



IRISH MEDICINES BOARD

# EDQM Inspections of API Sites

---

*The Crowne Plaza Hotel, Dublin 23<sup>rd</sup> October 2008*

---

Victor Garvin  
Inspector

# Agenda

- Introduction to EDQM
- EDQM Inspection Programme
- Triggers for Inspection
- Top Three Deficiencies found During Inspections
- Certificates of Suitability Suspended
- Deficiencies found in Dossier Submissions (Triggers for Inspection)



IRISH MEDICINES BOARD

# Introduction to EDQM

- The European Directorate for the Quality of Medicines (EDQM) & HealthCare is a Directorate of the Council of Europe located in Strasbourg.

The EDQM is responsible for the:

- Technical secretariat of the European Pharmacopoeia Commission,
- Preparation, establishment and distribution of Chemical Reference Standards, Biological Reference Preparations and Reference Spectra,
- Evaluation of applications for Certificates of Suitability of the Monographs of the European Pharmacopoeia and related coordination of related inspections



IRISH MEDICINES BOARD

# Introduction to EDQM

- Co-ordination of the European network of Official Medicines Control Laboratories (OMCL),
- Co-ordination of activities for the elaboration of guidelines and recommendations for blood transfusion and organ transplantation activities,
- Co-ordination of activities for the elaboration of programmes and policies linking the quality of medicines to the quality and safety of their use, in the fields of pharmaceutical practice and care, risk prevention and management as regards counterfeiting of medicines, and the classification of medicines as regards their supply,
- Publication and distribution of all EDQM publications, including the European Pharmacopoeia.



IRISH MEDICINES BOARD

# Introduction to EDQM

**The European Pharmacopoeia Department (EPD)** This department is responsible for the secretariat of the European Pharmacopoeia Commission and for preparing the chapters and monographs of the European Pharmacopoeia with the groups of experts.

**The Publications and Multimedia Department (DPM)**  
This department is responsible for the production of EDQM publications and databases.

**The Laboratory Department (DLab)**  
The laboratory takes part in the elaboration and revision of European Pharmacopoeia monographs and also establishes and monitors all the reference standards. It also participates in the activities of the European network of OMCL's, in the establishment of proficiency testing studies (PTS) and international standards for antibiotics (ISA).



IRISH MEDICINES BOARD

# Introduction to EDQM

The Network of Official Medicines Control Laboratories (OMCL), Biological Standardisation and HealthCare Department (DBO)

The Biological Standardisation, Network of Official Medicines Control Laboratories (OMCL) and HealthCare Department (DBO) is responsible for the Biological Standardisation Programme.



IRISH MEDICINES BOARD

# Introduction to EDQM

## Public Relations and Documentation Division (PRDD)

This division is responsible for the EDQM's communications, for supplying information and answering questions about the various activities of the EDQM to the health authorities, the general public, the media, etc. maintenance of the website, participation in trade fairs and seminars, organisation of scientific conferences, and the production of all presentation material. It is also responsible for documentation and general archiving and the EDQM's library.



IRISH MEDICINES BOARD

# Introduction to EDQM

## Reference Standards and Samples Division (DRS)

This division is specialised in sample procurement, in production, and in distribution of reference standards (identification, purity tests, and assays). It also provides the samples to be analysed when monographs are elaborated by the various groups of experts.

## The Certification of Substances Division (DCEP)

It is responsible for implementing the procedure for certification of suitability of monographs of the European Pharmacopoeia. Assessment and approval of dossiers.



IRISH MEDICINES BOARD

# EDQM Inspection Programme

- The EDQM inspection programme is aimed at assessing compliance with both current Good Manufacturing Practices (GMP)\* and the Certificate of Suitability (CEP) application dossier (and any updates) at the manufacturing/distribution sites covered by CEPs.
- The annual programme of inspection is elaborated based on prioritisation in accordance with the EMEA/EU recommendations# and is adopted by the Certification Steering Committee.

#Ref. EMEA/INS/GMP/3351/03/Rev 5 - Compliance of Community Procedures on Inspections and Exchange of Information



IRISH MEDICINES BOARD

# EDQM Inspection Programme

- The EDQM's Certification Division is responsible for co-ordinating any inspection. The inspections are run by official inspectors from the European Pharmacopoeia member states.
- For inspections in non-European Pharmacopoeia member states, local official inspectors are invited.
- When the conclusion of the inspection is favourable, an attestation of compliance with GMP and CEP dossier is issued by the EDQM.



IRISH MEDICINES BOARD

# EDQM Inspection Programme

- In the case of major/critical deficiencies notices during the inspection, the corresponding CEPs may be suspended.
- The suspension is reported on the EDQM's website and all the authorities concerned are immediately informed so that any necessary action regarding related marketing authorisation(s) can be taken.
- The holder has to inform all their customer(s). The suspension will end only when the company takes satisfactory corrective actions and the implementation of the corrective actions is confirmed by a re-inspection.



