



Good Manufacturing Practice: An analysis of regulatory inspection findings in the centralised procedure in 2006 and PMF procedure during 2004-2006 period

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 in 2006 in the context of the centralised procedure. In addition, a similar analysis is described in this document for inspections carried out of Blood Establishments in third countries during the period 2004 – 2006 in the context of the Plasma Master File (PMF) evaluation.

This is the first analysis of the deficiencies of Blood Establishments since the EMEA started the first evaluation of a PMF in 2004. It has been decided to separate in this document the deficiencies of inspections of Blood Establishments in the context of the PMF evaluation since the results for this category of inspections differ considerably from those for inspections of pharmaceutical manufacturers. Otherwise, a combined analysis could provide wrong conclusions on inspections performed in 2006.

A total of 881 deficiencies, comprising 0 critical (0%), 144 major (16%) and 737 other deficiencies (84%) were recorded in the EMEA database as a result of the 69 inspections carried out by EEA inspectors in 2006 in the context of the centralised procedure.

A total of 1072 deficiencies, comprising 239 critical (22%), 335 major (31%) and 498 other deficiencies (46%) were recorded in the EMEA database as a result of the 74 inspections carried out by EEA inspectors during the above referenced period in the context of the PMF procedure.

The deficiencies reported following the GMP inspections are classified by the EMEA GMP scientific administrators according to a procedure described in the analysis of the previous 10 years (see <http://www.emea.europa.eu/Inspections/docs/2302207en.pdf>).

This document describes the findings in year 2006 of inspections of manufacturers of medicinal products and compares it with the deficiencies reported in the previous analysis for the period of 1995-2005 and in inspections of Blood Establishments in the context of the PMF procedure.

2. Triggers for inspections

The following two sections summarises the triggers and standards for inspections of the two categories analysed in this document: i.e. inspections in the context of the centralised procedure (CP) and inspections in the context of the evaluation of a Plasma Master File (PMF).

A. Inspections in the context of a Centralised Procedure (CP)

Directives 2001/83/EC (Human medicinal products) and 2001/82/EC (Veterinary medicinal products), as amended, states that Manufacturing Authorisation Holders are obliged to comply with Good Manufacturing Practice (GMP) for medicinal products and to use as starting materials only active substances that have been manufactured in accordance with the detailed guidelines on Good Manufacturing Practice for starting materials.

The EMEA may request GMP inspections to be carried out to verify compliance with European Community Good Manufacturing Practice principles and guidelines and/or to cover product or process related issues arising from the assessment of the application. Inspections may cover the following activities:

Manufacture of the Active Substance:

The detailed guidelines on Good Manufacturing Practice adopted by the EEA for the manufacture of the active substance, are contained in part II of the EU Guide to Good Manufacturing Practice. Inspectors of the competent authorities in the EEA inspect against the requirements of this guidance.

Apart from manufacturers of sterile and biological active substances, inspections of manufacturers of active substance are not required to be inspected on a regular basis. Guidance on the occasions when it is appropriate for National Competent Authorities to conduct inspections at the premises of Manufacturers of active substances used as starting materials is published as part of the Compilation of Community Procedures on Inspections and Exchange of Information in the EMEA web page (see http://www.emea.europa.eu/Inspections/docs/CoCP/CoCP_APIGMPInspTriggers.pdf)

Manufacture of the Finished Product:

The GMP principles and guidelines applying to the manufacture of medicinal products for the EEA are laid down in Commission Directive 2003/94/EC, which are further elaborated in part I of the EU Guide to Good Manufacturing Practice. Since all manufacturing sites in the EEA are required to be regularly inspected by the relevant authorities, EMEA does not normally request a GMP inspection of sites located in the EEA.

An inspection will normally be requested to confirm the GMP compliance status of manufacturing sites in third countries (non-EEA) unless satisfactory information is available from an inspection of the same or similar category of product carried out during the last 2-3 years by an EEA competent authority or by the competent authority of a country where a MRA is in operation, as applicable. In addition, these sites have to be re-inspected every 2-3 years.

