European Medicines Agency
Inspections

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COMMUNITY PROJECT ON THE PRACTICAL IMPLEMENTATION OF THE NEW OBLIGATIONS FOR MANUFACTURING AUTHORISATION HOLDERS (Art. 46f/50f Directive 2001/83(2)/EC).

Executive Summary
A survey has been carried out by the GMP inspectorates of the EEA to examine how manufacturing authorisation holders are fulfilling their legal obligation to ensure that only active substances that have been manufactured in accordance with GMP are used as starting materials.

The survey, carried out between May 2005 and May 2006, reveals that manufacturing authorisation holders are aware of their new obligations and have taken measures to comply. Most have set up an audit programme of their active substance suppliers, although some deficiencies have been found with these programmes. The survey reveals that importers and smaller companies are most likely to fail in taking adequate measures to ensure compliance. In some cases companies are being refused access to conduct audits.

There are isolated cases where companies are refusing to allow inspectors access to audit reports of active substance suppliers.

The survey provides some information on the activities of brokers and traders and the issues that arise from their activities, such as loss of traceability. Readers will note that since this exercise was carried out, these issues and others outlined in this report have been the subject of attention in the context of the European Commission's strategy for combating counterfeit medicines as outlined in the public consultation paper on legal proposals published in March 2008.

The report concludes that improvements can be expected in compliance as a result of routine inspections of manufacturing authorisation holders but problems such as audit access will require greater cooperation between manufacturing authorisation holders.

The report also suggests that more attention by the authorities on compliance of importers may be appropriate.

Background
As part of the 2001 review of pharmaceutical legislation coming into force by 30 October 2005, new obligations were introduced for manufacturing authorisation holders. Art. 46f/50f of Directive 2001/83(2)/EC obliges manufacturing authorisation holders to, inter alia, *"….use as starting materials only active substances which have been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials"*.

The European Commission asked EMEA's Ad Hoc GMP Inspection Services Group (now the GMP/GDP Inspectors Working Party) to conduct a review of the practical implementation of this new requirement and this project was undertaken between May 2005 and May 2006.

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@europa.emea.eu http://www.emea.europa.eu

Methodology
GMP Inspectorates from all 25 Member States were invited to take part in the project. At the time the project was initiated Romania and Bulgaria had not acceded to the EU and were consequently not involved. Participation by Member States was optional.

The primary aim of the project was for a number of routine inspections to focus on the measures taken by manufacturing authorisation holders to comply with the new requirements and to report on findings. The number of inspections to be used for the project was left to the discretion of each inspectorate but was expected to be a representative sample of manufacturing authorisation holders under their supervision.

An aide-memoire was developed for the project, which was designed to help inspectors focus in more detail on the issues to be addressed during relevant parts of the sample inspections. Use of the aide-memoire was optional and could equally also be used during routine inspections not related to the project. It is understood that in at least one Member State the aide-memoire was sent to manufacturers in the form of a questionnaire advance of the inspection to assist them with preparation. The aide-memoire is appended to this report.

Site summary report and national summary report formats were also agreed by the Ad Hoc GMP Inspection Services Group.

Key Findings
The number of inspections of manufacturing authorisation holders included in the survey is 517. Reports were submitted by 24 National Competent Authorities. Additional information was provided by an authority with experience from 42 inspections between 2003 and 2006 of active substance manufacturers located in third countries. Although outside of the project it was decided that taking this feedback from a different perspective into account would be useful.

In the period in question, May 2006-May 2007, these authorities reported that they had also carried out 202 inspections of active substance manufacturers. The majority of these inspections were reported as "routine" and it was noted that some Member States have licensing systems in place for active substance manufacturers, which include sites other than those manufacturing biological substances or sterile active substances. The reason for inspecting in 49 cases was stated as "other", mostly without clarification, although several of these were reported as requests by the active substance manufacturer itself. Some of these 49 inspections were triggered by suspicion of non-compliance, but inadequate specific information is available to state categorically that this accounted for the majority of the 49 cases. Only 2 of the 192 inspections of active substance manufacturers were in response to assessor requests arising from dossier assessment although it was noted that 6 requests from EDQM in connection with the Ph. Eur. Certificate of Suitability scheme were listed as "other reasons for inspection".

The authority reporting separately on its experience of third country inspections had carried these out according to draft national legislation obliging importers of active substances to hold an import licence. A GMP certificate is required in order to allow the import of active substances. Of the 42 inspections performed only 27 resulted in the grant of a GMP certificate. The authority in question noted that its decision not to grant a GMP certificate did not prevent the active substance being imported into the EEA elsewhere.

