EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL

Single market, implementation and legislation for consumer goods
Pharmaceuticals : regulatory framework and market authorisations

Brussels, March 2002
DG ENTR F2/EC/mcd D(2002)

Guidance Document

Implications of the Operational phase of the GMP annexes to the *P*rotocol to the *E*uropean agreement on *C*onformity assessment and *A*cceptance of industrial products (PECA) with European Union associated countries

Executive Summary

The aim of this paper is to describe and provide guidance on the key activities which should be undertaken by industry and regulators in the EU and in an associated country with which a ***P*rotocol to the *E*uropean agreement on *C*onformity assessment and *A*cceptance of industrial products (PECA)** concerning Good Manufacturing Practice (GMP) has entered into force. It has been prepared in order to facilitate the operation of the annex on GMP for medicinal products: inspections and batch certification to such PECAs. Procedures for the exchange of certificates relating to manufacturers of medicinal products and the contents of the batch certificates referred to in the PECAs are provided. The type of information which should be exchanged in the context of a PECA with an annex on GMP (alert information, inspection reports, general information) and the circumstances in which this would be applicable are described. Obligations with respect to joint inspections and training of inspectors are also delineated.

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1. Purpose of PECAs with Associated countries - in particular the annex on medicinal products GMP inspection and batch certification.

The objective of PECAs is to provide for an extension of certain benefits of the internal market to European Union associated countries in sectors where the legislation has already been aligned with the *acquis communitaire* in advance of accession. They are intended to operate only during the pre-accession period and will expire on accession of the country to the European Union.
The purpose of the annex on GMP and batch certification is to establish the mutual recognition of the conclusions of each party's GMP inspections based on the implementation of the same legislative standards and by so doing to remove the need for duplicating analytical control procedures and inspections.

2. Scope and coverage

The annex on GMP and batch certification may apply to medicinal products for human and/or veterinary use. Details of the specificities of individual agreements are in Appendix A.

It applies to medicinal products which have been industrially manufactured in the associated country or in the European Community, and to which good manufacturing practice requirements apply. It is limited to the manufacturing process(es) actually carried out and subject to inspections in the respective territories of the associated country and the European Community.

3. Certification of GMP compliance of manufacturers

3.1. Purpose of the certification of manufacturers

The annex on GMP and batch certification establishes the mutual recognition of the conclusions of each party's GMP inspections. Article 4 provides for a system of exchange of certificates issued by a regulatory authority with respect to the status of compliance of a manufacturer with GMP. The purpose of the certificates is to certify that the sites used for manufacture and/or control of the relevant medicinal product or to carry out the relevant specified operations, are regularly inspected by the authorities and comply with either the Community or the other party's GMP requirements.

The certificate of GMP compliance of a manufacturer will also identify the sites of manufacture.

3.2. Requesting a certificate of GMP compliance of a manufacturer

At the request of an exporter, an importer or of the competent authority of the other party, the authorities responsible for granting manufacturing authorisations and for supervision of the manufacture and control of medicinal products will issue the certificates. A list of contacts for request of certificates is available on the EMEA website.

Certificates of GMP compliance of manufacturers are required to be issued expeditiously, and the time taken should not exceed 30 days. In cases when a new inspection has to be carried out, this period may be extended to 60 days.

3.3. Validity of a Certificate of GMP compliance of a manufacturer

Certificates of GMP compliance of manufacturers are valid for the period specified on the Certificate from the date of last inspection.

3.4. Content of the Certificate of GMP Compliance

The content of the Certificate is provided in Appendix B.

4. Batch Certification

4.1 Purpose of the batch certificate

As with other mutual recognition agreements, the GMP annex to PECAs provides for a batch certification scheme for medicinal products which come within the scope of the annex. The purpose of these certificates is to provide assurance that the quality of the products complies with the product specification and with requirements of the marketing authorisation. Each batch exported must be accompanied by a batch certificate in line with the requirements detailed below.

