

CEP/GMP certificate/written confirmation: How do they relate to each other?

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Contents

1. What is a CEP?
2. What is a GMP certificate?
3. What is a written confirmation?
4. How do these documents relate to each other?
5. Issues with written confirmations.
6. Conclusions

How to register APIs in EU?

1. Certificate of Suitability to the Monograph of the European Pharmacopoeia (CEP)
2. Active Substance Master File (ASMF) Procedure
3. Full details of manufacture

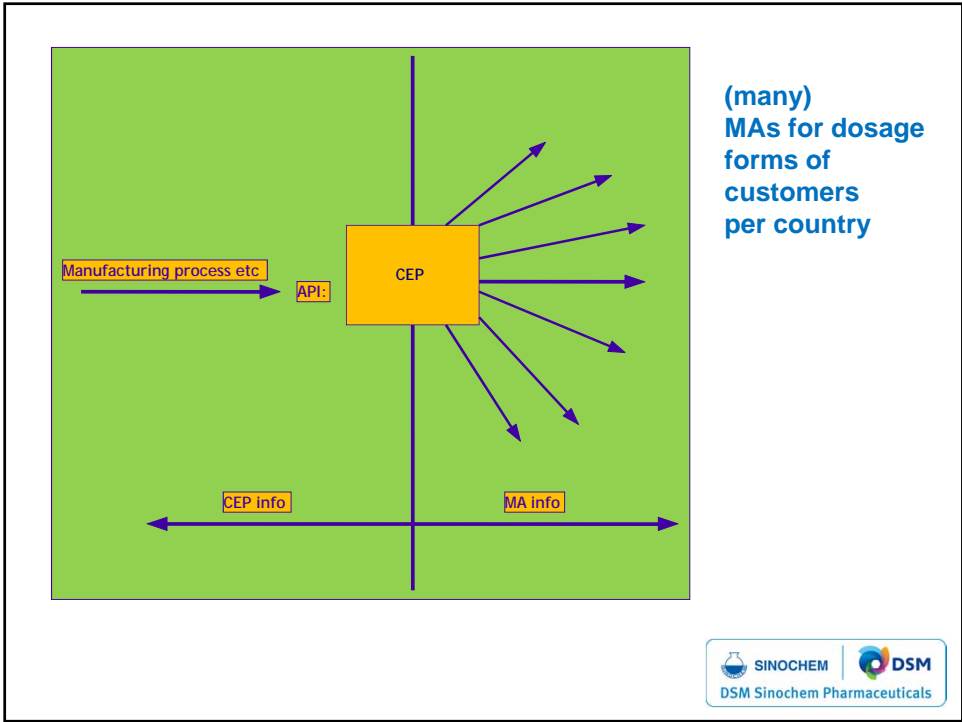
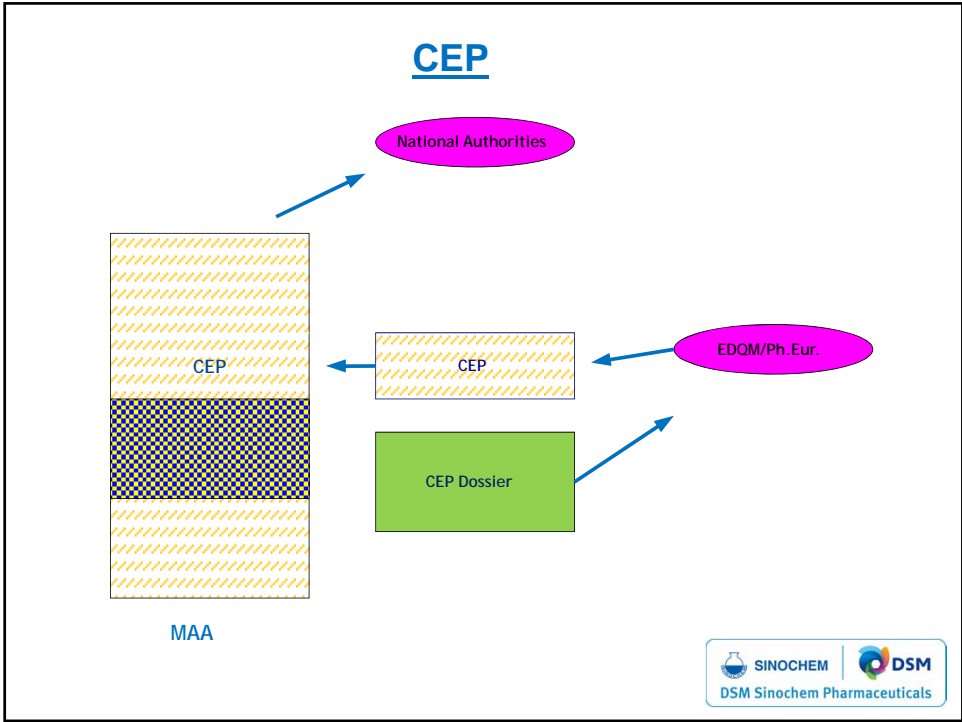
See: CHMP/QWP/297/97Rev1: "Note for Guidance on Summary of Requirements for Active Substances in the Quality Part of the Dossier".



