.23%) |
| **Total deficiencies** | 3735 | 5784 |
| **Average deficiencies per inspection** | 20 | 23 |

**Table 8. Comparison of the deficiencies found in 1995/2005 between manufacture of sterile vs. non-sterile medicinal products.**

Similar analyses may be carried out with different groups (e.g. veterinary vs. human inspections, EEA vs. third country manufacturers, trends in different years, inspections carried out by different EEA Inspectorates)

## 5. Discussion

GMP Inspection is, by its nature, a sampling exercise, as an inspector cannot examine everything so normally he/she concentrates on those operations where, in his/her judgment, any failure to comply with GMP is likely to give rise to the greatest risk to the patient or animal. Thus the incidence of deficiencies reported reflects both their real incidence and the extent to which, based on risk analysis, the inspector has been looking for them.

Inspectors refer to the appropriate section of the relevant official guide when reporting deficiencies to companies. This helps to explain the deficiency and place it in context. Consideration was given to using these references when analysing deficiencies but it proved difficult because the guide often refers to a particular aspect of GMP in more than one place. The difficulty is avoided by structuring the categories differently.

Lack of control of cross-contamination and problems with design and maintenance of premises were by far the two most frequently reported critical deficiencies during the period from 1995/2005. Deficiencies concerning documentation is the most reported observation compared with the total, but inspectors typically classify this category of deficiency as a lower risk.

The number of critical deficiencies recorded in product-related inspections has been observed to be significantly more than those found for general GMP inspections. There is a number of contributing factors to consider in determining the reason for this, not least, of which the (Co)-Rapporteurs usually identify concerns during the evaluation for the adherence of the manufacturer to the marketing authorisation dossiers. These concerns are confirmed by the significant higher number of critical deficiencies for product-related inspections.

## 6. Conclusion

This analysis has been used within the EMEA to provide a basis for monitoring consistency between different parameters (e.g. inspectors, manufacturers in different areas or activities, etc). Examples of advantages of the use the deficiency database include:

- Data could be used in monitoring differences between different groups of manufacturers in order to identify and draw industry's attention to commonly found deficiencies.
- Industry may find the analysis helpful in comparing the industry-wide deficiencies with those found during internal audits and by other official inspections of their organisation.
- It can provide management among the EU National Competent Authorities with a measure of consistency of GMP inspection standards and indicate, for example, those areas where further training of inspectors and the provision of technical advice to industry may be of benefit.
- The analysis can be used within a EU National Competent Authority to provide a basis for monitoring consistency between inspectors in reporting deficiencies.
- The information generated could also be used to inform any revision of the EU guide on GMP by identifying those areas where more emphasis maybe needed.

This analysis is helpful in comparing the industry-wide deficiencies with those found during national inspections. This could provide a focus for discussion leading to quality improvements.

The deficiency database provides a valuable tool in identifying those practices of manufacturers which are of greatest concern to the EEA competent authorities and manufacturers. It can provide management within the EEA Inspectorates with a measure of consistency of GMP inspection standards and can also indicate those areas where further training of inspectors and the provision of technical advice to industry may be of benefit. The information generated might also be used to consider revisions of aspects of the EU guides to GMP by identifying those areas where more emphasis is needed.

## 7. Acknowledgments

We acknowledge the help provided by the MHRA for the new classification of deficiencies. We also acknowledge that the data presented in this paper were generated by all EEA inspectors who contributed through their valuable work in the centralised procedure.