





## Experience with CEPs from a European regulatory authority perspective

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## Agenda

-  Introduction (Focus of Presentation)
-  Legislation
-  Questionnaire (Answers from EDQM and National Authorities and EMA)
-  Conclusion

## Introduction

- ☉ CEP founded in 1994, collaboration between assessors of medicinal agencies and EDQM is listed under [Resolution AP-CSP \(07\) 1 on the 'Certification of Suitability to the Monographs of the European Pharmacopoeia \(Revised Version\)'](#) (Adopted by the Public Health Committee (CD-P-SP) on 21/02/2007)
- ☉ CEP is also explained under the text about organisation of CEP procedure on EDQM website

## Introduction

Claimed missions of CEP:

- facilitation** of exchanges between regulators and industry to ensure that the quality of substances in production of pharmaceutical products is guaranteed and
- optimisation** of the use of resources available to health authorities and the use of **scarce** resources available for the inspection through close collaboration with European and non-European authorities

## Focus of presentation

Acceptance of CEP by national health authorities in EU and EMA is well established as well as collaboration between EDQM and health authorities in case of withdrawal or suspension of CEP

**Focus of this presentation** will be on cases when a **suspension or withdrawal of CEP** is triggered.



## Legislation

☞ **Suspension or Withdrawal of a Certificate of Suitability, Closure of an Application** (*PA/PH/CEP (08) 17, R4*)

☞ **Compilation of Community Procedures on Inspections and Exchange of Information** (*EMA/INS/GMP/321252/2012 Rev 17*)

**Chapter: Procedure for Dealing With Serious GMP Non-compliance or Voiding/Suspension of CEPs Thus Requiring Co-ordinated Administrative Action**

## Suspension or Withdrawal of a Certificate of Suitability, Closure of an Application

### Definitions

- 🕒 **Suspension:** Temporary cancellation of a granted CEP made either upon request by the holder of the CEP or by a decision of the EDQM. Under certain conditions, the CEP may be restored.
  
- 🕒 **Withdrawal:** Definitive cancellation of a granted CEP made either upon request by the holder of the CEP or by a decision of the EDQM.
  
- 🕒 **Closure:** Cancellation of an on-going CEP application made either upon request of the holder of the CEP or by a decision of the EDQM.

## Suspension or Withdrawal of a Certificate of Suitability, Closure of an Application

- 🕒 Suspension due to major deficiencies
  - 🕒 Suspension by the request of holder (e.g. due to building of the new site)
- Suspension is limited to 2 years
- 🕒 Withdrawal due to major deficiencies where no corrective actions are possible
  - 🕒 Withdrawal by the request of holder (e.g. due to cessation of production)

## Suspension or Withdrawal of a Certificate of Suitability, Closure of an Application

Once a CEP has been suspended or withdrawn, the **CEP holder must immediately inform its customers** of the situation to allow them to take responsibility with regard to the substance concerned and any related marketing authorisation or marketing authorisation application

## Procedure for Dealing With Serious GMP Non-compliance or Voiding/Suspension of CEPs Thus Requiring Co-ordinated Administrative Action

A **consolidated procedure** for dealing with all circumstances of **serious GMP non-compliance**, whether found at a manufacturing or import authorisation holder, third country manufacturer or active substance manufacturer is necessary to ensure a coordinated approach to potential risks to public/animal health

## Procedure for Dealing With Serious GMP Non-compliance or Voiding/Suspension of CEPs Thus Requiring Co-ordinated Administrative Action


Suspension or voiding of a Certificate of suitability to the Monograph of the European Pharmacopoeia (CEP) may be a recommended action following an inspection of an active substance manufacturer but this **procedure** additionally **addresses action to be taken in the event of notification by EDQM** that a CEP has been voided or suspended for reasons other than serious GMP non-compliance as the actions and consequences are similar.

## Procedure for Dealing With Serious GMP Non-compliance or Voiding/Suspension of CEPs Thus Requiring Co-ordinated Administrative Action

The procedure requires **the inspectorate** discovering serious GMP non-compliance **to recommend appropriate action**, involving other authorities that share supervisory responsibility in developing those recommendations, and to communicate the recommendations to all other authorities in the Community.



## Procedure for Dealing With Serious GMP Non-compliance or Voiding/Suspension of CEPs Thus Requiring Co-ordinated Administrative Action

 **National competent authorities** must take into account the information on serious GMP non-compliance received and should follow the actions recommended, where the procedure requires it to do so, unless it can justify alternative action based on specific national considerations and where those alternative actions have no impact on other Member States.