The CEP procedure

- To demonstrate that the quality of a substance is controlled by the Ph. Eur. Monograph + additional tests if needed
- A CEP can be included in a Marketing Authorisation Application as replacement of the required API information.
- A CEP can be used for registration purposes of existing substances which have a monograph in the Ph. Eur.
- A CEP is **not** a GMP certificate or a CoA.





Inspection

EDQM may inspect CEP holders to check:

- cGMP for APIs
- if manufacturer works in accordance with contents of CEP dossier



Since October 2005, all MAA holders are responsible for using only APIs manufactured according to cGMP (ICH Q7A).

EDQM performs appr. 30 inspections in a year. About 80% is done in China and India based on a risk based approach.

Many CEPs have been cancelled/suspended in the last years as a result of the inspections.

Conclusion:

- approval based on only dossier review is clearly insufficient!
- MAA holders do/did not always perform a proper GMP audit
- As only a small number of all CEP holders will be inspected by EDQM a CEP is no guarantee for GMP compliance



What is a GMP certificate?

A certificate issued by a competent Health Authority which indicates that a company complies to applicable c-GMP regulations.

Such a certificate normally contains an expiration date (often 3 years).

For registration of APIs a GMP certificate is required in many countries.

Within the EU the QP should declare that all APIs are manufactured according to EU c-GMP for APIs.



Falsified Medicines Directive

July 1st, 2011 EU Directive 2011/62/EU on Falsified Medicines adopted.

Into force since 2 January 2013 (at least part of Directive):

- Combat of counterfeit human medicines, strengthening the rules for inspection and the requirements for imports.

Objective: increased compliance with GMP for all API manufacturers.
Equal rules for APIs, whether manufactured in the EU or imported

Manufacturing authorisation holder:

Audits manufacturers and distributors of APIs and ensures c-GMP and GDP;
ensures appropriate GMP compliance of excipients following risk assessment

API manufacturers/importers/distributors within EU shall register their activity with the competent authority of the member state in which they are established (registration form submitted by 2 March 2013).



Falsified Medicines Directive

“Written Confirmations” into National legislation by 2 July 2013:

-Shipments of APIs imported into the EU should be accompanied by a “**written confirmation**” from the health authorities of the country of origin that API manufacture was performed under EU/GMP (ICH/Q7) or at least an equivalent standard and was/is regularly inspected according to this standard.

- Written Confirmations for imported API shipments as described above can be waived when:

a) third countries are included in a to be compiled official list of countries that are equivalent to the EU in terms of GMP standards, inspections/enforcement and sanctions. After thorough auditing of their national systems by the EU an application of such a country may be rewarded.

b) a GMP certificate is issued by a EU member state. However only in exceptional cases to ensure availability of medicinal products.



Falsified Medicines Directive

Issues with “written confirmations”:

- Probably many local foreign authorities will not be ready/prepared to issue these documents before 2 July 2013
- Currently only Switzerland has been approved to be an equivalent country
- EU inspectorates are not/hardly cooperating to inspect non-EU API sites. If they would issue a cGMP certificate then at least there is a possibility for a waiver for the written confirmation.

Consequences:

- 1) API shortages on EU market
- 2) API companies with facilities outside EU and fully in compliance with EU GMP will have problems to import and will face financial problems.
- 3) A regulation that can not be complied with by compliant companies is harmful.

Page 10



Falsified Medicines Directive

Other Comments to written confirmations:

- 1) A good system to create level playing field within the GMP area of APIs worldwide is needed
- 2) The “written confirmation” will not/hardly help to reach this purpose as foreign authorities that do not have the same GMP standard as in the EU now should judge their API sites against this different standard. What will be the value of such a judgement?
- 3) If other countries in the world would decide to ask Europe to inspect against their own standards an unworkable situation will be created.
- 4) A good alternative could be to
 - a) hire more EU inspectors (perhaps build a fee system like in the US) and perform more EU inspections.
 - b) accept GMP certificates of countries with similar GMP standards like PIC/S (Pharmaceutical Inspection Convention)



Page 11



Falsified Medicines Directive

What can be done on a short term to avoid problems on 2 July 2013:

- 1) Postpone implementation date to give foreign countries more time to implement a system to issue written confirmations
- 2) Convert the waiver (GMP certificate by EU authorities) into an alternative of the written confirmation and also allow GMP certificates of other high standard GMP countries like PIC/S.
- 3) If there is no EU GMP certificate issued yet give API companies extra time if they have requested an EU inspection before July 2, 2013 but put on a waiting list.



Page 12



Conclusions



- 1) A CEP is a certificate that can be used for registration purposes of a generic API with a monograph in the Ph. Eur. and should not be mixed up with a GMP certificate.
- 2) A written confirmation is a kind of EU GMP certificate for APIs issued by non-EU Health Authorities and included in each shipment to EU.
- 3) The availability of written confirmations from 2 July 2013 onwards is very uncertain as many non-EU authorities just started with the implementation of a system needed to issue these documents.
- 4) It is questionable if the written confirmation will contribute to the safety of APIs coming from outside EU.
- 5) Transition measures are needed to avoid problems like API shortages
- 6) It is clear that many EU member states will not be ready with implementation in time.

Page 13