In all cases (for sites in the EEA and third countries), an inspection may be requested to cover product or process related issues arising from the assessment of a marketing authorisation application or to perform a “for cause” inspection following a report of a serious quality deficiency or indication of a specific problem.

B. Inspections in the context of a Plasma Master File (PMF)

In June 2003, European legislation (Commission Directive 2003/63/EC) established the concept of the ‘Plasma Master File’ (PMF). The PMF is a compilation of all the required scientific data on the quality and safety of human plasma relevant to the medicinal products, medical devices and investigational medicinal products that use human plasma in their manufacture. These data cover all aspects of the use of plasma, from collection to plasma pool. The PMF is a separate set of documentation to that required for a medicinal product dossier for a Marketing Authorisation.

PMF certification is an optional procedure that follows a similar system to the Marketing Authorisation evaluation procedure at the EMEA (the ‘centralised procedure’) but is limited to the information contained in the PMF documentation. This procedure is called the 1st step. Following a satisfactory outcome of an evaluation, the EMEA issues a PMF Certificate of compliance with Community legislation, which is valid throughout the European Community. After certification, it is the responsibility of the Marketing Authorisation Holder to update its medicinal product authorisation(s) and to incorporate the certified PMF in its Marketing Authorisation(s). This procedure is called the 2nd step.

An exhaustive list of names and addresses of blood establishments and centres, from which plasma is collected, tested, stored and distributed has to be included in the PMF application. When considered necessary, inspections of these blood establishments may be requested by the CHMP in order to complete the examination of the dossier.

The EMEA has evaluated 11 PMFs (see list of PMF issued by the EMEA on <http://www.emea.europa.eu/htms/human/pmf/pmflist.htm>) over the reference period covered by this document. Due to the high number of PMFs submitted and the lack of necessary resources to cover all the necessary blood establishments listed in the dossiers, the PMF inspections were selected on a risk-based approach in accordance with the Standard Operating Procedure (SOP) (see Annex 1 on document <http://www.emea.europa.eu/pdfs/human/pmf/SOP2009.pdf>). The EMEA selected only blood establishments in third countries (all of them in the USA, see in table 1) without any previous GMP inspection carried out by an EEA competent authority.

Inspectors of the competent authorities in the EEA currently inspect these blood establishments against the requirements of the GMP guideline contained in part II, the European Pharmacopoeia monographs and the blood directive 2002/98/EC.

3. General findings

Data from 143 inspections, comprising 69 inspections of manufacturers of medicinal products in 2006 and 74 of blood establishments during the period 2004-2006 is analysed in this document. The location of the manufacturers/centres inspected, the type of inspection and the average inspection time on site is summarised in table 1.

	Centralised Procedure (CP)	PMF Procedure
Period (year)	2006	2004 - 2006
Number of inspections	69	74
Location of the sites inspected and number of inspections	USA: 52 inspections Puerto Rico: 6 UK: 3 Germany: 2 Singapore: 1 Belgium: 1 Canada: 1 Japan: 1 Brazil: 1 India: 1	USA: 74
Category of inspections	Finished product (FP): 41 Active substance (API): 16 Combined (API + FP) : 12	Collection: 58 Testing: 11 Look back: 3 Storage: 1 Transportation: 1
	Manufacturers of sterile products: 31 Non-sterile products: 38	
	Re-inspections: 41 Pre-authorisations: 26 Variations: 2	All pre-authorisation
Average inspection time on site	3.5 days	2 days