## Procedure for Dealing With Serious GMP Non-compliance or Voiding/Suspension of CEPs Thus Requiring Co-ordinated Administrative Action

With regard to actions, directly or consequential, against marketing authorisations, the **Reference Member State** takes the initiative for mutual recognition/de-centralised products. The **European Medicines Agency** co-ordinates action for centrally authorised products. Each **national competent authority** takes responsibility for marketing authorisations that exist purely at national level.



# Questionnaire



## How many withdrawals in total for last years, how many GMP non-compliance?

The table is showing numbers of suspended and withdrawn CEPs (source EDQM)

Year	Suspensions of CEPs	Withdrawal of CEPs by EDQM
2016	51*	9
2015	26	16
2014	20	13
2013	18	26

\* Many CEPs suspended for a single site showing non-compliance



## Diapositive 16

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**HB5** Slide updated with recent data. I have also specified that withdrawals are by EDQM  
BRUGUERA Helene; 21/08/2017



**What steps are taken in your agency if withdrawal of CEP due to GMP non-compliance is submitted?**

- ☞ Step 1: checking database for drug substance and manufacturer
- ☞ Step 2: list of products affected - identifying the risk
- ☞ Step 3: notification and follow up discussion with MAH (note: MAH should take the responsibility at first instance, but most agencies make sure that MAH is aware of GMP issue with active substance.

**What steps are taken in your agency if withdrawal of CEP due to GMP non-compliance is submitted?**

- ☞ Step 4: Information about batches on the market, decision taking what should be done.
- ☞ Step 5: Trigger variation or suspension of Marketing authorisation, or if necessary.



## Are the steps taken depending on the type of registration procedure (DCP/ MRP/RMS/CMS, national)?

There is split view, but mostly the steps after withdrawal of CEP are taken only in case of national procedure and if the state is reference member state for this product.




In case the state is CMS it is considered a duty of RMS to deal with this issue.

This is also described in procedural guidance:

*CMDh best practice guidance on collaboration between member states in relation to serious GMP non-compliance issues*

[http://www.hma.eu/fileadmin/dateien/Human\\_Medicines/CMD\\_h\\_/procedural\\_guidance/01\\_General\\_Info/CMDh\\_316\\_2014\\_Rev0\\_2015\\_02.pdf](http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/01_General_Info/CMDh_316_2014_Rev0_2015_02.pdf)

## Do you have in your agency any department that is responsible for action in the case of withdrawals or is it done in cooperation of departments? Is pharmaceutical assessor involved and how?

-  Mostly cooperation between departments (often the inspection department takes the lead, but also cases where other departments are involved at first)
-  Few agencies have dedicated department to deal with this task
-  In all cases the pharmaceutical assessors are contacted on case by case basis

**Is the information on the CEP withdrawal form sufficient for you or do you often request for more information? What is missing from the CEP withdrawal document?**

- ☞ Mostly the provided information is sufficient
- ☞ In case of critical medicinal product where it has to be carefully decided how to approach the issue additional more detail information can be requested from EDQM
- ☞ It would be helpful to mention also manufacturing site
- ☞ Audit report is requested in some cases
- ☞ Reasons for suspension of the CEP – GMP non-compliance in more detail even with the first information would help

**Do you take different steps taking into account the kind of GMP non-compliance?**



- ☞ The risk analysis is performed in most cases taking into account – nature of the findings during inspection, products affected on the market – if they are critical or not, if the manufacturer of drug product has other sources of active substance

## How do you approach cases when the manufacturer asks for CEP withdrawal – is there any difference in comparison to GMP withdrawals? or not.

- ☞ Mostly same approach is taken as for GMP non-compliance, however the products with affected API often can stay on the market
- ☞ The critical products are discussed in detail – the way how to avoid shortage due to API is considered with MA holder



## Conclusion

- ☞ The guidance and legislations are followed
- ☞ Difficulties with identification if the product on the market is notified – database update not always possible
- ☞ Some more information about GMP issues needed for better assessment of the following steps

## Conclusion (continued)

- ☞ Drug shortages due to active substance GMP non-compliance not so pronounced, however in case when only one source of active substance is used for most of Europe the possible risk of shortage is high.
- ☞ Statements of Non-Compliance are public in the EudraGMDP database, and are helpful for everybody to find information about non-compliances (in particular for MAH)



### Acknowledgement and thanks to:

EDQM, EMA and medicinal agencies of member states of EU for completion of questionnaire

**THANK YOU FOR YOUR ATTENTION!**

Any questions, comments?