<u>Audit programmes</u>
Most inspectorates reported that the majority of manufacturing authorisation holders had audit programmes in place for their suppliers of active substances including those suppliers that are only involved in packaging or labelling. Audits were document-based only in some cases. Audits are performed by third parties in some cases. Three inspectorates found the reverse situation, i.e. audit programmes were in place only in the minority of cases. Two of these were small Member States where small companies made up a larger proportion of manufacturing authorisation holders than average. When specifically looking at importers, more inspectorates reported inadequacies with audit

approaches taken by those importers. Many importers were considered not to be in control of the process for assessment of active substance suppliers, often leaving this to the medicinal product manufacturer in the third country. Some cases of the supplier refusing access to the manufacturing authorisation holder for audit or charging a fee to allow audit were reported. This appears to be a particular problem when "Atypical actives"[1] are involved.

Accessibility of audit reports

While the majority of audit reports (when existing) are being made available to inspectors, a surprising nine inspectorates reported, mostly isolated cases, where such access was not available or access refused. Little information is given in the feedback from these inspectorates on how this issue was progressed, however one inspectorate reported that information not clearly related to GMP can sometimes be included in such reports.

Competence of auditors

In the vast majority of cases inspectorates were happy with the competence of auditors although some problems were noted, particularly with respect to the engagement of external parties, where the manufacturing authorisation holders sometimes had not taken adequate steps to demonstrate that auditors were suitably trained and qualified and that there is an absence of conflicts of interest.

Brokers and Traders

A secondary aim of the survey was to gain further information on the activities of intermediaries within the supply chain for active substances i.e. not the active substance manufacturer or medicinal product manufacturers using the active substances as a starting material. These companies are commonly referred to as traders or brokers. The use of traders and brokers varies between Member States. These companies were reported to be involved in supply of, but not necessary the storage of, active substances in the original packaging together with original certificates of analysis although sometimes breaking down of original packages followed by repackaging occurs. In some cases brokers furnish their own certificates of analysis and one case was reported in the survey where misleading information was provided in the certificate with respect to the origin of the material. Some traders/brokers hold Ph. Eur. Certificates of Suitability or Active Substance Master Files. It was reported that some traders/brokers perform audits and offer the audit reports to their customers, which raises questions about conflicts of interest.

It should be noted that traders or brokers who package, label or import active substances are, in the context of Community pharmaceutical legislation, active substance manufacturers.

Traceability to authorised manufacturing source

Two-thirds of the inspectorates reported that they were satisfied that manufacturing authorisation holders included in the sample had reliable systems in place to ensure that active substances approved for use in the manufacture of medicinal products had originated from the source authorised in the marketing authorisations. The remaining reports revealed weaknesses in some companies including the absence of change controls in this respect, problems caused by re-labelling by intermediaries or misleading documentation. One incidence was reported of the confirmed use of an unauthorised material and in other cases, the broker would not divulge the source of the active substance.

Audit reports and inspection reports

During the survey inspectorates were asked to comment on the comparison between audit reports carried out by, or on behalf of, manufacturing authorisation holders and inspection reports performed by the competent authorities. As this would require an inspection to be carried out at an active substance manufacturer connected with a manufacturing authorisation holder included in the survey within the timeframe of the survey it was anticipated that the likelihood of such feedback would be low. In the event no authorities reported any information under this heading. However the additional

[1] "Atypical actives" is a term that has been used for materials that may be classed as excipients or active ingredients depending on specific product and usage.

information on inspections of active substance manufacturers in third countries provided by one authority reported three cases of positive audit outcomes which were not borne out by inspection.

Significant non-compliances found

The most common reported failure to comply was the lack of knowledge of the GMP compliance status of the active substance supplier usually due to the absence of an audit programme. Small companies and importers were most likely to be in this situation. The main reason for this appears to be budgetary constraints (many active substance manufacturers are now located in India and China). In some cases, although an audit system was found to exist, it had not been fulfilled, for example because of delays in corporate programmes, or the programme was found to be deficient. Inspectorates often remarked that risk-based approaches are not well developed. Reported deficiencies included:

- Traders, distributors or brokers excluded from audit programmes
- Lack of training of auditors
- Inadequate or ill-defined auditor qualifications
- Inadequate depth of audit
- Assessment against ISO standards instead of GMP

Findings related to the above included acceptance of audits performed by the broker. In one case the reporting inspectorate was concerned about the acceptance of a GMP certificate issued by a third country authority that is not generally recognised as having developed regulatory requirements, although in this case the certificate was only used to justify the postponement of an audit.

One comment made in relation to importers was the lack of control of audit processes, which were delegated to the third country finished product manufacturer.

Other findings of note reported:

- Absence of technical agreements with the active substance manufacturer as a measure to ensure that no unauthorised changes are made.
- Lack of change control on the source of active substance itself.
- Misleading information on the source and the use of an authorised source.

Two miscellaneous findings reported were inadequate Certificates of Analysis (no details given) and in one case the manufacturing authorisation holder did not have a specification for the active substance.