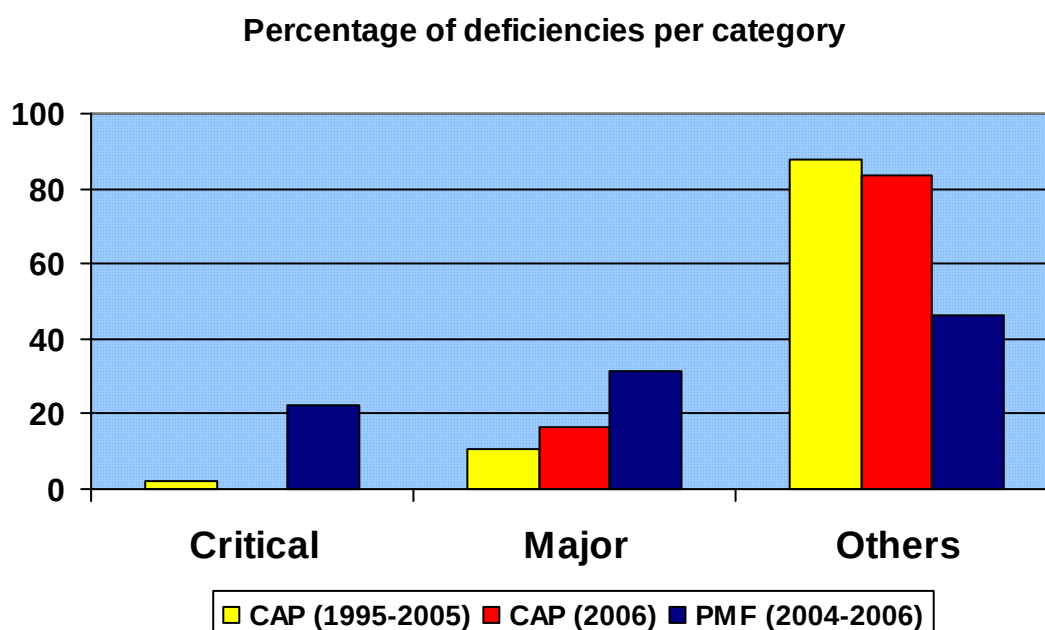
Table 1. Summary of the inspections analysed in this document

A total of 1953 deficiencies, comprising 239 critical (12%), 479 major (25%) and 1235 other deficiencies (63%) were recorded during the inspection of table 1. A summary of these deficiencies in each category is recorded in table 2 and it is compared with the deficiencies observed in previous analysis during the period 1995-2005.

	Centralised Procedure (CP)	Centralised Procedure (CP)	PMF Procedure
Period (year)	1995 - 2005	2006	2004 - 2006
Number of inspections	435	69	74
Number of critical deficiencies	193 (2.04%)	0 (0%)	239 (22.30%)
Number of major deficiencies	989 (10.44%)	144 (16.35%)	335 (31.25%)
Number of other significant deficiencies	8283 (87.51)	737 (83.65%)	498 (46.45%)
Total deficiencies	9465	881	1072
Average deficiencies per inspection	22	13	14

Table 2. Deficiencies found in 2006 in the context of the CP, the previous analysis of the CP inspection during period of 1995-2005 and during the period 2004-2006 for the PMF procedure.

The following graph 1 shows a comparison of each category of deficiency for the type of inspections described in table 1.



Graph 1. Comparison of deficiencies in table 1

The level of deficiencies observed in 2006 for the CP inspections is similar to the same procedure in the historical period 1995-2005. However, the most remarkable aspect of the analysis in this document is the observation of the high number of serious deficiencies (i.e. critical and major found) in the context of PMF inspections, compared with those under the centralised procedure. Ten times more critical deficiencies and two to three times more major deficiencies were found during PMF inspections, compared with inspections of pharmaceutical manufacturers under the centralised procedure.

There is a plausible justification for this relatively high number of serious deficiencies found in PMF inspections. As described in section 2.B on the triggers for PMF inspections, the EMEA selected only blood establishments in third countries without any previous GMP inspection carried out by an EEA competent authority. Although these centres were previously audited by the company and also inspected by the FDA, previous historical experience has showed that the number of serious deficiencies for first time inspections of blood establishments is very high. Directive 2005/62/EC, implementing the blood directive 2002/98/EC, states that blood and blood components imported from third countries should meet equivalent European community standards and specifications. There is a similar principle for inspections in the CP but, while most of the manufacturers of medicinal products have previously been inspected and supervised in the past by European inspectors and industry is aware of the European standards, there remains some lack of knowledge with respect to the European community standards in some blood establishments in third countries and the findings in this documents reflect this theory. In addition, the result of these findings show the effectiveness of the risk based approach – where only those categorised as high risk were selected for inspection. A detailed analysis of the main findings in PMF inspections is made in section 3.1

