



Making Medicines Affordable

Brussels, 4 April 2005

Mrs. Sabine Atzor
European Commission
Enterprise DG, Pharmaceuticals
Rue de Genève, 1
1049 Brussels

Dear Mrs. Atzor,

Re: Inspections at Manufacturers of Active Substances – Guidance on Grounds (Triggers) for Inspection (EMA/INS/GMP/50288/2005)

EGA welcomes the opportunity to comment on the recent GMP guidance documents and is pleased to submit comments.

The issues raised by our members deal particularly with the *'Guidance on the occasions when it is appropriate for Competent Authorities to conduct inspections at the premises of Manufacturers of Active Substances used as starting materials'* (EMA/INS/GMP/50288/2005).

The EGA's general and specific comments and concerns are as follows:

General comments

EGA welcomes the new EU legislation regarding mandatory GMP for APIs. We hope that Health Authorities use the opportunity of this new legislative framework to staff up their inspection teams to offer the service of voluntary inspection of API manufacturing sites. We also suggest discussing to what extent GMP certificates from the FDA or other non-European Inspection Authority using ICH Q7a as their guide for GMP requirements could be taken into account despite the absence of a MRA (Mutual Recognition Agreement).

Specific comments

Page 2, heading 'Principle', 3rd and 4th §

We welcome the possibility to include in the application a declaration from the manufacturing authorisation holder that the active substance(s) concerned has/have been manufactured in accordance with the detailed guidelines on GMP for starting materials. This appears to be a very pragmatic approach and which will help to avoid a bottleneck in the registration phase of medicinal products. GMP certificates are indeed not yet available for all APIs used in medicinal products marketed in Europe and all API manufacturer sites in and outside the EU cannot be inspected within a short period of time.



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It is expected that the holder of the manufacturing authorisation will base such a declaration on carrying out, or having carried out on his behalf, an audit of the manufacturers/distributors of the active substances concerned. We welcome the third party audit option, as this approach is particularly important for smaller companies. In addition, we suggest that further guidance be issued aimed at clarifying the framework of operation of third party audit organisations. Companies need assurance that the GMP certificate issued by a third party auditor will be accepted by the health authorities. True independence of third party auditors must also be assured.

Furthermore, we are concerned about the statement that the review of audit reports is one of the primary means by which Competent Authorities will determine whether manufacturing authorisation holders are in compliance with the new legislative requirements. This is considered to be inappropriate on two accounts:

- Firstly, due to reasons of secrecy, including official written secrecy agreements, between the finished product and the API manufacturers; and
- Secondly, as these documents are not necessarily or always the intellectual property of a particular Business Unit of a multinational finished product manufacturer which would not be at liberty to share such a document outside that particular Business Unit.

API audit reports and responses are widely considered internal documents and as such are generally not shown to the Competent Authorities for the reasons mentioned above. What is shown is the audit programme, which includes when the audits were actually performed as well as the SOP upon which the audit programme is based. The presentation of audit reports should be handled by the finished product manufacturer on a case-by-case basis when the Competent Authorities request to see such reports. However, such a definite right to see these reports should not figure as an actual clause in the Guidance.

The only other piece of information which we feel could, and possibly should, be shared with the Competent Authorities is one's conclusion regarding the API manufacturer, ie: 'Acceptable', 'Provisionally Acceptable', 'Re-audit Necessary', 'Rejected', etc.

Consequently, we suggest the following:

New wording of page 2, lines 17-20 (Principle):

'Examination, by inspectors, of the audit programmes used by authorisation holders for conducting regular audits (every 2-3 years), including dates of the audits and audit conclusions ~~review of audit reports~~, is one of the primary means by which Competent Authorities will determine if manufacturing authorisation holders are in compliance with the above articles'



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Page 2: Examples of when Inspection may be appropriate

1. Directly linked to EU legislation

We suggest amending the last sentence to take into account the future decentralised procedure

1.1.... 'This may apply in relation to marketing authorisation applications under national or mutual recognition or decentralised procedures ...'

GMP database

We would like to take the opportunity here also to suggest that the list of GMP certificates become publicly accessible along the lines of the publication of the CEP certificates by the EDQM. This would very much be welcomed by small companies in particular as it would help to avoid auditing API suppliers and would streamline the registration process.

The EGA has no comments on the draft format for the authorisation for manufacturing and import nor on the draft GMP certificate.

If you would like to further discuss our comments, please contact Suzette Kox, EGA Senior Director Scientific Affairs at +32 2 534 66 07.

Yours sincerely,

Greg Perry
Director General

(No signature, sent electronically)

Cc: GMP Department, EMEA, London