4.2. Content of the batch certificate

The certificates are required to attest that the batch meets the product's specifications and has been manufactured in accordance with GMP and the relevant marketing authorisation. The batch certificate is issued following a full qualitative analysis, a quantitative analysis of all the active constituents and all the other tests or checks necessary to ensure the quality of the product in accordance with its specifications. The specifications of the product and the analytical results should be provided, and the batch certificate should contain a statement that the batch processing and packaging records were reviewed and found in conformity with GMPs. The content of the batch certificate (Annex C) is identical with the internationally harmonised requirements for batch certificates agreed in the framework of other MRAs to which the EU is a partner.

The batch certificate is to be signed by the person responsible for releasing the batch for sale or supply/export at the manufacturing site.

4.3 Obligations of the importer

The importer of the batch, has to receive and maintain the batch certificate issued by the exporting manufacturer. In the EU, the importer must be in possession of a manufacturing authorisation. Upon request, it has to be readily available to the staff of the Regulatory Authority of the importing country. This certification by the manufacturer on the conformity of each batch is essential to exempt the importer from the obligation to re-control (re-analyse) in the importing country as required by the relevant legislation in the Community or the other party (as listed in Section I of the annex on GMP).

4.4. Duties of the qualified persons

Detailed guidance for batch release and certification are laid down in Annex 16 to the Rules Governing Medicinal Products in the European Community, Eudralex, Volume IV. The qualified person in the importing country is required in accordance with the relevant community or national legislation to certify in a register that each batch has been accompanied by the required certificate and thus has been manufactured and checked in

compliance with GMP and in accordance with the marketing authorisation. This register must be kept up to date and remain at the disposal of the competent authority.

5. Alert system

5.1 Rapid Alert Notifications

The Competent Authorities are required to inform the authorities of the other Party with the appropriate speed in case of quality defect, batch recalls, counterfeiting and other problems concerning quality, which could necessitate additional controls or suspension of the distribution of the batch. This shall be done for class I and II recalls using the rapid alert procedure described in "Procedure for handling rapid alerts and recalls arising from quality defects" published on the Commission web-site in the "Revised compilation of Community procedures on administrative collaboration and harmonisation of inspections" (May 2001).
http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2001/oct/compilationmay2001.pdf

For Class II defects, an alert notification should be sent to the other party only if it is known, or believed, that the batch has been distributed to the jurisdiction of the other party.

An alert notification must be sent to the other party for all Class I defects, irrespective of whether the product/batch was exported to the other party.

Information about Class III recalls are not notified through the Rapid Alert system.

5.2. Suspension or revocation of manufacturing authorisations

Information on any suspensions or revocation (total or partial) of a manufacturing authorisation notified within the previous three years should be communicated using the rapid alert procedure. This will also automatically invalidate the manufacturer's certificate of GMP compliance. When appropriate corrective actions have been taken by the company, this should also be communicated to the concerned authorities.

5.3. Other issues

The Rapid Alert System is also used to notify the respective regulatory authorities of the possible presence in the distribution network of counterfeit products.

6. Transmission of inspection reports

The annex on GMP provides for the provision of inspection reports upon reasoned request of one of the parties. This may be provided in the language in which the report has been issued. A summary in a language comprehensible by the other party should also be provided.

In the case of an inspection report which has been issued within the last two years, this should be forwarded to the requesting authority within 30 days.

If the manufacturing operations of the medicinal product in question have not been inspected recently or a particular need to inspect has been identified, a specific and

detailed inspection may be requested. In this case the inspection report should be forwarded within 60 days of the request.

7. Exchange of information between authorities and approximation of quality requirements

Competent authorities are required to exchange any information necessary for the mutual recognition of inspections. Representatives of the Competent Authority of an acceding country may take part in the ad hoc meetings of the EU GMP Inspection service for this purpose. Representatives from EU Competent authorities may also be invited to relevant meetings in acceding countries. In addition, in accordance with Article 4.15, the Competent Authorities shall keep each other informed of any new technical guidance or inspection procedure. This information shall be provided to the EMEA secretariat for distribution to the members of the ad hoc Inspection services group and the inspectorate of the PECA partner. Each Party shall consult the other before their adoption and will endeavour to proceed towards their approximation.

8. Training of Inspectors

Training sessions for inspectors, organised by the authorities, shall be accessible to inspectors of the other party. In order to facilitate this, both parties to the agreement must keep each other informed of these sessions.