Table 3 shows categories of GMP deficiencies and the number of deficiencies (critical, major and others) recorded for manufacturing sites (excluding PMF) in 2006, together with the incidence of each category as a percentage of the total number of deficiencies:

No	Category of GMP deficiency	Number of deficiencies	Incidence (%)
1	Documentation - quality system elements/procedures	96	10.9
2	Documentation - manufacturing	90	10.2
3	Design and maintenance of premises	57	6.5
4	Documentation - specification and testing	46	5.2
5	Status labelling - work in progress, facilities and equipment	41	4.7
6	Contamination, microbiological - potential for	41	4.7
7	Supplier and contractor audit and technical agreements	40	4.5
8	In-process controls - control and monitoring of production operations	38	4.3
9	Housekeeping - cleanliness, tidiness	36	4.1
10	Environmental monitoring	33	3.7
11	Process validation	27	3.1
12	Personnel issues: Hygiene/Clothing	26	3.0
13	Design and maintenance of equipment	25	2.8
14	Sterility Assurance	24	2.7
15	Environmental control	23	2.6
16	Equipment validation	23	2.6
17	Cleaning validation	23	2.6
18	Sampling - procedures and facilities	21	2.4
19	Line clearance, segregation and potential for mix-up	21	2.4
20	Investigation of anomalies	20	2.3
21	Contamination, chemical/physical - potential for	16	1.8
22	Starting material and packaging component testing	16	1.8
23	Warehousing and distribution activities	12	1.4
24	Personnel issues: Duties of key personnel	10	1.1
25	Handling and control of packaging components	10	1.1
26	Regulatory issues: Unauthorised activities	10	1.1
27	Calibration of measuring and test equipment	9	1.0
28	Batch release procedures	8	0.9
29	Complaints and product recall	7	0.8
30	Self-inspection	7	0.8
31	Personnel issues: Training	7	0.8
32	Analytical validation	5	0.6
33	Finished product testing	3	0.3
34	Regulatory issues: Non-compliance with marketing authorisation	3	0.3
35	Computerised systems - documentation and control	2	0.2
36	Intermediate and bulk product testing	2	0.2
37	Computerised systems - validation	1	0.1
38	Calibration of reference materials and reagents	1	0.1
39	Regulatory issues: Non-compliance with manufacturing authorisation	1	0.1
Total		881	

Table 3. Ranking of total GMP deficiencies for 2006 of manufacturers of medicinal products.

As was the case in the previous analysis for deficiencies in the period 1995-2005, concerns over documentation head the list by a significant margin. If all deficiencies relating to documentation (see rows 1, 2 and 4) were grouped together, they would make up 25% of the total. The same was found in the deficiencies analysis over the previous 10 years period.

Table 4 shows the comparison of the first 20 categories of deficiencies found in 2006 under the centralised procedure of manufacturers of medicinal products compared with the same category in the previous 10 years.

Category of GMP deficiency	Ranking 2006	Incidence (2006) (%)	Ranking 1995 – 2005	Incidence (1995-2005) (%)
Documentation - quality system elements/procedures	1	10.9	1	14.1
Documentation - manufacturing	2	10.2	4	5.5
Design and maintenance of premises	3	6.5	2	6.7
Documentation - specification and testing	4	5.2	6	4.5
Status labelling - work in progress, facilities and equipment	5	4.7	7	3.9
Contamination, microbiological - potential for	6	4.7	5	4.9
Supplier and contractor audit and technical agreements	7	4.5	11	3.1
In-process controls - control and monitoring of production operations	8	4.3	25	1.6
Housekeeping - cleanliness, tidiness	9	4.1	16	2.6
Environmental monitoring	10	3.7	8	3.5
Process validation	11	3.1	9	3.3
Personnel issues: Hygiene/Clothing	12	3.0	13	2.8
Design and maintenance of equipment	13	2.8	3	6.2
Sterility Assurance	14	2.7	20	2.0
Environmental control	15	2.6	21	2.0
Equipment validation	16	2.6	12	3.0
Cleaning validation	17	2.6	23	1.8
Sampling - procedures and facilities	18	2.4	10	3.1
Line clearance, segregation and potential for mix-up	19	2.4	17	2.5
Investigation of anomalies	20	2.3	24	1.7