IRISH MEDICINES BOARD

# EDQM Inspection Programme

- 152 EDQM inspections carried out in the period 2001 to 2008
- 157 since 1999
- 137 API Sites Inspected in the various countries
- 20 API Sites were re-inspected
- 17 Certificates of Suitability have been withdrawn since 2006



IRISH MEDICINES BOARD

# Triggers for Inspection

## Reference

EMA API GMP Inspection Triggers document (2005):

<http://www.emea.europa.eu/Inspections/GMPComproc.html>

- Mainly requested during assessment (2.4 “Triggers Document”)
- Also Sterile Substances (2.10 “Triggers Document”),
- Re-inspections (2.6 “Triggers Document”),
- Suspicion of Non-compliances (2.3, 1.7 “Triggers Document”)



IRISH MEDICINES BOARD

# Top Three Deficiencies found During Inspections

- Building & Facilities
- Materials Management
- Process equipment with 12% of the deficiencies



IRISH MEDICINES BOARD

# Certificates Suspended 2007

As a result of an inspection of the manufacturing sites :

- Piracetam CEP 2004-083
- Doxycycline Hydrate CEP 2003-225
- Doxycycline Monohydrate CEP 2003-226



IRISH MEDICINES BOARD

# Certificates Suspended 2007

Due to failure to meet commitments, refusal of inspection, reconstruction/restoration of sites to achieve GMP level, temporary closure of a site and/or to operate according to EU GMP :

- Doxycycline hyclate CEP 1992-018
- Doxycycline monohydrate CEP 1996-064
- Colistine sulphate CEP 2001-198



IRISH MEDICINES BOARD

# Certificates Suspended 2007

Due to a temporary inability to produce the API under the approved conditions:

- Carbidopa CEP 2007-067
- Methyldopa CEP 2003-241



IRISH MEDICINES BOARD

# Top Deficiencies Found in CEP Applications

The following should be of interest to those of you involved in preparing applications for CEPs

Top Deficiencies Found in CEP Applications:-

- Lack of information on declared starting materials: description of route of synthesis, data on impurity profile, absence of carry-over of impurities including related substances not demonstrated. Important for complex SMs, short syntheses (58.5% of Dossiers)



IRISH MEDICINES BOARD

# Top Deficiencies Found in CEP Applications

## Top Deficiencies Found in CEP Applications Continued:-

- Lack of assurance of absence of reagents used in synthesis in the final API: catalysts, alkylating agents. Limits not specified for toxic agents and analytical methods not available (45% of Dossiers)
- No impurity limits for Starting Materials: particularly related substances & solvents that may carry over into the finished API and impact on the impurity profile (42% of Dossiers)



IRISH MEDICINES BOARD

# Top Deficiencies Found in CEP Applications

## Top Deficiencies Found in CEP Applications Continued:-

- No demonstration to show that all solvents used in synthesis removed or appropriately limited in final API. ICH & CHMP Guidelines not followed. Assay methods not described and/or not validated (42% of Dossiers)
- Maximum/typical batch size & yields not stated (34% of Dossiers)



IRISH MEDICINES BOARD

# Top Deficiencies Found in CEP Applications

## Top Deficiencies Found in CEP Applications Continued:-

- Impurity limits set for API not in accordance with the Specific European Pharmacopoeia monograph or general monograph 2034 or Guideline CPMP/QWP/1529/04 (Control of Impurities in Pharmacopoeial substances). Spec of unknown impurities (impurities not named or specified in monograph)  $<0.10\%$  or  $0.05\%$  when daily dose is  $>2\text{g/day}$  (33% of Dossiers)



IRISH MEDICINES BOARD

# Top Deficiencies Found in CEP Applications

## Top Deficiencies Found in CEP Applications Continued:-

- Specifications for all reagent & solvents including recovered materials not specified. Quality of solvents and water used in final purification steps (32% Dossiers)
- Reference standards not characterised or in-house standards not characterized against Ph. Eur. CRS (29% of Dossiers)



IRISH MEDICINES BOARD

# Top Deficiencies Found in CEP Applications

## Top Deficiencies Found in CEP Applications Continued:-

- Discussion on Impurities not satisfactory. The origin of all potential impurities (by-product & degradation) not listed and results not provided. The suitability or otherwise of the European Pharmacopoeia monograph to detect and limit related substances from a particular synthetic process not demonstrated (Applies even when suitable in-house methods are available) (26% of Dossiers)



IRISH MEDICINES BOARD

# Top Deficiencies Found in CEP Applications

## Top Deficiencies Found in CEP Applications Continued:-

- Description of in-process controls (IPCs) not sufficiently detailed. No information on the tests performed or description of analytical method to guarantee quality of the final API and justify specifications (24% of Dossiers)
- No detailed test results provided for three recently manufactured API batches or results not presented as actual values (24% of Dossiers)



IRISH MEDICINES BOARD