9. Joint Inspections

In accordance with Article 4.17, joint inspections may be authorised and conducted by mutual agreement between the parties. These inspections are intended to develop common understanding and interpretation of practice and requirements.

The setting up of these inspections and their form are required to be agreed by both parties.

10. General provisions

10.1 Divergence of views

Both parties to the agreement are required to use their best endeavours to resolve any divergence of views. Unresolved divergences of views shall be referred to the Association Council.

10.2 Safeguard clauses

Where a party has reason to believe that the other Party may be failing to comply with the conditions of this Annex, and supports this in writing in an objective and reasoned manner, it may consult the Association Council. The Association Council may decide on measures to be taken.

In exceptional cases, each party has the right to conduct its own inspection for reasons identified to the other party. Such inspections are to be notified in advance to the other Party, which has the option of joining the inspection.

List of References

Protocol to the Europe Agreement establishing an Association between the European Communities and their Member States, of the one part, and the Republic of Hungary, of the other part, on Conformity Assessment and Acceptance of Industrial Products (PECA): Annex on mutual recognition of results of conformity assessment: Good Manufacturing Practices (GMP) for medicinal products for human use: Inspection and batch certification[1]

Protocol to the Europe Agreement establishing an Association between the European Communities and their Member States, of the one part, and the Czech Republic, of the other part, on Conformity Assessment and Acceptance of Industrial Products (PECA): Annex on mutual recognition of results of conformity assessment: Good Manufacturing Practices (GMP) for medicinal products: Inspection and batch certification[2]

Protocol to the Europe Agreement establishing an Association between the Czech Republic, of the one part, and the European Communities and their Member States, of the other part, on Conformity Assessment and Acceptance of Industrial Products (PECA): Annex on mutual recognition of results of conformity assessment: Good Manufacturing Practices (GMP) for medicinal products: Inspection and batch certification[3]

Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products[4]Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use[5]

Rapid Alert System: "Procedure for handling rapid alerts and recalls arising from quality defects" published on the Commission web-site in the "Revised compilation of Community procedures on administrative collaboration and harmonisation of inspections" (May 2001). [6]

Act No 79/1997 Coll. on pharmaceuticals and on amendments to some Acts, as amended (Czech Republic)

Decree No. 296/2000 Coll. on the good manufacturing practice, good distribution practice, and on more detailed conditions for granting of manufacturing and distribution authorisation, including the medicated feeding stuffs (Czech Republic)

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[1] Official Journal L 135 , 17/05/2001 P. 0003 - 0034

[2] Official Journal L 135 , 17/05/2001 P. 0037 – 0066

[3] Collection of International Agreements of the Czech Republic No. 56/2001

[4] Official Journal L 311 , 28/11/2001 P. 0001 - 0066

[5] Official Journal L 311 , 28/11/2001 P. 0067 – 0128

[6] http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2001/oct/compilationmay2001.pdf

Appendix A – Applicability of the specific PECA agreements on GMP

Hungary

Medicinal Products for Human Use

Czech Republic

Medicinal Products for Human Use

Medicinal products for Veterinary use (provided the manufacturer has been subject to a joint inspection involving EU inspectors)

Appendix B Certificate of GMP compliance of a manufacturer

(LETTERHEAD OF COMPETENT AUTHORITY)

Certificate No: _ _ _/_ _ _/_ _

CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER

ISSUED UNDER THE PROVISIONS OF THE PROTOCOL TO THE EUROPE AGREEMENT ESTABLISHING AN ASSOCIATION BETWEEN THE EUROPEAN COMMUNITIES AND THEIR MEMBER STATES, OF THE ONE PART, AND *XXX* OF THE OTHER PART, ON CONFORMITY ASSESSMENT AND ACCEPTANCE OF INDUSTRIAL PRODUCTS (PECA), ANNEX ON GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS FOR HUMAN/VETERINARY(*) USE: INSPECTION AND BATCH CERTIFICATION.

As requested by ..... on ...../...../..... (date), the Competent Authority of.....(Country) confirms the following:

The company .....,
whose legally registered address is:
.....

.....

.....