Table 4. Comparison of the 20 top ranking deficiencies found during CP inspections of manufacturers of medicinal products

In general, the distribution of deficiencies in 2006 follows the same pattern as the previous 10 years. Relevant differences in 2 categories (see rows highlighted in bold) corresponding to “in-process controls” and “design and maintenance of equipment” were observed.

3.1. Analysis of PMF inspections.

Table 4 shows the total of deficiencies found in inspections of blood establishments in the period 2004-2006 for 79 inspections.

No	Category of GMP deficiency	Number of deficiencies	Incidence (%)
1	Personnel issues: Duties of key personnel	233	21.74
2	Line clearance, segregation and potential for mix-up	102	9.51
3	Contamination, microbiological - potential for	100	9.33
4	Documentation - specification and testing	69	6.44
5	Documentation - quality system elements/procedures	65	6.06
6	Documentation - manufacturing	59	5.50
7	Equipment validation	56	5.22
8	Supplier and contractor audit and technical agreements	41	3.82
9	Design and maintenance of premises	33	3.08
10	Status labelling - work in progress, facilities and equipment	31	2.89
11	Regulatory issues: Unauthorised activities	26	2.43
12	Housekeeping - cleanliness, tidiness	23	2.15
13	Design and maintenance of equipment	22	2.05
14	Calibration of measuring and test equipment	22	2.05
15	Process validation	21	1.96
16	Environmental control	20	1.87
17	Personnel issues: Training	20	1.87
18	Computerised systems - documentation and control	17	1.59
19	Investigation of anomalies	16	1.49
20	Environmental monitoring	10	0.93
21	In-process controls - control and monitoring of production operations	10	0.93
22	Regulatory issues: Non-compliance with marketing authorisation	10	0.93
23	Self-inspection	8	0.75
24	Batch release procedures	8	0.75
25	Sterility Assurance	7	0.65
26	Warehousing and distribution activities	7	0.65
27	Sampling - procedures and facilities	6	0.56
28	Starting material and packaging component testing	6	0.56
29	Handling and control of packaging components	5	0.47
30	Personnel issues: Hygiene/Clothing	5	0.47
31	Analytical validation	3	0.28
32	Complaints and product recall	3	0.28
33	Regulatory issues: Non-compliance with manufacturing authorisation	2	0.19
34	Contamination, chemical/physical - potential for	1	0.09
35	Finished product testing	1	0.09
36	Computerised systems - validation	1	0.09
37	Calibration of reference materials and reagents	1	0.09
38	Production planning and scheduling	1	0.09
39	Cleaning validation	1	0.09
Total		1072	

Table 4. GMP deficiencies found during PMF inspections

It is very clear from table 4 that the distribution and incidence of deficiencies found during PMF inspections are very different from those discussed in the previous section for manufacturers of medicinal products. The three categories of deficiencies concerning documentation still represent a high value (18% in total) but there are significant differences in the first two deficiencies (“Personnel issues: duties of key personnel” and “line clearance”), which represent 22% and 10% of the total, respectively, whereas these deficiencies are observed at levels of only 1.1% and 2.4%, respectively for manufacturers of medicinal products.

Key personnel in blood establishments include

- the responsible person who should have the qualifications and responsibilities as set out in Article 9 of Directive 2002/98/EC
- the processing manager¹ and the quality assurance manager who are responsible for ensuring that the requirements of the quality systems are implemented and maintained and that there are appropriate systems and protocols in place for the safe and secure release of all materials, equipment, reagents and products.