Conclusions

The survey indicates that manufacturing authorisation holders are aware of their new obligations and are taking steps to demonstrate compliance. Many have put audit systems in place, which is the recommended practice. Some manufacturing authorisation holders have not taken adequate measures. This appears to be a particular problem for small companies who have not made financial provision. Small companies are also experiencing problems caused by the refusal of their suppliers to allow audits. Where “Atypical actives” are involved, larger companies face similar problems because of the often relatively small pharmaceutical use of these compounds. Cooperation between manufacturing authorisation holders may solve some of these problems as many companies are likely to use a small number of common sources.

For those companies that have audit systems in place, these can be document-based, or involve on-site audits performed by third parties as well as the performance of their own audit visits. Deficiencies are being reported but it is to be expected that improvements will be made as a result of future routine inspections of manufacturing authorisation holders. It should be stressed that the survey was a fact-finding exercise on a topic that should be addressed in most routine inspections, given that it is concerned with a legal obligation for manufacturing authorisation holders.

One of the key concerns noted is confirming the source of active substances. It seems that confirmation is usually through details on the label and/or accompanying documentation although more sophisticated systems such as coding systems or impurity "fingerprint" libraries are emerging. There are still cases of brokers refusing to reveal the source to manufacturing authorisation holders although this is unacceptable business practice in the pharmaceuticals field.

Importers of medicinal products are slightly more remote from the active substance suppliers and the survey suggests that they need to take more control of arrangements to ensure compliance. This seems to be in line with anecdotal evidence that importers are generally poor at complying with the requirements pertaining to manufacturing authorisation holders and suggests that regulatory authorities might consider whether further work targeted at importers is called for.

Finally, the report provided by one inspectorate on its experiences with inspections of active substance manufacturers casts some concern on the reliability of the GMP assessment of active substance manufacturers by manufacturing authorisation holders. However it is difficult to draw concrete conclusions on the basis of one such report. Furthermore that particular report extends back to 2003 before the new requirements for manufacturing authorisations were legally in force. This additional report raises the lack of communication when authorities discover GMP non-compliance at an active substance manufacturer reinforcing the need for an effective Community procedure. Work is ongoing on this as well as related developments to the EudraGMP database.

Final Note

Readers are reminded that the above report relates to an exercise conducted between 2005 and 2006 and although the performance of manufacturing authorisation holders was expected to improve in this new area of compliance, the European Commission is planning legal proposals to improve the regulatory framework to protect patients from the growing threat from counterfeit medicinal products. We can therefore expect specific measures designed to address many of the issues identified in this report.

Appendix: Aide memoire

1. Does the manufacturing authorisation holder have an audit programme for all of its suppliers of active substances?
1.1 Does the audit programme include brokers and distributors who package and label?
2. Are brokers, traders and distributors used, and if so what function(s) do they carry out?
3. For importers only: Does the importer audit active substance suppliers or does it delegate this to the 3rd country manufacturer?
3.1 If this is delegated, is this specifically included in the technical contract with the 3rd country manufacturer?
4. What is the audit frequency (or see next question)?
4.1. Are audits based on the application of quality risk management?
4.2 What criteria are taken into account in the QRM process?
5. What use is made, if any, by the manufacturing authorisation holder of GMP inspection information?
6. Are audit reports available for inspection?
7. Are auditors suitably trained?
8. Do SOPs cover the planning, conduct, reporting and follow-up of audits?

9. Is the scope of audits relevant to the active substances actually used?
10. Are 3rd party auditors used?
10.1 Do adequate technical contracts exist with 3rd party auditors?
10.2 What measures are undertaken to ensure that 3rd party auditors are competent and have no conflict of interest?
11. Are audit reports shared with other manufacturing authorisation holders procuring active substances from the same source?
11.1 What steps are taken to ensure that reports shared from other manufacturing authorisation holders are wholly relevant to its own active substances?
12. Does the manufacturing authorisation holder have a list of approved suppliers, which clearly identifies the manufacturing source of active substances from distributors, traders and brokers?
12.1 Is there a system that ensures all changes to this list are in compliance with affected marketing authorisations?
13. Is there a system that ensures that active substances cannot be approved for use if the source is not as stipulated in the relevant marketing authorisations?
14. What steps are taken to verify the identity of the source of each batch of active substance received?
15. Are adequate records kept that demonstrate that every batch of active substance is received only from approved sources?

16. Does the manufacturing authorisation holder have a technical contract with its active substance suppliers that oblige the latter to notify it of changes from the approved manufacturing and control procedures?
18. Is there a change control system that ensures that notified changes are reviewed for assessment of the need for variations before affected material is approved for use?
19. Are adequate records kept of notified changes and the change control activities?
20. Please list any other observations from the inspection relating to assurance that the active substances used are manufactured in accordance with GMP.