.....

has been authorised, in accordance with the [relevant Associated country legislation*; Directive 2001/83/EC, Article 40 or Article 77, **Directive 2001/82/EC, Article 44 or Article 65**] transposed in the following national legislation:*

.....(*).]

under the authorisation reference number ....., covering the following sites of manufacture:

1.....

2.....

to carry out the following operations:

- total manufacture(*) or
- partial manufacture(*)

- import of medicinal products from third countries (applicable only for the EC)(*)

of the following medicinal product or group of products for human use :

.....

in the following dosage forms / product types: (see overleaf).

.....
.....

_____

(*): Delete that which does not apply

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on …../...…/...… (*date*), it is considered that the company complies with the Good Manufacturing Practice requirements referred to in the Protocol to the Europe Agreement establishing an Association between the European Communities and their Member States, of the one part, and [Associated Country], of the other part, on Conformity Assessment and Acceptance of Industrial Products (PECA).

This certificate remains valid for 3 years from the date of last inspection.

…../...…/.....… (*date*)

Name and signature of the authorised person of the Competent Authority of (*country*)

…….

(name)

(title)

(Competent Authority)

(phone & fax numbers)

Dosage forms / product types of which manufacture is authorized (*):

(Suggested categories for inclusion on the certificate at page 1)

Sterile products:

Liquid dosage forms (Large Volume Parenterals)
- aseptically prepared
- terminally sterilized

Liquid dosage forms (Small Volume Parenterals)
- aseptically prepared
- terminally sterilized
- eye drops

Semi-solid dosage forms

Solid dosage forms
- solid fill
- freeze-dried

Non-sterile products:

Liquid dosage forms

Semi-solid dosage forms

Solid dosage forms
- unit dose form (tablets, capsules, suppositories, pessaries)
- multi dose form (powders, granules)

Biological products:

Vaccines

Sera

Blood products

Allergens

Other (describe: e.g. hormones, enzymes of human or animal origin, genetically engineered products)

Packaging only:

Liquid dosage form

Semi-solid dosage form

Solid dosage form

Content of the Fabricator's/Manufacturer's Batch Certificate for

Drug/Medicinal Products Exported to Countries

under the Scope of a MRA or PECA

[LETTER HEAD OF EXPORTING MANUFACTURER]

1. **Name of product.**
   Proprietary, brand or trade name in the importing country.
2. **Importing Country.**
3. **Marketing Authorisation Number.**
   The marketing authorisation number of the product in the importing country should be provided.
4. **Strength/Potency.**
   Identity (name) and amount per unit dose required for all active ingredients/constituents.
5. **Dosage form** (pharmaceutical form).
6. **Package size** (contents of container) and **type** (e.g. vials, bottles, blisters).
7. **Lot/batch number**.
   As related to the product.
8. **Date of fabrication/manufacture**.
   In accordance with national (local) requirements.
9. **Expiry date**.
10. **Name and address of fabricator(s)/manufacturer(s) - manufacturing site(s).**
    All sites involved in the manufacture including packaging and quality control of the batch should be listed with name and address. The name and address must correspond to the information provided on the Manufacturing Authorisation/Establishment Licence.
11. **Number of Manufacturing Authorisation / Licence or Certificate of GMP Compliance of a manufacturer/fabricator.**
    Number should be given for each site listed under item 10.
12. **Results of analysis.**
    Should include the authorised specifications, all results obtained and refer to the methods used (may refer to a separate certificate of analysis which must be dated, signed and attached).
13. **Comments/remarks.**
    Any additional information that can be of value to the importer and/or inspector verifying the compliance of the batch certificate (e.g. specific storage or transportation conditions).
14. **Certification statement.**
    This statement should cover the fabrication/manufacturing, including packaging and quality control. The following text should be used: "I hereby certify that the above information is authentic and accurate. This batch of product has been fabricated/manufactured, including packaging and quality control at the above

mentioned site(s) in full compliance with the GMP requirements of the local Regulatory Authority and with the specifications in the Marketing Authorisation of the importing country. The batch processing, packaging and analysis records were reviewed and found to be in compliance with GMP".

15. **Name and position/title of person authorising the batch release.**

    Including its company/site name and address, if more than one company is mentioned under item 10.

16. **Signature of person authorising the batch release**.

17. **Date of signature**.