The main problems observed with respect to the duties of key personnel are a high turn around of key personnel, failure to comply with their responsibilities (e.g. delegation to train individuals) and failure to comply with the release procedure.

The main problem found with regard to the “line clearance, segregation and potential for mix-up” concerned the blood donation area. EU legislation requires the consultation area to be set aside to allow for confidential personal interviews with and examination of individuals to determine their suitability as blood donors. This area should be separated from all production areas. This was not the case in many establishments.

As mentioned in section 2 (General findings), 16 inspections out of 74 resulted in negative outcomes. This is attributed to the use of a risk-based approach for the selection of which inspections to perform. Table 5 represents comparison of the top 10 ranking of findings for both positive and negative inspections.

Category of GMP deficiency	Ranking in negative reports	Incidence Negative (%)	Ranking in positive reports	Incidence Positive (%)
Personnel issues: Duties of key personnel	1	28.60	1	14.53
Line clearance, segregation and potential for mix-up	2	11.06	6	6.51
Contamination, microbiological - potential for	3	7.10	2	11.71
Documentation - quality system elements/procedures	4	6.26	7	5.86
Supplier and contractor audit and technical agreements	5	5.22	12	2.17
Documentation - specification and testing	6	3.97	3	10.63
Equipment validation	7	3.76	5	6.72
Environmental control	8	3.34	30	0.22
Status labelling - work in progress, facilities and equipment	9	3.13	16	1.95
Housekeeping - cleanliness, tidiness	10	2.71	18	1.52

Table 5. Comparison of the ranking of the top 10 GMP deficiencies for positive vs negative PMF inspections

This shows that “Personnel issues” have a large impact on negative outcomes (28%) while the same category of deficiency represents 14% in positive reports. This is a clear indication that this category of deficiency in PMF inspections leads inspectors to consider a negative outcome.

¹ Processing manager is different from the quality assurance manager.

Table 6 shows the classification of the top 10 ranking categories per severity (i.e. critical, major and others). The first row confirms that the category “Personnel issues: duties of the key personnel” is normally considered by Inspectors as a critical deficiency, whereas “line clearance, segregation and potential for mix-up” is more likely to be considered as a major deficiency.

It is also noticed that “potential for microbiological contamination” is classified in PMF inspections as “other” deficiency. The same category in GMP inspections of manufacturers of medicinal products is classified as critical or major. The majority of deficiencies found under this category in PMF inspections concern the extraction of blood from the donor. This is an important step but the production of blood derived medicinal products is subject to many inactivation steps, so that the final product is not normally affected by an initial potential contamination.

Category of GMP deficiency	Critical		Major		Others	
	Ranking	Incidence (%)	Ranking	Incidence (%)	Ranking	Incidence (%)
Personnel issues: Duties of key personnel	1	30.13	1	21.79	1	17.67
Line clearance, segregation and potential for mix-up	2	10.88	2	12.84	5	6.63
Documentation - quality system elements/procedures	3	8.37	7	3.88	6	6.43
Equipment validation	4	7.53	5	7.16	14	2.81
Supplier and contractor audit and technical agreements	5	7.11	12	1.79	10	3.61
Contamination, microbiological - potential for	6	5.86	3	9.55	2	10.84
Process validation	7	4.60	16	1.49	20	1.00
Status labelling - work in progress, facilities and equipment	8	2.51	18	1.49	7	4.02
Environmental control	9	2.51	10	2.39	19	1.20
Computerised systems - documentation and control	10	2.09	9	2.39	23	0.80

Table 6. Comparison of the top 10 ranking category of deficiencies (PMF inspections)

The European blood directive 2002/98/EC entered into force on 8 February 2005 defining duties and responsibilities for key personnel. This entry into force of the new directive point along with the fact that these blood establishments selected in the USA had never previously been inspected by an EEA competent authority could be a plausible reason for high values.

Table 6 also shows how other categories change the ranking depending on the seriousness of the deficiency. For example, “equipment validation” is normally considered by inspectors as a “critical” or “major” deficiency with rankings 4 and 5, respectively. The same category is found as ranking 14 in “others” deficiency. Most of these deficiencies are related to freezer validation. The European Pharmacopoeia monograph on Human plasma for fractionation does not define the freezing process time but does define the freezing temperature (-30°C or below). Initial freezing conditions are

considered crucial for the quality of plasma. These conditions were intended to preserve labile proteins such as Factor 8 (FVIII), but they can also be considered favourable for the plasma quality in general. Equivalent USA standards require plasma to be frozen at 20°C or below. This difference in standards means that many centres do not comply with EU requirements on plasma freezing and, mean that therefore, the EEA cannot accept the sourcing of labile proteins from these centres.

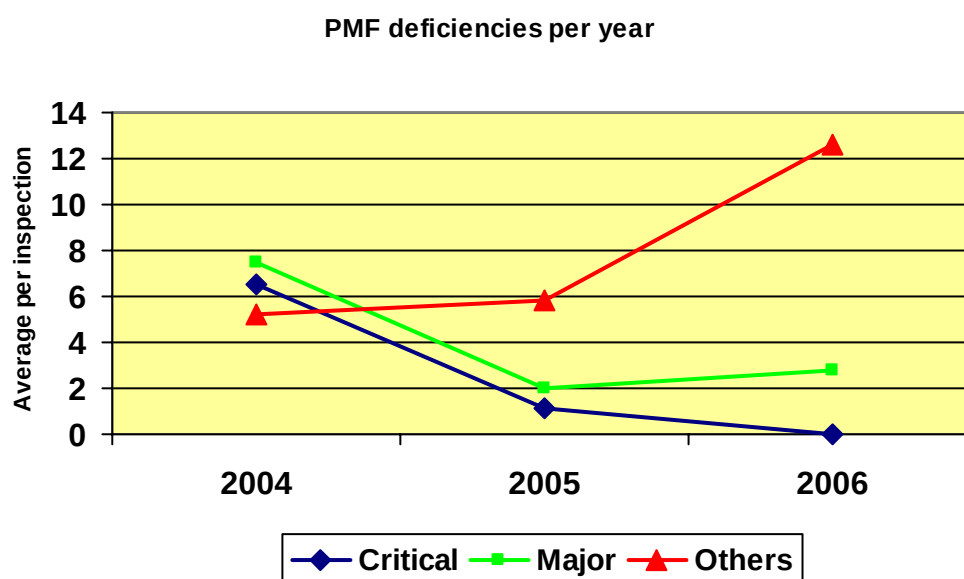
This issue has been extensively discussed at the EMEA and European Pharmacopoeia with representatives of plasma industry as a consequence of these discussions. A study has been presented by industry with the evaluation of the effect of freezing temperatures to labile coagulation factors. The results obtained from this study supported that plasma might also be frozen at -25°C or below without any impact on its quality, and that sporadic and short term deviations from -30°C or below up to -25°C would not have an effect on the recovery of labile factors. This is a very good example of how this analysis of deficiencies may be used to identify revisions of the EU guide or European Pharmacopoeia standards that may be necessary.

Finally, it is interesting to make an analysis of the trends found during PMF inspections over the years. Table 6 shows a comparison of the different categories (i.e. critical, major and others) in the 3 years under study.

	2004	Average per inspection (2004)	2005	Average per inspection (2005)	2006	Average per inspection (2006)
Critical	208	6.5	31	1.1	0	0
Major	241	7.5	57	2.0	37	2.8
Minor	165	5.2	169	5.8	164	12.6
Number of inspections	32		29		13	

Table 6. Comparison of PMF deficiencies per year

It is very interesting to remark that high numbers of “critical” and “major” deficiencies have been decreasing over the years leading to 0% of critical deficiencies and all positive outcomes of inspections in 2006. Paradoxically, the number of “other” deficiencies has increased in the same period (see graph 2).



Graph 2. Comparison of PMF deficiencies per year

It should be noted that most of the centres with negative inspections outcomes in 2004 (12 in total) were re-inspected in 2005 and 2006 once they had implemented the corrective actions proposed. In addition, other blood establishments corresponding to the same blood organisations were covered in the next round of inspections when initial inspections revealed a degree of non-compliance. The figures in 2006 show that in 2006 distribution of deficiencies in PMF inspections is equivalent to the same category of deficiencies of manufacturers of medicinal products in 2006 (see table 7).

This reflects the fact that initial knowledge gaps had been filled.

	CP (2006) Percentage of deficiencies	PMF (2006) Percentage of deficiencies
Critical	0%	0%
Major	16.35%	18.40%
Minor	83.65%	81.60%

Table 7. Comparison of deficiencies in 2006 between CP and PMF

In conclusion, the above figures in table 6 and 7 show that continuous monitoring of blood centres and organisations, which have shown serious GMP problems, is a successful exercise to improve the quality of medicinal products derived from human blood or plasma. The experience in these initial 3 years has proven that the risk-based approach used in the selection of the inspections is a successful tool in identifying the centres of concern and bringing them to a satisfactory compliance comparable with inspections of manufacturers of medicinal products under the centralised procedure.

4. Discussion

The analysis 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 GMP guidance by identifying those areas where more emphasis is needed.

The analysis in this document has been used within the EMEA to provide a basis for monitoring consistency in the following two areas:

- Deficiencies observed in inspections of manufacturers of medicinal products under the centralised procedure in year 2006 with the same analysis made for the same category of inspections during the period 1995-2005.
- Deficiencies observed in inspections of blood establishments under the PMF certification system. The results have been also compared with the deficiencies observed in inspections of manufacturers of medicinal products.

The pattern observed in deficiencies of GMP inspections of manufacturers of medicinal products in 2006 follows a similar distribution of deficiencies to that found as a result of the same analysis for the period 1995-2005. Deficiencies concerning documentation are the most reported observations compared with the total. However, inspectors typically classify this category of deficiencies as a lower risk (i.e. mainly as a minor deficiency).

It is important to remark that no critical deficiencies were observed in 2006 for this category of inspections. Re-inspections of manufacturers represented 60% of the total of the inspections, which indicated that continuous monitoring of the same manufacturing sites brings them into a high level of GMP compliance.

This is the first time that an analysis of deficiencies has been carried out for inspections of blood establishments in the context of the PMF certification system. The results of this analysis have confirmed the capacity of this tool. It has confirmed that the risk-based approach used in the selection of inspections has been successful in identifying sites of concern. The analysis has also shown that the distribution of the deficiencies in this area follows a different pattern from the deficiencies of manufacturers with a special remark on “Personal issues: duties of key personnel” and “Line clearance, segregation and potential for mix-up”. An attempt to analyse and explain these results is made.

The recurring findings in the freezing conditions of the PMF inspections have triggered a need to revise the European Pharmacopoeia monograph based on scientific justification from industry. Finally, continuous monitoring of this category of inspections (PMF) has helped to bring those manufacturers to a satisfactory level of GMP compliance, i.e. to the same level as found in inspections of manufacturers of medicinal products.

During the coming years, the EMEA will continue to analyse inspections for deficiencies observed in order to identify trends or areas of concerns. EMEA is particularly interested in monitoring differences between groups/types of manufacturers in order to identify and draw industry and regulator’s attention to commonly found deficiencies. The outcome of these analyses will be published on a regular basis by the EMEA.

5. References

- a. Analysis of deficiencies in the period 1995-2005:
<http://www.emea.europa.eu/Inspections/docs/2302207en.pdf>
- b. Compilation of Community Procedures on Inspections and Exchange of Information:
<http://www.emea.europa.eu/Inspections/GMPCompproc.html>
- c. Information on PMF procedure:
<http://www.emea.europa.eu/htms/human/pmf/pmf.htm>